# FIRST AID FOR THE®

# USMLE® - STEP



**Time-proven blueprint** for Step 1 success

1,300+ must-know concepts with many new high-yield facts

1,200+ color photos and illustrations, expanded and revised

Student-proven exam strategies designed to boost your score



TAO LE VIKAS BHUSHAN MATTHEW SOCHAT VAISHNAVI VAIDYANATHAN

## FIRST AID FOR THE®

# USMLE STEP 1 2020

#### TAO LE, MD, MHS

Founder, ScholarRx Associate Clinical Professor, Department of Medicine University of Louisville School of Medicine

#### **VIKAS BHUSHAN, MD**

**Boracay** 

## MATTHEW SOCHAT Fellow, Department of Hema Constructions St. Louis University School of Westigne

#### SARAH SCHIMANSKY, MB BCh BAO

Resident, Department of Ophthalmology Royal United Hospitals Bath

#### KIMBERLY KALLIANOS, MD

Assistant Professor, Department of Radiology and Biomedical Imaging University of California, San Francisco School of Medicine

#### VAISHNAVI VAIDYANATHAN, MD

Resident, Department of Pediatric Neurology Barrow Neurological Institute at Phoenix Children's Hospital

#### **JORDAN ABRAMS**

St. George's University School of Medicine Class of 2020



New York / Chicago / San Francisco / Athens / London / Madrid / Mexico City Milan / New Delhi / Singapore / Sydney / Toronto

FAS1\_2019\_00\_Frontmatter.indd 1 11/14/19 4:35 PM

Copyright © 2020 by Tao Le and Vikas Bhushan. All rights reserved. Except as permitted under the United States Copyright Act of 1976, no part of this publication may be reproduced or distributed in any form or by any means, or stored in a database or retrieval system, without the prior written permission of the publisher.

ISBN: 978-1-26-046205-0 MHID: 1-26-046205-6

The material in this eBook also appears in the print version of this title: ISBN: 978-1-26-046204-3,

MHID: 1-26-046204-8.

eBook conversion by codeMantra

Version 1.0

All trademarks are trademarks of their respective owners. Rather than put a trademark symbol after every occurrence of a trademarked name, we use names in an editorial fashion only, and to the benefit of the trademark owner, with no intention of infringement of the trademark. Where such designations appear in this book, they have been printed with initial caps.

McGraw-Hill Education eBooks are available at special quantity discounts to use as premiums and sales promotions or for use in corporate training programs. To contact a representative, please visit the Contact Us page at www.mhprofessional.com.

#### **Notice**

Medicine is an ever-changing science. As new research and clinical experience broaden our knowledge, changes in treatment and drug therapy are required. The authors and the publisher of this work have checked with sources believed to be reliable in their efforts to provide information that is complete and generally in accord with the standards accepted at the time of publication. However, in view of the possibility of human error or changes in medical sciences, neither the authors nor the publisher nor any other party who has been involved in the preparation or publication of this work warrants that the information contained herein is in every respect accurate or complete, and they disclaim all responsibility for any errors or omissions or for the results obtained from use of the information contained in this work. Readers are encouraged to confirm the information contained herein with other sources. For example and in particular, readers are advised to check the product information sheet included in the package of each drug they plan to administer to be certain that the information contained in this work is accurate and that changes have not been made in the recommended dose or in the contraindications for administration. This recommendation is of particular importance in connection with new or infrequently used drugs.

#### TERMS OF USE

This is a copyrighted work and McGraw-Hill Education and its licensers reserve all rights in and to the work. Use of this work is subject to these terms. Except as permitted under the Copyring Wf 176 and 18 Tights to store and retrieve one copy of the work, you may not decompile, disassemble, reverse engineer, reproduce, modify, create derivative works based upon, transmit, distribute, disseminate, sell, publish or sublicense the work or any part of it without McGraw-Hill Education's prior consent. You may use the work for your own noncommercial and personal use; any other use of the work is strictly prohibited. Your right to use the work may be terminated if you fail to comply with these terms.

THE WORK IS PROVIDED "AS IS." McGRAW-HILL EDUCATION AND ITS LICENSORS MAKE NO GUARANTEES OR WARRANTIES AS TO THE ACCURACY, ADEQUACY OR COMPLETENESS OF OR RESULTS TO BE OBTAINED FROM USING THE WORK, INCLUDING ANY INFORMATION THAT CAN BE ACCESSED THROUGH THE WORK VIA HYPERLINK OR OTHERWISE, AND EXPRESSLY DISCLAIM ANY WARRANTY, EXPRESS OR IMPLIED, INCLUDING BUT NOT LIMITED TO IMPLIED WARRANTIES OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE. McGraw-Hill Education and its licensors do not warrant or guarantee that the functions contained in the work will meet your requirements or that its operation will be uninterrupted or error free. Neither McGraw-Hill Education nor its licensors shall be liable to you or anyone else for any inaccuracy, error or omission, regardless of cause, in the work or for any damages resulting therefrom. McGraw-Hill Education has no responsibility for the content of any information accessed through the work. Under no circumstances shall McGraw-Hill Education and/ or its licensors be liable for any indirect, incidental, special, punitive, consequential or similar damages that result from the use of or inability to use the work, even if any of them has been advised of the possibility of such damages. This limitation of liability shall apply to any claim or cause whatsoever whether such claim or cause arises in contract, tort or otherwise.

#### **Dedication**

To the contributors to this and past editions, who took time to share their knowledge, insight, and humor for the benefit of students and physicians everywhere.



FAS1\_2019\_00\_Frontmatter.indd 3 11/14/19 4:35 PM

(c) ketabton.com: The Digital Library

This page intentionally left blank

FAS1\_2019\_00\_Frontmatter.indd 4 11/14/19 4:35 PM

## **Contents**

Contributing Authors	vii	General Acknowledgments	XV
Associate Authors	viii	How to Contribute	xvii
Faculty Advisors	ix	How to Use This Book	xix
Thirtieth Anniversary Foreword	xi	Selected USMLE Laboratory Values	XX
Preface	xiii	First Aid Checklist for the USMLE Step 1	xxii
Special Acknowledgments	xiv		

▶ SECTION I	GUIDE TO EFFICIENT E	XAM PREPARATION	1
Introduction	2	Test-Taking Strategies	22
USMLE Step 1—The Basics	2	Clinical Vignette Strategies	23
Defining Your Goal	12	If You Think You Failed	24
Learning Strategies	13	Testing Agencies	24
Timeline for Study	16	References	25
Study Materials	20		

▶ SECTION I SUPPLEMENT SPECIAL SITUATIONS	27
---	----

► SECTION II	HIGH-YIELD GEN	ERAL PRINCIPLES	29
How to Use the Database	30	Pathology	205
Biochemistry	33	Pharmacology	229
Immunology	95	Public Health Sciences	255
Microbiology	123		

FAS1\_2019\_00\_Frontmatter.indd 5 11/14/19 4:35 PM

► SECTION III	HIGH-YIELD ORG	AN SYSTEMS	275
Approaching the Organ Systems	276	Neurology and Special Senses	489
Cardiovascular	279	Psychiatry	553
Endocrine	325	Renal	577
Gastrointestinal	357	Reproductive	611
Hematology and Oncology	403	Respiratory	659
Musculoskeletal, Skin, and Connective Tiss	ue 445	Rapid Review	689

► SECTION IV	TOP-RATED REVIEW RESOURCES		711
How to Use the Database	712	Biochemistry	716
Question Banks and Books	714	Cell Biology and Histology	716
Web and Mobile Apps	714	Microbiology and Immunology	717
Comprehensive	715	Pathology	717
Anatomy, Embryology, and Neuroscience	715	Pharmacology	718
Behavioral Science	716	Physiology	718
Abbreviations and Symbols	719	Index	749
Image Acknowledgments	727	About the Editors	808

FAS1\_2019\_00\_Frontmatter.indd 6 11/14/19 4:35 PM

## **Contributing Authors**

#### **MAJED H. ALGHAMDI, MBBS**

Resident, Joint Program of Preventive Medicine Jeddah, Saudi Arabia

#### **LILIT ASLANYAN**

New York Institute of Technology College of Osteopathic Medicine Class of 2020

#### **HUMOOD BOQAMBAR, MB BCh BAO**

Assistant Registrar, Department of Orthopaedic Surgery Farwaniya Hospital

#### **WEELIC CHONG**

Sidney Kimmel Medical College at Thomas Jefferson University MD/PhD Candidate

#### **KRISTINA DAMISCH**

University of Iowa Carver College of Medicine Class of 2020

#### YUMI KOVIC, MD

Resident, Department of Psychiatry University of Massachusetts Medical School

#### IMAGE AND ILLUSTRATION TEAM

#### **CAROLINE COLEMAN**

FAS1\_2019\_00\_Frontmatter.indd 7

Emory University School of Medicine Class of 2020

#### **MATTHEW HO ZHI GUANG**

University College Dublin (MD), DFCI (PhD) MD/PhD Candidate

#### **KAITLYN MELNICK, MD**

Resident, Department of Neurological Surgery University of Florida College of Medicine, Gainesville

#### MARY KATHERINE MONTES de OCA, MD

Resident, Department of Obstetrics and Gynecology Duke University Hospital

#### **SCOTT MOORE, DO**

Assistant Professor of Medical Laboratory Sciences Weber State University

#### **VASILY OVECHKO, MD**

Resident, Department of Surgery Russian Medical Academy of Continuous Professional Education

#### **VIVEK PODDER**

MBBS Student Tairunnessa Memorial Medical College and Hospital, Bangladesh

#### **CONNIE QIU**

Lewis Katz School of Medicine at Temple University MD/PhD Candidate

#### **VICTOR JOSE MARTINEZ LEON, MD**

Central University of Venezuela

#### **ALIREZA ZANDIFAR, MD**

Research Fellow Isfahan University of Medical Sciences, Iran

Vİİ

## **Associate Authors**

#### **HUZAIFA AHMAD, MD**

Resident, Department of Medicine Georgetown University Hospital/MedStar Washington Hospital Center

#### **ALEXANDER R. ASLESEN**

Kirksville College of Osteopathic Medicine Class of 2020

#### **ANUP K. BHATTACHARYA, MD**

Resident, Mallinckrodt Institute of Radiology Washington University School of Medicine

#### **ANUP CHALISE, MBBS**

Resident, Department of General Surgery Nepal Medical College and Teaching Hospital

#### **ASHTEN R. DUNCAN, MPH**

University of Oklahoma-Tulsa School of Community Medicine Class of 2021

#### **SARINA KOILPILLAI**

St. George's University School of Medicine Class of 2020

#### LAUREN N. LESSOR, MPH, MD

Resident, Department of Pediatrics Mercy Health – St. Vincent Medical Center

#### **ROHAN BIR SINGH, MD**

Fellow, Department of Ophthalmology Massachusetts Eye and Ear Harvard Medical School

#### **IMAGE AND ILLUSTRATION TEAM**

#### YAMNA JADOON, MD

Research Associate Aga Khan University

#### **DANA M. JORGENSON**

Chicago College of Osteopathic Medicine Class of 2020

#### **MITCHELL A. KATONA**

University of Texas Health Science Center, Long School of Medicine Class of 2020

#### **TAYLOR MANEY, MD**

Resident, Department of Anesthesiology Brigham and Women's Hospital

viii

FAS1\_2019\_00\_Frontmatter.indd 8 11/14/19 4:35 PM

## **Faculty Advisors**

#### **DIANA ALBA, MD**

Clinical Instructor University of California, San Francisco School of Medicine

#### MARK A.W. ANDREWS, PhD

Professor of Physiology Lake Erie College of Osteopathic Medicine at Seton Hill

#### **MARIA ANTONELLI, MD**

Assistant Professor, Division of Rheumatology MetroHealth Medical Center, Case Western Reserve University

#### **HERMAN SINGH BAGGA, MD**

Urologist, Allegheny Health Network University of Pittsburgh Medical Center Passavant

#### SHIN C. BEH, MD

Assistant Professor, Department of Neurology & Neurotherapeutics UT Southwestern Medical Center at Dallas

#### JOHN R. BUTTERLY, MD

Professor of Medicine
Dartmouth Geisel School of Medicine

#### SHELDON CAMPBELL, MD, PhD

Professor of Laboratory Medicine Yale School of Medicine

#### **BROOKS D. CASH, MD**

Professor of Medicine, Division of Gastroenterology University of South Alabama School of Medicine

#### SHIVANI VERMA CHMURA, MD

Adjunct Clinical Faculty, Department of Psychiatry Stanford University School of Medicine

#### **BRADLEY COLE, MD**

Assistant Professor of Basic Sciences Loma Linda University School of Medicine

#### LINDA S. COSTANZO, PhD

Professor, Physiology & Biophysics Virginia Commonwealth University School of Medicine

#### MANAS DAS, MD, MS

Director, Clinical Anatomy, Embryology, and Histology University of Massachusetts Medical School

#### **ANTHONY L. DeFRANCO, PhD**

Professor, Department of Microbiology and Immunology University of California, San Francisco School of Medicine

#### CHARLES S. DELA CRUZ, MD, PhD

Associate Professor, Department of Pulmonary and Critical Care Medicine Yale School of Medicine

#### SAKINA FARHAT, MD

Consulting Gastroenterologist State University of New York Downstate Medical Center

#### **CONRAD FISCHER, MD**

Associate Professor, Medicine, Physiology, and Pharmacology Touro College of Medicine

#### **RAYUDU GOPALAKRISHNA, PhD**

Associate Professor, Department of Integrative Anatomical Sciences Keck School of Medicine of University of Southern California

#### **RYAN C.W. HALL, MD**

Assistant Professor, Department of Psychiatry University of South Florida School of Medicine

#### **LOUISE HAWLEY, PhD**

Immediate Past Professor and Chair, Department of Microbiology Ross University School of Medicine

#### JEFFREY W. HOFMANN, MD, PhD

Resident, Department of Pathology University of California, San Francisco School of Medicine

#### **CLARK KEBODEAUX, PharmD**

Clinical Assistant Professor, Pharmacy Practice and Science University of Kentucky College of Pharmacy

#### KRISTINE KRAFTS, MD

Assistant Professor, Department of Basic Sciences University of Minnesota School of Medicine

#### **MATTHEW KRAYBILL, PhD**

Clinical Neuropsychologist Cottage Health, Santa Barbara, California

#### **GERALD LEE, MD**

Assistant Professor, Departments of Pediatrics and Medicine Emory University School of Medicine

ix

#### **KACHIU C. LEE, MD, MPH**

Assistant Clinical Professor, Department of Dermatology The Warren Alpert Medical School of Brown University

#### WARREN LEVINSON, MD, PhD

Professor, Department of Microbiology and Immunology University of California, San Francisco School of Medicine

#### **JAMES LYONS, MD**

Professor of Pathology and Family Medicine Alabama College of Osteopathic Medicine

#### PETER MARKS, MD, PhD

Center for Biologics Evaluation and Research US Food and Drug Administration

#### **DOUGLAS A. MATA, MD, MPH**

Brigham Education Institute and Brigham and Women's Hospital Harvard Medical School

#### VICKI M. PARK, PhD, MS

Assistant Dean University of Tennessee College of Medicine

#### **SOROUSH RAIS-BAHRAMI, MD**

Assistant Professor, Departments of Urology and Radiology University of Alabama at Birmingham School of Medicine

#### **SASAN SAKIANI, MD**

Fellow, Transplant Hepatology Cleveland Clinic

#### **MELANIE SCHORR, MD**

Assistant in Medicine Massachusetts General Hospital

#### **SHIREEN MADANI SIMS, MD**

Chief, Division of Gynecology, Gynecologic Surgery, and Obstetrics University of Florida School of Medicine

#### **NATHAN W. SKELLEY, MD**

Assistant Professor, Department of Orthopaedic Surgery University of Missouri, The Missouri Orthopaedic Institute

#### **HOWARD M. STEINMAN, PhD**

Assistant Dean, Biomedical Science Education Albert Einstein College of Medicine

#### SUPORN SUKPRAPRUT-BRAATEN, PhD

Director of Research, Graduate Medical Education Unity Health, Searcy, Arkansas

#### **RICHARD P. USATINE, MD**

Professor, Dermatology and Cutaneous Surgery University of Texas Health Science Center San Antonio

#### J. MATTHEW VELKEY, PhD

Assistant Dean, Basic Science Education Duke University School of Medicine

#### TISHA WANG, MD

Associate Clinical Professor, Department of Medicine David Geffen School of Medicine at UCLA

#### SYLVIA WASSERTHEIL-SMOLLER, PhD

Professor Emerita, Department of Epidemiology and Population Health Albert Einstein College of Medicine

#### **ADAM WEINSTEIN, MD**

Assistant Professor, Pediatric Nephrology and Medical Education Geisel School of Medicine at Dartmouth

#### **ABHISHEK YADAV, MBBS, MSc**

Associate Professor of Anatomy Geisinger Commonwealth School of Medicine

#### **KRISTAL YOUNG, MD**

Clinical Instructor, Department of Cardiology Huntington Hospital, Pasadena, California

## **Thirtieth Anniversary Foreword**

Our exam experiences remain vivid in our minds to this day as we reflect on 30 years of *First Aid*. In 1989, our big idea was to cobble together a "quick and dirty" study guide so that we would never again have to deal with the USMLE Step 1. We passed, but in a Faustian twist, we now relive the exam yearly while preparing each new edition.

Like all students before us, we noticed that certain topics tended to appear frequently on examinations. So we compulsively bought and rated review books and pored through a mind-numbing number of "recall" questions, distilling each into short facts. We had a love-hate relationship with mnemonics. They went against our purist desires for conceptual knowledge, but remained the best way to absorb the vocabulary and near-random associations that unlocked questions and eponyms.

To pull it all together, we used a then "state-of-the-art" computer database (Paradox/MS DOS 4) that fortuitously limited our entries to 256 characters. That length constraint (which predated Twitter by nearly two decades) imposed extreme brevity. The three-column layout created structure—and this was the blueprint upon which *First Aid* was founded.

The printed, three-column database was first distributed in 1989 at the University of California, San Francisco. The next year, the official first edition was self-published under the title *High-Yield Basic Science Boards Review:* A *Student-to-Student Guide.* The following year, our new publisher dismissed the *High-Yield* title as too confusing and came up with *First Aid for the Boards.* We thought the name was a bit cheesy, but it proved memorable. Interestingly, our "High-Yield" name resurfaced years later as the title of a competing board review series.

We lived in San Francisco and Los Angeles during medical school and residency. It was before the Web, and before med students could afford cell phones and laptops, so we relied on AOL e-mail and bulky desktops. One of us would drive down to the other person's place for multiple weekends of frenetic revisions fueled by triple-Swiss white chocolate lattes from the Coffee Bean & Tea Leaf, with R.E.M. and the Nusrat Fateh Ali Khan playing in the background. Everything was marked up on 11- by 17-inch "tearsheets," and at the end of the marathon weekend we would converge at the local 24-hour Kinko's followed by the FedEx box near LAX (10 years before these two great institutions merged). These days we work with our online collaborative platform A.nnotate, GoToMeeting, and ubiquitous broadband Internet, and sadly, we rarely get to see each other.

What hasn't changed, however, is the collaborative nature of the book. Thousands of authors, editors, and contributors have enriched our lives and made this book possible. Most helped for a year or two and moved on, but a few, like Ted Hon, Chirag Amin, and Andi Fellows, made lasting contributions. Like the very first edition, the team is always led by student authors who live and breathe (and fear) the exam, not professors years away from that reality.

We're proud of the precedent that *First Aid* set for the many excellent student-to-student publications that followed. More importantly, *First Aid* itself owes its success to the global community of medical students and international medical graduates (IMGs) who each year contribute ideas, suggestions, and new content. In the early days, we used book coupons and tear-out business reply mail forms. These days, we get many thousands of comments and suggestions each year via our blog FirstAidTeam.com and A.nnotate.

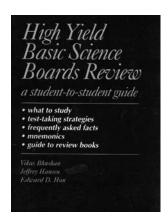
FAS1\_2019\_00\_Frontmatter.indd 11 11/14/19 4:35 PM

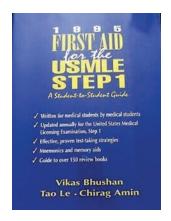
At the end of the day, we don't take any of this for granted. Students are expected to synthesize an ever increasing amount of information, and we have a bigger challenge ahead of us to try to keep *First Aid* indispensable to students and IMGs. We want and need your participation in the *First Aid* community. (See How to Contribute, p. xvii.) With your help, we hope editing *First Aid* will continue to be just as fun and rewarding as the past 30 years have been.

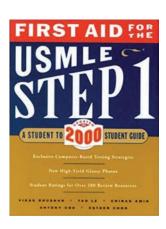
Louisville Tao Le Boracay Vikas Bhushan

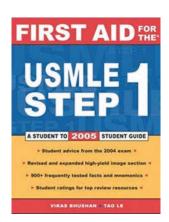
#### First Aid for the USMLE Step 1 Through the Years

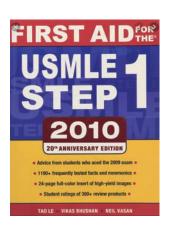


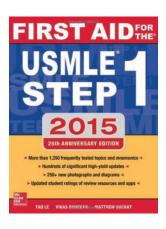














Xii

FAS1\_2019\_00\_Frontmatter.indd 12 11/14/19 4:35 PM

## **Preface**

With the 30th edition of *First Aid for the USMLE Step 1*, we continue our commitment to providing students with the most useful and up-to-date preparation guide for the USMLE Step 1. This edition represents an outstanding revision in many ways, including:

- 50 entirely new or heavily revised high-yield topics reflecting evolving trends in the USMLE Step 1.
- Reorganization of high-yield topics in Pharmacology, Endocrine, and Reproductive chapters for improved study.
- Extensive text revisions, new mnemonics, clarifications, and corrections curated by a team of more than 30 medical student and resident physician authors who excelled on their Step 1 examinations and verified by a team of expert faculty advisors and nationally recognized USMLE instructors.
- Updated with 178 new and revised diagrams and illustrations as part of our ongoing collaboration with USMLE-Rx and ScholarRx (MedIQ Learning, LLC).
- Updated with 75 new and revised photos to help visualize various disorders, descriptive findings, and basic science concepts. Additionally, revised imaging photos have been labeled and optimized to show both normal anatomy and pathologic findings.
- Updated study tips on the opening page of each chapter.
- Improved integration of clinical images and illustrations to better reinforce and learn key anatomic concepts.
- Improved organization and integration of text, illustrations, clinical images, and tables throughout for focused review of high-yield topics.
- Revised and expanded ratings of current, high-yield review resources, with clear explanations of their relevance to USMLE review.
- Real-time Step 1 updates and corrections can be found exclusively on our blog, www.firstaidteam.com.

We invite students and faculty to share their thoughts and ideas to help us continually improve *First Aid for the USMLE Step 1* through our blog and collaborative editorial platform. (See How to Contribute, p. xvii.)

Louisville Tao Le
Boracay Vikas Bhushan
St. Louis Matthew Sochat
Phoenix Vaishnavi Vaidyanathan
Bristol Sarah Schimansky
New York City Jordan Abrams
San Francisco Kimberly Kallianos

FAS1\_2019\_00\_Frontmatter.indd 13 11/14/19 4:35 PM

## **Special Acknowledgments**

This has been a collaborative project from the start. We gratefully acknowledge the thousands of thoughtful comments, corrections, and advice of the many medical students, international medical graduates, and faculty who have supported the authors in our continuing development of *First Aid for the USMLE Step 1*.

For support and encouragement throughout the process, we are grateful to Thao Pham, Jinky Flang, and Jonathan Kirsch, Esq. Thanks to Louise Petersen for organizing and supporting the project. Thanks to our publisher, McGraw-Hill, for the valuable assistance of its staff, including Bob Boehringer, Jeffrey Herzich, and Christina Thomas.

We are also very grateful to Dr. Fred Howell and Dr. Robert Cannon of Textensor Ltd for providing us extensive customization and support for their powerful Annotate.co collaborative editing platform (www.annotate.co), which allows us to efficiently manage thousands of contributions. Thanks to Dr. Richard Usatine and Dr. Kristine Krafts for their outstanding image contributions. Thanks also to Jean-Christophe Fournet (www.humpath.com), Dr. Ed Uthman, and Dr. Frank Gaillard (www.radiopaedia.org) for generously allowing us to access some of their striking photographs.

For exceptional editorial leadership, enormous thanks to Kathleen Naylor, Christine Diedrich and Emma Underdown. Thank you to our USMLE-Rx/ScholarRx team of editors, Jessie Schanzle, Ruth Kaufman, Janene Matragrano, Susan Mazik, Isabel Nogueira, Sharon Prevost, Jen Shimony, and Hannah Warnshuis. Special thanks to our indexer Dr. Anne Fifer. We are also grateful to our medical illustrator, Hans Neuhart, for his creative work on the new and updated illustrations. Lastly, tremendous thanks to Graphic World, especially Anne Banning, Sandy Brown, Gary Clark, and Cindy Geiss.

Louisville Tao Le
Boracay Vikas Bhushan
St. Louis Matthew Sochat
Phoenix Vaishnavi Vaidyanathan
Bristol Sarah Schimansky
New York City Jordan Abrams
San Francisco Kimberly Kallianos

xiv

## **General Acknowledgments**

Each year we are fortunate to receive the input of thousands of medical students and graduates who provide new material, clarifications, and potential corrections through our website and our collaborative editing platform. This has been a tremendous help in clarifying difficult concepts, correcting errata from the previous edition, and minimizing new errata during the revision of the current edition. This reflects our long-standing vision of a true, student-to-student publication. We have done our best to thank each person individually below, but we recognize that errors and omissions are likely. Therefore, we will post an updated list of acknowledgments at our website, www. firstaidteam.com/bonus/. We will gladly make corrections if they are brought to our attention.

For submitting contributions and corrections, many thanks to Raed Ababneh, Antara Afrin, Rasim Agaev, Vanya Aggarwal, Ataa Ahmed, Hasan Alarouri, Basim Ali, Muhammad Faizan Ali, Moatasem Al-Janabi, Mohamed Almahmodi, Chima Amadi, Arman Amin, Jacqueline Aredo, Ranya Baddourah, Daniel Badin, Nida Bajwa, Dileni Bandarage, Jerrin Bawa, Esra Bayram, Craig Beavers, Jacqueline Bekhit, Matthias Bergmann, Stephanie Biecker, Aaron Birnbaum, Prateek Bommu, Nathaniel Borochov, Susan Brands, Olivia W. Brooks, Meghan Brown, Stanley Budzinski, Kevin Budziszewski, Pavel Burski, Elisa M. Cairns, Sergio Camba, Katie Carsky, Esteban Casasola, Marielys Castro, Jesse Chait, Bliss Chang, Santosh Cherian, Heewon Choi, Charilaos Chourpiliadis, Maruf Chowdhury, Matthew J. Christensen, Matthew Yat Hon Chung, Alexander Ciaramella, Dillon Clancy, Sofija Conic, M. Marwan Dabbagh, Parag Das, Ketan Dayma, Elmer De Camps, Charles de Leeuw, Xavier De Pena, Christopher DeAngelo, Elliott Delgado, Anthony DeMarinis, Stacy Diaz, Evan Dishion, Nicola Helen Duzak, Emily Edwards, Alec Egan, Mohamed Elashwal, Osama El-Gabalawy, Matthew Eli, Awab Elnaeem, Sally El Sammak, Dylan Erwin, Stephanie Estevez-Marin, Gray Evans, Najat Fadlallah, Aria Fariborzi, Richard Ferro, Adam Fletcher, Kimberly A. Foley, Kyle Fratta, Samantha Friday, Nikhila Gandrakota, Siva Garapati, Nicolas Curi Gawlinski, Joanna Georgakas, Beth Anne George, Ashley Ghaemi, E. Sophia Gonzalez, Justin Graff, Gabriel Graham, Donovan Griggs, David Gruen, Gursewak Hadday, Jacqueline Hairston, Hunter Harrison, Gull Shahmir Hasnat, Maximillan Hawkins, Grecia Haymee, Briana Hernandez, Robin Hilder, Tammy Hua, Derrek Humphries, Audrey Hunt, Nanki Hura, Danny Ibrahim, Jyothik Varun Inampudi, Hnin Ingyin, Maham Irfan, Mina Iskandar, Kritika Iyer, Christina Jacobs, Arpit Jain, Neil K. Jain, Ala Jamal, Natalie Jansen, Jordan Jay, Mohammad Jmasi, Colton Junod, Talia Kamdjou, Filip Kaniski, Lydia Kaoutzani, Panagiotis Kaparaliotis, Srikrishna Karnatapu, Patrick Keller, Olivia Keller-Baruch, Cameron Kerl, Ahmed Ali Khan, Sara Khan, Shaima Khandaker, Samir Khouzam, Sonya Klein, Elana Kleinman, Andrew Ko, Soheil Kooraki, Anna Kukharchuk, Dennis Vu Kulp, Anil A. Kumar, Julie Kurek, Chloe Lahoud, Mike Lawandy, Ramy Lawandy, Jessica Lazar, Andrea Leal-Lopez, Lynda Lee, Chime Lhatso, Christine Lin, Benjamin Lodge, Soon Khai Low, Estefanía Henríquez Luthje, Lisa-Qiao MacDonald, Divya Madhavarapu, Mahir Mameledzija, Keerer Mann, Rajver Mann, Nadeen Mansour, Yusra Mansour, Bridget Martinez, Ahmad Mashlah, Rick Mathews, Amy McGregor, Alexandra & Joshua Medeiros & Fowler, Viviana Medina, Areeka Memon, Pedro G. R. Menicucci, Ben Meyers, Stephan A. Miller, Fatima Mirza, Murli Mishra, Elana Molcho, Guarina Molina, John Moon, Nayla Mroueh, Neha Mylarapu, Behnam Nabavizadeh, Moeko Nagatsuka, Ghazal Naghibzadeh, Alice Nassar, Nadya Nee, Lucas Nelson, Zach Nelson, Monica Nemat, Kenneth Nguyen, Michael Nguyen, Christian

FAS1\_2019\_00\_Frontmatter.indd 15 11/14/19 4:35 PM

Nieves, Nyia Njamfa, Ahmed Noor, Kyle Nyugen, Ahamd Obeidat, Gerald Olayan, Anndres Olson, Hasaan Omar, Daniel Ortiz, Michael O'Shea, Zonghao Pan, Vasilis Sebastian Paraschos, Christopher Parrino, Janak Patel, Vanisha Patel, Cyril Patra, Rita Paulis, Dmytro Pavlenko, Nancy A. Pina, Alexander Polyak, Jackeline Porto, Shannon D. Powell, Jacob Pruett, Laith Rahabneh, Kamleshun Ramphul, Janhvi Rana, Nidaa Rasheed, Abdul Sattar Raslan, Tomas Ream, Rashelle Ripa, Amanda Michelle Ritchie, Helio Manuel Grullón Rodríguez, Sarah Rohrig, Gessel Romero, Alexander Rose, Rachel Rose, Erica Rubin, Areesha Saati, Jeffrey Sackey, Raza H. Sagarwala, Chhavi Saini, Sergii Sakhno, Allie Sakowicz, Shadia Saleh, Roshun Sangani, Dhruv Sarwal, Abeer Sarwar, M. Sathyanarayanan, Neetu Scariya, Tonio Felix Schaffert, Melissa Schechter, Kathryn Scheinberg, Emma Schnuckle, Emma Schulte, Taylor Schweigert, Lee Seifert, Sheila Serin, Deeksha Seth, Omid Shafaat, Nirav Shah, Samir K. Shah, Wasif Nauman Shah, Muhanad Shaib, Ahmed Shakir, Purnima Sharma, Tina Sharma, Kayla Sheehan, Dr. Priya Shenwai, Sami Shoura, Kris Sifeldeen, Akhand Singh, Manik Inder Singh, Ramzi Y. Skaik, Samantha A. Smith, Timothy Smith, Emilie Song, Hang Song, Shichen Song, Luke Sorensen, Charles Starling, Jonathan Andrew Stone, Nathan Stumpf, Johnny Su, Bahaa Eddine Succar, Saranya Sundaram, Steven Svoboda, Clara Sze, Olive Tang, Brian Tanksley, Omar Tayh, Joshua Taylor, Valerie Teano, Warren Teltser, Steffanie Camilo Tertulien, Roger Torres, Michael Trainer, Andrew Trinh, Aalap K. Trivedi, Georgeanna Tsoumas, Elizabeth Tsui, Cem Turam, Methma Udawatta, Daramfon Udofia, Adaku Ume, Rio Varghese, Judith Vásquez, Earl Vialpando, Sagar Vinayak, Phuong Vo, Habiba Wada, Jason Wang, Tiffany Wang, Zoe Warczak, Mitchell Waters, Rachel Watson, Elizabeth Douglas Weigel, Rabbi Michael Weingarten, Kaystin Weisenberger, Aidan Woodthorpe, Mattia Wruble, Angela Wu, Catherine Xie, Rebecca Xu, Nicholas Yeisley, Sammy Yeroushalmi, Melissas Yuan, Sahil Zaveri, and Yolanda Zhang.

XVİ

## **How to Contribute**

This version of *First Aid for the USMLE Step 1* incorporates thousands of contributions and improvements suggested by student and faculty advisors. We invite you to participate in this process. Please send us your suggestions for:

- Study and test-taking strategies for the USMLE Step 1
- New facts, mnemonics, diagrams, and clinical images
- High-yield topics that may appear on future Step 1 exams
- Personal ratings and comments on review books, question banks, apps, videos, and courses

For each new entry incorporated into the next edition, you will receive **up to a \$20 Amazon.com gift card** as well as personal acknowledgment in the next edition. Significant contributions will be compensated at the discretion of the authors. Also, let us know about material in this edition that you feel is low yield and should be deleted.

All submissions including potential errata should ideally be supported with hyperlinks to a dynamically updated Web resource such as UpToDate, AccessMedicine, and ClinicalKey.

We welcome potential errata on grammar and style if the change improves readability. Please note that *First Aid* style is somewhat unique; for example, we have fully adopted the *AMA Manual of Style* recommendations on eponyms ("We recommend that the possessive form be omitted in eponymous terms") and on abbreviations (no periods with eg, ie, etc). We also avoid periods in tables unless required for full sentences. Kindly refrain from submitting "style errata" unless you find specific inconsistencies with the *AMA Manual of Style*.

The preferred way to submit new entries, clarifications, mnemonics, or potential corrections with a valid, authoritative reference is via our website: www.firstaidteam.com.

This website will be continuously updated with validated errata, new high-yield content, and a new online platform to contribute suggestions, mnemonics, diagrams, clinical images, and potential errata.

Alternatively, you can email us at: firstaid@scholarrx.com.

Contributions submitted by May 15, 2020, receive priority consideration for the 2021 edition of *First Aid for the USMLE Step 1*. We thank you for taking the time to share your experience and apologize in advance that we cannot individually respond to all contributors as we receive thousands of contributions each year.

XVII

FAS1\_2019\_00\_Frontmatter.indd 17 11/14/19 4:35 PM

#### ► NOTE TO CONTRIBUTORS

All contributions become property of the authors and are subject to editing and reviewing. Please verify all data and spellings carefully. Contributions should be supported by at least two high-quality references.

Check our website first to avoid duplicate submissions. In the event that similar or duplicate entries are received, only the first complete entry received with valid, authoritative references will be credited. Please follow the style, punctuation, and format of this edition as much as possible.

#### ▶ JOIN THE FIRST AID TEAM

The *First Aid* author team is pleased to offer part-time and full-time paid internships in medical education and publishing to motivated medical students and physicians. Internships range from a few months (eg, a summer) up to a full year. Participants will have an opportunity to author, edit, and earn academic credit on a wide variety of projects, including the popular *First Aid* series.

For 2020, we are actively seeking passionate medical students and graduates with a specific interest in improving our medical illustrations, expanding our database of medical photographs, and developing the software that supports our crowdsourcing platform. We welcome people with prior experience and talent in these areas. Relevant skills include clinical imaging, digital photography, digital asset management, information design, medical illustration, graphic design, tutoring, and software development.

Please email us at firstaid@scholarrx.com with a CV and summary of your interest or sample work.

XVIII

## **How to Use This Book**

CONGRATULATIONS: You now possess the book that has guided nearly two million students to USMLE success for 30 years. With appropriate care, the binding should last the useful life of the book. Keep in mind that putting excessive flattening pressure on any binding will accelerate its failure. If you purchased a book that you believe is defective, please **immediately** return it to the place of purchase. If you encounter ongoing issues, you can also contact Customer Service at our publisher, McGraw-Hill Education, at https://www.mheducation.com/contact.html.

**START EARLY:** Use this book as early as possible while learning the basic medical sciences. The first semester of your first year is not too early! Devise a study plan by reading Section I: Guide to Efficient Exam Preparation, and make an early decision on resources to use by checking Section IV: Top-Rated Review Resources. Note that *First Aid* is neither a textbook nor a comprehensive review book, and it is not a panacea for inadequate preparation.

**CONSIDER FIRST AID YOUR ANNOTATION HUB:** Annotate material from other resources, such as class notes or comprehensive textbooks, into your book. This will keep all the high-yield information you need in one place. Other tips on keeping yourself organized:

- For best results, use fine-tipped ballpoint pens (eg, BIC Pro+, Uni-Ball Jetstream Sports, Pilot Drawing Pen, Zebra F-301). If you like gel pens, try Pentel Slicci, and for markers that dry almost immediately, consider Staedtler Triplus Fineliner, Pilot Drawing Pen, and Sharpies.
- Consider using pens with different colors of ink to indicate different sources of information (eg, blue for USMLE-Rx Step 1 Qmax, green for UWorld Step 1 Qbank).
- Choose highlighters that are bright and dry quickly to minimize smudging and bleeding through the page (eg, Tombow Kei Coat, Sharpie Gel).
- Many students de-spine their book and get it 3-hole-punched. This will allow you to insert materials from other sources, including curricular materials.

INTEGRATE STUDY WITH CASES, FLASH CARDS, AND QUESTIONS: To broaden your learning strategy, consider integrating your *First Aid* study with case-based reviews (eg, *First Aid Cases for the USMLE Step 1*), flash cards (eg, First Aid Flash Facts), and practice questions (eg, the USMLE-Rx Step 1 Qmax). Read the chapter in the book, then test your comprehension by using cases, flash cards, and questions that cover the same topics. Maintain access to more comprehensive resources (eg, *First Aid for the Basic Sciences: General Principles* and *Organ Systems* and First Aid Express videos) for deeper review as needed.

**PRIME YOUR MEMORY:** Return to your annotated Sections II and III several days before taking the USMLE Step 1. The book can serve as a useful way of retaining key associations and keeping high-yield facts fresh in your memory just prior to the exam. The Rapid Review section includes high-yield topics to help guide your studying.

**CONTRIBUTE TO FIRST AID:** Reviewing the book immediately after your exam can help us improve the next edition. Decide what was truly high and low yield and send us your comments. Feel free to send us scanned images from your annotated *First Aid* book as additional support. Of course, always remember that all examinees are under agreement with the NBME to not disclose the specific details of copyrighted test material.

xix

## **Selected USMLE Laboratory Values**

\* = Included in the Biochemical Profile (SMA-12)

Blood, Plasma, Serum	Reference Range	SI Reference Intervals
*Alanine aminotransferase (ALT, GPT at 30°C)	8–20 U/L	8–20 U/L
Amylase, serum	25–125 U/L	25–125 U/L
*Aspartate aminotransferase (AST, GOT at 30°C)	8–20 U/L	8–20 U/L
Bilirubin, serum (adult) Total // Direct	0.1–1.0 mg/dL // 0.0–0.3 mg/dL	2–17 μmol/L // 0–5 μmol/L
*Calcium, serum (Total)	8.4–10.2 mg/dL	2.1–2.8 mmol/L
*Cholesterol, serum (Total)	Rec: < 200 mg/dL	< 5.2 mmol/L
*Creatinine, serum (Total)	0.6–1.2 mg/dL	53–106 μmol/L
Electrolytes, serum Sodium (Na+) Chloride (Cl-) * Potassium (K+) Bicarbonate (HCO <sub>3</sub> -) Magnesium (Mg <sup>2+</sup> )	136–145 mEq/L 95–105 mEq/L 3.5–5.0 mEq/L 22–28 mEq/L 1.5–2 mEq/L	136–145 mmol/L 95–105 mmol/L 3.5–5.0 mmol/L 22–28 mmol/L 0.75–1.0 mmol/L
Gases, arterial blood (room air) $\begin{array}{c} P_{_{\mathrm{O}_2}} \\ P_{_{\mathrm{CO}_2}} \\ pH \end{array}$	75–105 mm Hg 33–45 mm Hg 7.35–7.45	10.0–14.0 kPa 4.4–5.9 kPa [H+] 36–44 nmol/L
*Glucose, serum	Fasting: 70–110 mg/dL 2-h postprandial: < 120 mg/dL	3.8–6.1 mmol/L < 6.6 mmol/L
Growth hormone – arginine stimulation	Fasting: < 5 ng/mL provocative stimuli: > 7 ng/mL	< 5 μg/L > 7 μg/L
Osmolality, serum	275–295 mOsm/kg	275–295 mOsm/kg
*Phosphatase (alkaline), serum (p-NPP at 30°C)	20–70 U/L	20–70 U/L
*Phosphorus (inorganic), serum	3.0-4.5 mg/dL	1.0-1.5 mmol/L
Prolactin, serum (hPRL)	< 20 ng/mL	< 20 μg/L
*Proteins, serum Total (recumbent) Albumin Globulins	6.0–7.8 g/dL 3.5–5.5 g/dL 2.3–3.5 g/dL	60–78 g/L 35–55 g/L 23–35 g/L
Thyroid-stimulating hormone, serum or plasma	0.5–5.0 μU/mL	0.5-5.0 mU/L
*Urea nitrogen, serum (BUN)	7–18 mg/dL	1.2–3.0 mmol/L
*Uric acid, serum	3.0-8.2 mg/dL	0.18-0.48 mmol/L
		(continues)

XX

FAS1\_2019\_00\_Frontmatter.indd 20 11/14/19 4:35 PM

Cerebrospinal Fluid	Reference Range	SI Reference Intervals
Glucose	40–70 mg/dL	2.2–3.9 mmol/L
Hematologic		
Erythrocyte count	Male: 4.3–5.9 million/mm <sup>3</sup> Female: 3.5–5.5 million/mm <sup>3</sup>	$4.3-5.9 \times 10^{12}/L$ $3.5-5.5 \times 10^{12}/L$
Erythrocyte sedimentation rate (Westergen)	Male: 0–15 mm/h Female: 0–20 mm/h	0–15 mm/h 0–20 mm/h
Hematocrit	Male: 41–53% Female: 36–46%	0.41-0.53 0.36-0.46
Hemoglobin, blood	Male: 13.5–17.5 g/dL Female: 12.0–16.0 g/dL	2.09–2.71 mmol/L 1.86–2.48 mmol/L
Hemoglobin, plasma	1–4 mg/dL	0.16–0.62 μmol/L
Leukocyte count and differential Leukocyte count Segmented neutrophils Band forms Eosinophils Basophils Lymphocytes Monocytes Mean corpuscular hemoglobin Mean corpuscular volume Partial thromboplastin time (activated) Platelet count	4,500–11,000/mm³ 54–62% 3–5% 1–3% 0–0.75% 25–33% 3–7%  25.4–34.6 pg/cell 80–100 μm³ 25–40 seconds 150,000–400,000/mm³	$4.5-11.0 \times 10^{9}$ /L 0.54-0.62 0.03-0.05 0.01-0.03 0-0.0075 0.25-0.33 0.03-0.07 0.39-0.54 fmol/cell 80-100 fL 25-40 seconds $150-400 \times 10^{9}$ /L
Prothrombin time	11–15 seconds	11–15 seconds
Reticulocyte count	0.5–1.5% of red cells	0.005-0.015
Sweat		
Chloride	0–35 mmol/L	0–35 mmol/L
Urine		
Creatinine clearance	Male: 97–137 mL/min Female: 88–128 mL/min	
Osmolality	$50-1,400 \text{ mOsmol/kg } \text{H}_2\text{O}$	
Proteins, total	< 150 mg/24 h	< 0.15 g/24 h

FAS1\_2019\_00\_Frontmatter.indd 21 11/14/19 4:35 PM

#### First Aid Checklist for the USMLE Step 1

This is an example of how you might use the information in Section I to prepare for the USMLE Step 1. Refer to corresponding topics in Section I for more details.

	<ul> <li>□ Use top-rated review resources for first-year medical school courses.</li> <li>□ Ask for advice from those who have recently taken the USMLE Step 1.</li> </ul>
Months Prior —	<ul> <li>□ Review computer test format and registration information.</li> <li>□ Register six months in advance.</li> <li>□ Carefully verify name and address printed on scheduling permit. Make sure the name on scheduling permit matches the name printed on your photo ID.</li> <li>□ Go online for test date ASAP.</li> <li>□ Define your exam goals (pass comfortably, beat the mean, ace the test)</li> <li>□ Set up a realistic timeline for study. Cover less crammable subjects first.</li> <li>□ Evaluate and choose study materials (review books, question banks).</li> <li>□ Use a question bank to simulate the USMLE Step 1 to pinpoint strengths and weaknesses in knowledge and test-taking skills.</li> </ul>
Weeks Prior —	<ul> <li>□ Do another test simulation in a question bank.</li> <li>□ Assess how close you are to your goal.</li> <li>□ Pinpoint remaining weaknesses. Stay healthy (exercise, sleep).</li> <li>□ Verify information on admission ticket (eg, location, date).</li> </ul>
One Week Prior —	<ul> <li>□ Remember comfort measures (loose clothing, earplugs, etc).</li> <li>□ Work out test site logistics (eg, location, transportation, parking, lunch).</li> <li>□ Print or download your Scheduling Permit and Scheduling Confirmation to your phone.</li> </ul>
One Day Prior —	<ul> <li>□ Relax.</li> <li>□ Lightly review short-term material if necessary. Skim high-yield facts.</li> <li>□ Get a good night's sleep.</li> </ul>
Day of Exam —	<ul> <li>□ Relax.</li> <li>□ Eat breakfast.</li> <li>□ Minimize bathroom breaks during exam by avoiding excessive morning caffeine.</li> </ul>
After Exam	<ul> <li>□ Celebrate, regardless of how well you feel you did.</li> <li>□ Send feedback to us on our website at www.firstaidteam.com.</li> </ul>

XXII

#### SECTION I

# **Guide to Efficient Exam Preparation**

"I don't love studying. I hate studying. I like learning. Learning is beautiful."

-Natalie Portman

"Finally, from so little sleeping and so much reading, his brain dried up and he went completely out of his mind."

-Miguel de Cervantes Saavedra, Don Quixote

"Sometimes the questions are complicated and the answers are simple."

—Dr. Seuss

"He who knows all the answers has not been asked all the questions."

—Confucius

"The expert in anything was once a beginner."

-Helen Hayes

"It always seems impossible until it's done."

-Nelson Mandela

▶Introduction	2
► USMLE Step 1—The Basics	2
▶ Defining Your Goal	12
▶ Learning Strategies	13
▶ Timeline for Study	16
▶ Study Materials	20
▶ Test-Taking Strategies	22
Clinical Vignette Strategies	23
▶ If You Think You Failed	24
▶ Testing Agencies	24
N Poforoncos	25

FAS1\_2019\_00\_Section\_Lindd 1 11/7/19 2:48 PM

#### **▶** INTRODUCTION

Relax.

This section is intended to make your exam preparation easier, not harder. Our goal is to reduce your level of anxiety and help you make the most of your efforts by helping you understand more about the United States Medical Licensing Examination, Step 1 (USMLE Step 1). As a medical student, you are no doubt familiar with taking standardized examinations and quickly absorbing large amounts of material. When you first confront the USMLE Step 1, however, you may find it all too easy to become sidetracked from your goal of studying with maximal effectiveness. Common mistakes that students make when studying for Step 1 include the following:

- Starting to study (including First Aid) too late
- Starting to study intensely too early and burning out
- Starting to prepare for boards before creating a knowledge foundation
- Using inefficient or inappropriate study methods
- Buying the wrong resources or buying too many resources
- Buying only one publisher's review series for all subjects
- Not using practice examinations to maximum benefit
- Not understanding how scoring is performed or what the score means
- Not using review books along with your classes
- Not analyzing and improving your test-taking strategies
- Getting bogged down by reviewing difficult topics excessively
- Studying material that is rarely tested on the USMLE Step 1
- Failing to master certain high-yield subjects owing to overconfidence
- Using First Aid as your sole study resource
- Trying to prepare for it all alone

In this section, we offer advice to help you avoid these pitfalls and be more productive in your studies.

#### ▶ The test at a glance:

- 8-hour exam
- Up to a total of 280 multiple choice items
- 7 test blocks (60 min/block)
- Up to 40 test items per block
- 45 minutes of break time, plus another 15 if you skip the tutorial

#### ▶ USMLE STEP 1—THE BASICS

The USMLE Step 1 is the first of three examinations that you must pass in order to become a licensed physician in the United States. The USMLE is a joint endeavor of the National Board of Medical Examiners (NBME) and the Federation of State Medical Boards (FSMB). The USMLE serves as the single examination system for US medical students and international medical graduates (IMGs) seeking medical licensure in the United States.

FAS1 2019 00 Section Lindd 2 11/7/19 2:48 PM

The Step 1 exam includes test items that can be grouped by the organizational constructs outlined in Table 1 (in order of tested frequency).

TABLE 1. Frequency of Various Constructs Tested on the USMLE Step 1.\*

Competency	Range, %	System	Range, %
Medical knowledge: applying foundational science concepts	52–62	General principles	13–17
Patient care: diagnosis	20-30	Behavioral health & nervous systems/special senses	9–13
Patient care: management	7–12	Respiratory & renal/urinary systems	9–13
Practice-based learning & improvement	5–7	Reproductive & endocrine systems	9–13
Communication/professionalism	2–5	Blood & lymphoreticular/immune systems	7–11
Discipline	Range, %	Multisystem processes & disorders	7–11
Pathology	45–52	Musculoskeletal, skin & subcutaneous tissue	6-10
Physiology	26–34	Cardiovascular system	6-10
Pharmacology	16–23	Gastrointestinal system	5–9
Biochemistry & nutrition	14–24	Biostatistics & epidemiology/population health	5–7
Microbiology & immunology	15–22	Social sciences: communication skills/ethics	3–5
Gross anatomy & embryology	11–15		
Histology & cell biology	9–13		
Behavioral sciences	8–12		
Genetics	5–9		

<sup>\*</sup>Percentages are subject to change at any time. www.usmle.org

#### **How Is the Computer-Based Test (CBT) Structured?**

The CBT Step 1 exam consists of one "optional" tutorial/simulation block and seven "real" question blocks of up to 40 questions per block with no more than 280 questions in total, timed at 60 minutes per block. A short 11-question survey follows the last question block. The computer begins the survey with a prompt to proceed to the next block of questions.

Once an examinee finishes a particular question block on the CBT, he or she must click on a screen icon to continue to the next block. Examinees cannot go back and change their answers to questions from any previously completed block. However, changing answers is allowed within a block of questions as long as the block has not been ended and if time permits.

#### What Is the CBT Like?

Given the unique environment of the CBT, it's important that you become familiar ahead of time with what your test-day conditions will be like. You can access a 15-minute tutorial and practice blocks at http://orientation.nbme.org/Launch/USMLE/STPF1. This tutorial interface is very similar to the one you will use in the exam; learn it now and you can skip taking it during the exam, giving you up to 15 extra minutes of break time. You can gain experience with the CBT format by taking the 120 practice questions (3 blocks with 40 questions each) available online or by signing up for a practice session at a test center for a fee.

FAS1\_2019\_00\_Section\_Lindd 3 11/7/19 2:48 PM

4

For security reasons, examinees are not allowed to bring any personal electronic equipment into the testing area. This includes both digital and analog watches, iPods, tablets, calculators, cell phones, and electronic paging devices. Examinees are also prohibited from carrying in their books, notes, pens/pencils, and scratch paper. Food and beverages are also prohibited in the testing area. The testing centers are monitored by audio and video surveillance equipment. However, most testing centers allot each examinee a small locker outside the testing area in which he or she can store snacks, beverages, and personal items.

- ▶ Keyboard shortcuts:
- A, B, etc—letter choices
- Enter or spacebar—move to next auestion
- Esc—exit pop-up Calculator and Notes windows
- Heart sounds are tested via media questions. Make sure you know how different heart diseases sound on auscultation.
- ▶ Be sure to test your headphones during the tutorial.
- ► Familiarize yourself with the commonly tested lab values (eg, Hgb, WBC, platelets, Na+, K+).
- ▶ Illustrations on the test include:
  - Gross specimen photos
- Histology slides
- Medical imaging (eg, x-ray, CT, MRI)
- Electron micrographs
- Line drawings
- ► Ctrl-Alt-Delete are the keys of death during the exam. Don't touch them at the same time!

Questions are typically presented in multiple choice format, with 4–5 possible answer options. There is a countdown timer on the lower left corner of the screen as well. There is also a button that allows the examinee to mark a question for review. If a given question happens to be longer than the screen (which occurs very rarely), a scroll bar will appear on the right, allowing the examinee to see the rest of the question. Regardless of whether the examinee clicks on an answer choice or leaves it blank, he or she must click the "Next" button to advance to the next question.

The USMLE features a small number of media clips in the form of audio and/or video. There may even be a question with a multimedia heart sound simulation. In these questions, a digital image of a torso appears on the screen, and the examinee directs a digital stethoscope to various auscultation points to listen for heart and breath sounds. The USMLE orientation materials include several practice questions in these formats. During the exam tutorial, examinees are given an opportunity to ensure that both the audio headphones and the volume are functioning properly. If you are already familiar with the tutorial and planning on skipping it, first skip ahead to the section where you can test your headphones. After you are sure the headphones are working properly, proceed to the exam.

The examinee can call up a window displaying normal laboratory values. In order to do so, he or she must click the "Lab" icon on the top part of the screen. Afterward, the examinee will have the option to choose between "Blood," "Cerebrospinal," "Hematologic," or "Sweat and Urine." The normal values screen may obscure the question if it is expanded. The examinee may have to scroll down to search for the needed lab values. You might want to memorize some common lab values so you spend less time on questions that require you to analyze these.

The CBT interface provides a running list of questions on the left part of the screen at all times. The software also permits examinees to highlight or cross out information by using their mouse. There is a "Notes" icon on the top part of the screen that allows students to write notes to themselves for review at a later time. Finally, the USMLE has recently added new functionality including text magnification and reverse color (white text on black background). Being familiar with these features can save time and may help you better view and organize the information you need to answer a question.

For those who feel they might benefit, the USMLE offers an opportunity to take a simulated test, or "CBT Practice Session" at a Prometric center. Students are eligible to register for this three-and-one-half-hour practice session after they have received their scheduling permit.

The same USMLE Step 1 sample test items (120 questions) available on the USMLE website, www.usmle.org, are used at these sessions. **No new items will be presented.** The practice session is available at a cost of \$75 (or more if taken outside of the US and Canada) and is divided into a short tutorial and three 1-hour blocks of ~40 test items each. Students receive a printed percent-correct score after completing the session. **No explanations of questions are provided.** 

You may register for a practice session online at www.usmle.org. A separate scheduling permit is issued for the practice session. Students should allow two weeks for receipt of this permit.

► You can take a shortened CBT practice test at a Prometric center.

#### How Do I Register to Take the Exam?

Prometric test centers offer Step 1 on a year-round basis, except for the first two weeks in January and major holidays. The exam is given every day except Sunday at most centers. Some schools administer the exam on their own campuses. Check with the test center you want to use before making your exam plans.

US students can apply to take Step 1 at the NBME website. This application allows you to select one of 12 overlapping three-month blocks in which to be tested (eg, April–May–June, June–July–August). Choose your three-month eligibility period wisely. If you need to reschedule outside your initial three-month period, you can request a one-time extension of eligibility for the next contiguous three-month period, and pay a rescheduling fee. The application also includes a photo ID form that must be certified by an official at your medical school to verify your enrollment. After the NBME processes your application, it will send you a scheduling permit.

The scheduling permit you receive from the NBME will contain your USMLE identification number, the eligibility period in which you may take the exam, and two additional numbers. The first of these is known as your "scheduling number." You must have this number in order to make your exam appointment with Prometric. The second number is known as the "candidate identification number," or CIN. Examinees must enter their CINs at the Prometric workstation in order to access their exams. However, you will not be allowed to bring your permit into the exam and will be asked to copy your CIN onto your scratch paper. Prometric has no access to the codes. Make sure to bring a paper or electronic copy of your permit with you to the exam! Also bring an unexpired, government-issued photo ID that includes your signature (such as a driver's license or passport). Make sure the name on your photo ID exactly matches the name that appears on your scheduling permit.

The Prometric website will display a calendar with open test dates.

FAS1\_2019\_00\_Section\_Lindd 5 11/7/19 2:48 PM

**SECTION I** 

#### **GUIDE TO EFFICIENT EXAM PREPARATION**

- ► The confirmation emails that Prometric and NBME send are not the same as the scheduling permit.
- ► Test scheduling is done on a "first-come, first-served" basis. It's important to schedule an exam date as soon as you receive your scheduling permit
- an exam date as soon as you receive your scheduling permit.

 Register six months in advance for seating and scheduling preference. Once you receive your scheduling permit, you may access the Prometric website or call Prometric's toll-free number to arrange a time to take the exam. You may contact Prometric two weeks before the test date if you want to confirm identification requirements. Although requests for taking the exam may be completed more than six months before the test date, examinees will not receive their scheduling permits earlier than six months before the eligibility period. The eligibility period is the three-month period you have chosen to take the exam. Most medical students choose the April–June or June–August period. Because exams are scheduled on a "first-come, first-served" basis, it is recommended that you book an exam date on the Prometric website as soon as you receive your permit. Prometric will provide appointment confirmation on a print-out and by email. Be sure to read the latest USMLE Bulletin of Information for further details.

#### What If I Need to Reschedule the Exam?

You can change your test date and/or center by contacting Prometric at 1-800-MED-EXAM (1-800-633-3926) or www.prometric.com. Make sure to have your CIN when rescheduling. If you are rescheduling by phone, you must speak with a Prometric representative; leaving a voicemail message will not suffice. To avoid a rescheduling fee, you will need to request a change at least 31 calendar days before your appointment. Please note that your rescheduled test date must fall within your assigned three-month eligibility period.

#### When Should I Register for the Exam?

You should plan to register as far in advance as possible ahead of your desired test date (eg, six months), but, depending on your particular test center, new dates and times may open closer to the date. Scheduling early will guarantee that you will get either your test center of choice or one within a 50-mile radius of your first choice. For most US medical students, the desired testing window is in June, since most medical school curricula for the second year end in May or June. Thus, US medical students should plan to register before January in anticipation of a June test date. The timing of the exam is more flexible for IMGs, as it is related only to when they finish exam preparation. Talk with upperclassmen who have already taken the test so you have real-life experience from students who went through a similar curriculum, then formulate your own strategy.

#### Where Can I Take the Exam?

Your testing location is arranged with Prometric when you book your test date (after you receive your scheduling permit). For a list of Prometric locations nearest you, visit www.prometric.com.

FAS1\_2019\_00\_Section\_Lindd 6 11/7/19 2:48 PM

#### How Long Will I Have to Wait Before I Get My Scores?

The USMLE reports scores in three to four weeks, unless there are delays in score processing. Examinees will be notified via email when their scores are available. By following the online instructions, examinees will be able to view, download, and print their score report online for ~120 days after score notification, after which scores can only be obtained through requesting an official USMLE transcript. Additional information about score timetables and accessibility is available on the official USMLE website.

#### **What About Time?**

Time is of special interest on the CBT exam. Here's a breakdown of the exam schedule:

15 minutes Tutorial (skip if familiar with test format and features)

7 hours Seven 60-minute question blocks 45 minutes Break time (includes time for lunch)

The computer will keep track of how much time has elapsed on the exam. However, the computer will show you only how much time you have remaining in a given block. Therefore, it is up to you to determine if you are pacing yourself properly (at a rate of approximately one question per 90 seconds).

The computer does not warn you if you are spending more than your allotted time for a break. You should therefore budget your time so that you can take a short break when you need one and have time to eat. You must be especially careful not to spend too much time in between blocks (you should keep track of how much time elapses from the time you finish a block of questions to the time you start the next block). After you finish one question block, you'll need to click to proceed to the next block of questions. If you do not click within 30 seconds, you will automatically be entered into a break period.

Break time for the day is 45 minutes, but you are not required to use all of it, nor are you required to use any of it. You can gain extra break time (but not extra time for the question blocks) by skipping the tutorial or by finishing a block ahead of the allotted time. Any time remaining on the clock when you finish a block gets added to your remaining break time. Once a new question block has been started, you may not take a break until you have reached the end of that block. If you do so, this will be recorded as an "unauthorized break" and will be reported on your final score report.

Finally, be aware that it may take a few minutes of your break time to "check out" of the secure resting room and then "check in" again to resume testing, so plan accordingly. The "check-in" process may include fingerprints, pocket checks, and metal detector scanning. Some students recommend pocketless clothing on exam day to streamline the process.

 Gain extra break time by skipping the tutorial or finishing a block early.

► Be careful to watch the clock on your break time.

FAS1\_2019\_00\_Section\_Lindd 7 11/7/19 2:48 PM

#### If I Freak Out and Leave, What Happens to My Score?

Your scheduling permit shows a CIN that you will need to enter to start your exam. Entering the CIN is the same as breaking the seal on a test book, and you are considered to have started the exam when you do so. However, no score will be reported if you do not complete the exam. In fact, if you leave at any time from the start of the test to the last block, no score will be reported. The fact that you started but did not complete the exam, however, will appear on your USMLE score transcript. Even though a score is not posted for incomplete tests, examinees may still get an option to request that their scores be calculated and reported if they desire; unanswered questions will be scored as incorrect.

The exam ends when all question blocks have been completed or when their time has expired. As you leave the testing center, you will receive a printed test-completion notice to document your completion of the exam. To receive an official score, you must finish the entire exam.

#### **What Types of Questions Are Asked?**

All questions on the exam are **one-best-answer multiple choice items.** Most questions consist of a clinical scenario or a direct question followed by a list of five or more options. You are required to select the single best answer among the options given. There are no "except," "not," or matching questions on the exam. A number of options may be partially correct, in which case you must select the option that best answers the question or completes the statement. Additionally, keep in mind that experimental questions may appear on the exam, which do not affect your score.

#### **How Is the Test Scored?**

Each Step 1 examinee receives an electronic score report that includes the examinee's pass/fail status, a three-digit test score, a bar chart comparing the examinee's performance to that of other examinees', and a graphic depiction of the examinee's performance by physician task, discipline and organ system.

The USMLE score report highlights the examinee's strength and weaknesses by providing an overview of their performance by physician task, discipline and organ system compared to their overall performance on the exam. Each of the questions (minus experimental questions) is tagged according to any or all relevant content areas. Yellow-colored boxes (lower, same, higher) on your score report indicate your performance in each specific content area relative to your overall performance on the exam. This is often a direct consequence of the total number of questions for each physician task, discipline or system, which is indicated by percentage range after each specified content area on the score report (see Figure 1).

Nearly three fourths of Step 1 questions begin with a description of a patient.

FAS1\_2019\_00\_Section\_Lindd 8 11/7/19 2:48 PM



FIGURE 1. Samples from the USMLE Step 1 Performance Profile.

The NBME provides a three-digit test score based on the total number of items answered correctly on the examination, which corresponds to a particular percentile (see Figure 2). Your three-digit score will be qualified by the mean and standard deviation of US and Canadian medical school first-time examinees.

ird error of the estimate (SEE) of your current

Your score +/- SEE: 245 - 261

Since some questions may be experimental and are not counted, it is possible to get different scores for the same number of correct answers. In 2018, the mean score was 230 with a standard deviation of 19.

The passing score for Step 1 is 194. The NBME does not report the minimum number of correct responses needed to pass, but estimates that it is roughly 60–70%. The NBME may adjust the minimum passing score in the future, so please check the USMLE website or www.firstaidteam.com for updates.

According to the USMLE, medical schools receive a listing of total scores and pass/fail results plus group summaries by discipline and organ system. Students can withhold their scores from their medical school if they wish. Official USMLE transcripts, which can be sent on request to residency programs, include only total scores, not performance profiles.

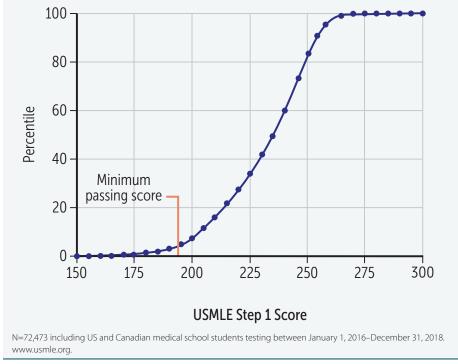
► The mean Step 1 score for US medical students continues to rise, from 200 in 1991 to 230 in 2018.

(9-13N)

(8-12%)

FAS1\_2019\_00\_Section\_Lindd 9 11/7/19 2:48 PM

FIGURE 2. Score and Percentile for First-time Step 1 Takers.



Consult the USMLE website or your medical school for the most current and accurate information regarding the examination.

#### What Does My Score Mean?

The most important point with the Step 1 score is passing versus failing. Passing essentially means, "Hey, you're on your way to becoming a fully licensed doc." As Table 2 shows, the majority of students pass the exam, so remember, we told you to relax.

TABLE 2. Passing Rates for the 2017–2018 USMLE Step 1.2

	201	2017		18
	No. Tested	% Passing	No. Tested	% Passing
Allopathic 1st takers	20,353	96%	20,670	96%
Repeaters	1,029	67%	941	67%
Allopathic total	21,382	94%	21,611	95%
Osteopathic 1st takers	3,786	95%	4,092	96%
Repeaters	49	76%	44	73%
Osteopathic total	3,835	95%	4,136	96%
Total US/Canadian	25,217	94%	25,747	94%
IMG 1st takers	14,900	78%	14,332	80%
Repeaters	2,303	41%	2,111	44%
IMG total	17,203	73%	16,443	75%
Total Step 1 examinees	42,420	85%	42,190	86%

FAS1\_2019\_00\_Section\_Lindd 10 11/7/19 2:48 PM

Beyond that, the main point of having a quantitative score is to give you a sense of how well you've done on the exam and to help schools and residencies rank their students and applicants, respectively.

#### Official NBME/USMLE Resources

The NBME offers a Comprehensive Basic Science Examination (CBSE) for practice that is a shorter version of the Step 1. The CBSE contains four blocks of 50 questions each and covers material that is typically learned during the basic science years. Scores range from 45 to 95 and correlate with a Step 1 equivalent (see Table 3). The standard error of measurement is approximately 3 points, meaning a score of 80 would estimate the student's proficiency is somewhere between 77 and 83. In other words, the actual Step 1 score could be predicted to be between 218 and 232. Of course, these values do not correlate exactly, and they do not reflect different test preparation methods. Many schools use this test to gauge whether a student is expected to pass Step 1. If this test is offered by your school, it is usually conducted at the end of regular didactic time before any dedicated Step 1 preparation. If you do not encounter the CBSE before your dedicated study time, you need not worry about taking it. Use the information to help set realistic goals and timetables for your success.

The NBME also offers six forms of Comprehensive Basic Science Self-Assessment (CBSSA). Students who prepared for the exam using this web-based tool reported that they found the format and content highly indicative of questions tested on the actual exam. In addition, the CBSSA is a fair predictor of USMLE performance (see Table 4). The test interface, however, does not match the actual USMLE test interface, so practicing with these forms alone is not advised.

The CBSSA exists in two formats: standard-paced and self-paced, both of which consist of four sections of 50 questions each (for a total of 200 multiple choice items). The standard-paced format allows the user up to 75 minutes to complete each section, reflecting time limits similar to the actual exam. By contrast, the self-paced format places a 5-hour time limit on answering all multiple choice questions. Every few years, a new form is released and an older one is retired, reflecting changes in exam content. Therefore, the newer exams tend to be more similar to the actual Step 1, and scores from these exams tend to provide a better estimation of exam day performance.

Keep in mind that this bank of questions is available only on the web. The NBME requires that users start and complete the exam within 90 days of purchase. Once the assessment has begun, users are required to complete the sections within 20 days. Following completion of the questions, the CBSSA provides a performance profile indicating the user's relative strengths and weaknesses, much like the report profile for the USMLE Step 1 exam. The profile is scaled with an average score of 500 and a standard deviation of 100. In addition to the performance profile, examinees will be informed of the number of questions answered incorrectly. You will have the ability to review the text of the incorrect question with the correct answer.

TABLE 3. CBSE to USMLE Score Prediction.

CBSE Score	Step 1 Equivalent
≥ 94	≥ 260
92	255
90	250
88	245
86	240
84	235
82	230
80	225
78	220
76	215
74	210
72	205
70	200
68	195
66	190
64	185
62	180
60	175
58	170
56	165
54	160
52	155
50	150
48	145
46	140
≤ 44	≤ 135

FAS1\_2019\_00\_Section\_Lindd 11 11/7/19 2:48 PM

Practice questions may be easier than the actual exam.

TABLE 4. CBSSA to USMLE Score Prediction.

CBSSA Score	Approximate USMLE Step 1 Score
150	155
200	165
250	175
300	186
350	196
400	207
450	217
500	228
550	238
600	248
650	259
700	269
750	280
800	290

Explanations for the correct answer, however, will not be provided. The NBME charges \$60 for assessments with expanded feedback. The fees are payable by credit card or money order. For more information regarding the CBSE and the CBSSA, visit the NBME's website at www.nbme.org.

The NBME scoring system is weighted for each assessment exam. While some exams seem more difficult than others, the score reported takes into account these inter-test differences when predicting Step 1 performance. Also, while many students report seeing Step 1 questions "word-for-word" out of the assessments, the NBME makes special note that no live USMLE questions are shown on any NBME assessment.

Lastly, the International Foundations of Medicine (IFOM) offers a Basic Science Examination (BSE) practice exam at participating Prometric test centers for \$200. Students may also take the self-assessment test online for \$35 through the NBME's website. The IFOM BSE is intended to determine an examinee's relative areas of strength and weakness in general areas of basic science—not to predict performance on the USMLE Step 1 exam—and the content covered by the two examinations is somewhat different. However, because there is substantial overlap in content coverage and many IFOM items were previously used on the USMLE Step 1, it is possible to roughly project IFOM performance onto the USMLE Step 1 score scale. More information is available at http://www.nbme.org/ifom/.

#### ► DEFINING YOUR GOAL

It is useful to define your own personal performance goal when approaching the USMLE Step 1. Your style and intensity of preparation can then be matched to your goal. Furthermore, your goal may depend on your school's requirements, your specialty choice, your grades to date, and your personal assessment of the test's importance. Do your best to define your goals early so that you can prepare accordingly.

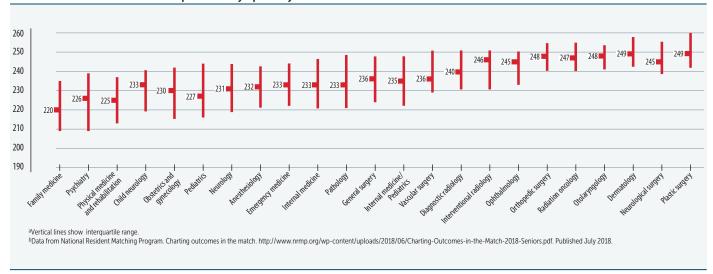
The value of the USMLE Step 1 score in selecting residency applicants remains controversial, and some have called for less emphasis to be placed on the score when selecting or screening applicants.<sup>3</sup> For the time being, however, it continues to be an important part of the residency application, and it is not uncommon for some specialties to implement filters that screen out applicants who score below a certain cutoff. This is more likely to be seen in competitive specialties (eg, orthopedic surgery, ophthalmology, dermatology, otolaryngology). Independent of your career goals, you can maximize your future options by doing your best to obtain the highest score possible (see Figure 3). At the same time, your Step 1 score is only one of a number of factors that are assessed when you apply for residency. In fact, many residency programs value other criteria such as letters of recommendation, third-year clerkship grades, honors, and research experience more than a high score on Step 1. Fourth-year medical students who have recently completed the residency application process can be a valuable resource in this regard.

FAS1\_2019\_00\_Section\_l.indd 12 11/7/19 2:48 PM

Some competitive residency programs place more weight on Step 1 scores when choosing candidates to interview.

Fourth-year medical students have the best feel for how Step 1 scores factor into the residency application process.

FIGURE 3. Median USMLE Step 1 Score by Specialty for Matched US Seniors. a,b



#### ▶ LEARNING STRATEGIES

Many students feel overwhelmed during the preclinical years and struggle to find an effective learning strategy. Table 5 lists several learning strategies you can try and their estimated effectiveness for Step 1 preparation based on the literature (see References). These are merely suggestions, and it's important to take your learning preferences into account. Your comprehensive learning approach will contain a combination of strategies (eg, elaborative interrogation followed by practice testing, mnemonics review using spaced repetition, etc). Regardless of your choice, the foundation of knowledge you build during your basic science years is the most important resource for success on the USMLE Step 1.

▶ The foundation of knowledge you build during your basic science years is the most important resource for success on the USMLE Step 1.

#### **HIGH EFFICACY**

#### **Practice Testing**

Also called "retrieval practice," practice testing has both direct and indirect benefits to the learner. Effortful retrieval of answers does not only identify weak spots—it directly strengthens long-term retention of material. The more effortful the recall, the better the long-term retention. This advantage has been shown to result in higher test scores and GPAs. In fact, research has shown a positive correlation between the number of boards-style practice questions completed and Step 1 scores among medical students.

Practice testing should be done with "interleaving" (mixing of questions from different topics in a single session). Question banks often allow you to intermingle topics. Interleaved practice helps learners develop their ability to focus on the relevant concept when faced with many possibilities. Practicing topics in massed fashion (eg, all cardiology, then all dermatology) may seem intuitive, but there is strong evidence that interleaving correlates with longer-

Research has shown a positive correlation between the number of boards-style practice questions completed and Step 1 scores among medical students.

FAS1\_2019\_00\_Section\_Lindd 13 11/7/19 2:48 PM

TABLE 5. Effective Learning Strategies.

EFFICACY	STRATEGY	EXAMPLE RESOURCES
High efficacy	Practice testing (retrieval practice)	UWorld Qbank NBME Self-Assessments USMLE-Rx QMax Kaplan Qbank
	Distributed practice	USMLE-Rx Flash Facts Anki Firecracker Memorang Osmosis
Moderate efficacy	Mnemonics	Pre-made: SketchyMedical Picmonic Self-made: Mullen Memory
	Elaborative interrogation/ self-explanation	
	Concept mapping	Coggle FreeMind XMind MindNode
Low efficacy	Rereading	
	Highlighting/underlining	
	Summarization	

term retention and increased student achievement, especially on tasks that involve problem solving.<sup>5</sup>

In addition to using question banks, you can test yourself by arranging your notes in a question-answer format (eg, via flash cards). Testing these Q&As in random order allows you to reap the benefit of interleaved practice. Bear in mind that the utility of practice testing comes from the practice of information retrieval, so simply reading through Q&As will attenuate this benefit.

### **Distributed Practice**

Also called "spaced repetition," distributed practice is the opposite of massed practice or "cramming." Learners review material at increasingly spaced out intervals (days to weeks to months). Massed learning may produce more short-term gains and satisfaction, but learners who use distributed practice have better mastery and retention over the long term.<sup>5,9</sup>

Flash cards are a simple way to incorporate both distributed practice and practice testing. Studies have linked spaced repetition learning with flash

FAS1\_2019\_00\_Section\_Lindd 14 11/7/19 2:48 PM

cards to improved long-term knowledge retention and higher exam scores. <sup>6,8,10</sup> Apps with automated spaced-repetition software (SRS) for flash cards exist for smartphones and tablets, so the cards are accessible anywhere. Proceed with caution: there is an art to making and reviewing cards. The ease of quickly downloading or creating digital cards can lead to flash card overload (it is unsustainable to make 50 flash cards per lecture!). Even at a modest pace, the thousands upon thousands of cards are too overwhelming for Step 1 preparation. Unless you have specific high-yield cards (and have checked the content with high-yield resources), stick to pre-made cards by reputable sources that curate the vast amount of knowledge for you.

If you prefer pen and paper, consider using a planner or spreadsheet to organize your study material over time. Distributed practice allows for some forgetting of information, and the added effort of recall over time strengthens the learning.

### **MODERATE EFFICACY**

### **Mnemonics**

A "mnemonic" refers to any device that assists memory, such as acronyms, mental imagery (eg, keywords with or without memory palaces), etc. Keyword mnemonics have been shown to produce superior knowledge retention when compared with rote memorization in many scenarios. However, they are generally more effective when applied to memorization-heavy, keyword-friendly topics and may not be broadly suitable.<sup>5</sup> Keyword mnemonics may not produce long-term retention, so consider combining mnemonics with distributed, retrieval-based practice (eg, via flash cards with SRS).

Self-made mnemonics may have an advantage when material is simple and keyword friendly. If you can create your own mnemonic that accurately represents the material, this will be more memorable. When topics are complex and accurate mnemonics are challenging to create, pre-made mnemonics may be more effective, especially if you are inexperienced at creating mnemonics.<sup>11</sup>

# **Elaborative Interrogation/Self-Explanation**

Elaborative interrogation ("why" questions) and self-explanation (general questioning) prompt learners to generate explanations for facts. When reading passages of discrete facts, consider using these techniques, which have been shown to be more effective than rereading (eg, improved recall and better problem-solving/diagnostic performance).<sup>5,12,13</sup>

# **Concept Mapping**

Concept mapping is a method for graphically organizing knowledge, with concepts enclosed in boxes and lines drawn between related concepts.

 Studies have linked spaced repetition learning with flash cards to improved longterm knowledge retention and higher exam scores

► Elaborative interrogation and selfexplanation prompt learners to generate explanations for facts, which improves recall and problem solving.

FAS1\_2019\_00\_Section\_Lindd 15 11/7/19 2:48 PM

16 SECTION I

### **GUIDE TO EFFICIENT EXAM PREPARATION**

Creating or studying concept maps may be more effective than other activities (eg, writing or reading summaries/outlines). However, studies have reached mixed conclusions about its utility, and the small size of this effect raises doubts about its authenticity and pedagogic significance.<sup>14</sup>

### **LOW EFFICACY**

# Rereading

While the most commonly used method among surveyed students, rereading has not been shown to correlate with grade point average. Due to its popularity, rereading is often a comparator in studies on learning. Other strategies that we have discussed (eg, practice testing) have been shown to be significantly more effective than rereading.

# **Highlighting/Underlining**

Because this method is passive, it tends to be of minimal value for learning and recall. In fact, lower-performing students are more likely to use these techniques. Students who highlight and underline do not learn how to actively recall learned information and thus find it difficult to apply knowledge to exam questions.

### **Summarization**

While more useful for improving performance on generative measures (eg, free recall or essays), summarization is less useful for exams that depend on recognition (eg, multiple choice). Findings on the overall efficacy of this method have been mixed.<sup>5</sup>

# ► TIMELINE FOR STUDY

# **Before Starting**

Your preparation for the USMLE Step 1 should begin when you enter medical school. Organize and commit to studying from the beginning so that when the time comes to prepare for the USMLE, you will be ready with a strong foundation.

### Make a Schedule

After you have defined your goals, map out a study schedule that is consistent with your objectives, your vacation time, the difficulty of your ongoing coursework, and your family and social commitments (see Figure 4). Determine whether you want to spread out your study time or concentrate it into 14-hour study days in the final weeks. Then factor in your own history in

FAS1\_2019\_00\_Section\_Lindd 16 11/7/19 2:48 PM

FIGURE 4. Typical Timeline for the USMLE Step 1.



 Customize your schedule. Tackle your weakest section first.

preparing for standardized examinations (eg, SAT, MCAT). Talk to students at your school who have recently taken Step 1. Ask them for their study schedules, especially those who have study habits and goals similar to yours. Sample schedules can be found at https://firstaidteam.com/schedules/.

Typically, US medical schools allot between four and eight weeks for dedicated Step 1 preparation. The time you dedicate to exam preparation will depend on your target score as well as your success in preparing yourself during the first two years of medical school. Some students reserve about a week at the end of their study period for final review; others save just a few days. When you have scheduled your exam date, do your best to adhere to it. Studies show that a later testing date does not translate into a higher score, so avoid pushing back your test date without good reason.<sup>15</sup>

Make your schedule realistic, and set achievable goals. Many students make the mistake of studying at a level of detail that requires too much time for a comprehensive review—reading *Gray's Anatomy* in a couple of days is not a realistic goal! Have one catch-up day per week of studying. No matter how well you stick to your schedule, unexpected events happen. But don't let yourself procrastinate because you have catch-up days; stick to your schedule as closely as possible and revise it regularly on the basis of your actual progress. Be careful not to lose focus. Beware of feelings of inadequacy when comparing study schedules and progress with your peers. **Avoid others who stress you out.** Focus on a few top-rated resources that suit your learning style—not on some obscure books your friends may pass down to you. Accept the fact that you cannot learn it all.

You will need time for uninterrupted and focused study. Plan your personal affairs to minimize crisis situations near the date of the test. Allot an adequate number of breaks in your study schedule to avoid burnout. Maintain a healthy lifestyle with proper diet, exercise, and sleep.

Another important aspect of your preparation is your studying environment. Study where you have always been comfortable studying. Be sure to include everything you need close by (review books, notes, coffee, snacks, etc). If you're the kind of person who cannot study alone, form a study group with other students taking the exam. The main point here is to create a comfortable environment with minimal distractions.

Avoid burnout. Maintain proper diet, exercise, and sleep habits.

FAS1 2019 00 Section Lindd 17 11/7/19 2:48 PM

18

**SECTION I** 

### **GUIDE TO EFFICIENT EXAM PREPARATION**

Buy review books early (first year) and use while studying for courses.

 Simulate the USMLE Step 1 under "real" conditions before beginning your studies.

In the final two weeks, focus on review, practice questions, and endurance. Stay confident!

# Year(s) Prior

The knowledge you gained during your first two years of medical school and even during your undergraduate years should provide the groundwork on which to base your test preparation. Student scores on NBME subject tests (commonly known as "shelf exams") have been shown to be highly correlated with subsequent Step 1 scores. Moreover, undergraduate science GPAs as well as MCAT scores are strong predictors of performance on the Step 1 exam. To

We also recommend that you buy highly rated review books early in your first year of medical school and use them as you study throughout the two years. When Step 1 comes along, these books will be familiar and personalized to the way in which you learn. It is risky and intimidating to use unfamiliar review books in the final two or three weeks preceding the exam. Some students find it helpful to personalize and annotate *First Aid* throughout the curriculum.

### **Months Prior**

Review test dates and the application procedure. Testing for the USMLE Step 1 is done on a year-round basis. If you have disabilities or special circumstances, contact the NBME as early as possible to discuss test accommodations (see the Section I Supplement at www.firstaidteam.com/bonus).

Use this time to finalize your ideal schedule. Consider upcoming breaks and whether you want to relax or study. Work backward from your test date to make sure you finish at least one question bank. Also add time to redo missed or flagged questions (which may be half the bank). This is the time to build a structured plan with enough flexibility for the realities of life.

Begin doing blocks of questions from reputable question banks under "real" conditions. Don't use tutor mode until you're sure you can finish blocks in the allotted time. It is important to continue balancing success in your normal studies with the Step 1 test preparation process.

### **Weeks Prior (Dedicated Preparation)**

Your dedicated prep time may be one week or two months. You should have a working plan as you go into this period. Finish your schoolwork strong, take a day off, and then get to work. Start by simulating a full-length USMLE Step 1 if you haven't yet done so. Consider doing one NBME CBSSA and the free questions from the NBME website. Alternatively, you could choose 7 blocks of randomized questions from a commercial question bank. Make sure you get feedback on your strengths and weaknesses and adjust your studying accordingly. Many students study from review sources or comprehensive programs for part of the day, then do question blocks. Also, keep in mind that reviewing a question block can take upward of two hours. Feedback from CBSSA exams and question banks will help you focus on your weaknesses.

FAS1 2019 00 Section Lindd 18 11/7/19 2:48 PM

### **One Week Prior**

Make sure you have your CIN (found on your scheduling permit) as well as other items necessary for the day of the examination, including a current driver's license or another form of photo ID with your signature (make sure the name on your ID exactly matches that on your scheduling permit). Confirm the Prometric testing center location and test time. Work out how you will get to the testing center and what parking and traffic problems you might encounter. Drive separately from other students taking the test on the same day, and exchange cell phone numbers in case of emergencies. If possible, visit the testing site to get a better idea of the testing conditions you will face. Determine what you will do for lunch. Make sure you have everything you need to ensure that you will be comfortable and alert at the test site. It may be beneficial to adjust your schedule to start waking up at the same time that you will on your test day. And of course, make sure to maintain a healthy lifestyle and get enough sleep.

# **One Day Prior**

Try your best to relax and rest the night before the test. Double-check your admissions and test-taking materials as well as the comfort measures discussed earlier so that you will not have to deal with such details on the morning of the exam. At this point it will be more effective to review short-term memory material that you're already familiar with than to try to learn new material. The Rapid Review section at the end of this book is high yield for last-minute studying. Remember that regardless of how hard you have studied, you cannot know everything. There will be things on the exam that you have never even seen before, so do not panic. Do not underestimate your abilities.

Many students report difficulty sleeping the night prior to the exam. This is often exacerbated by going to bed much earlier than usual. Do whatever it takes to ensure a good night's sleep (eg, massage, exercise, warm milk, no back-lit screens at night). Do not change your daily routine prior to the exam. Exam day is not the day for a caffeine-withdrawal headache.

### Morning of the Exam

On the morning of the Step 1 exam, wake up at your regular time and eat a normal breakfast. If you think it will help you, have a close friend or family member check to make sure you get out of bed. Make sure you have your scheduling permit admission ticket, test-taking materials, and comfort measures as discussed earlier. Wear loose, comfortable clothing. Plan for a variable temperature in the testing center. Arrive at the test site 30 minutes before the time designated on the admission ticket; however, do not come too early, as doing so may intensify your anxiety. When you arrive at the test site, the proctor should give you a USMLE information sheet that will explain critical factors such as the proper use of break time. Seating may be assigned, but ask to be reseated if necessary; you need to be seated in an area

- One week before the test:
- Sleep according to the same schedule you'll use on test day
- Review the CBT tutorial one last time
- Call Prometric to confirm test date and time

▶ No notes, books, calculators, pagers, cell phones, recording devices, or watches of any kind are allowed in the testing area, but they are allowed in lockers.

FAS1\_2019\_00\_Section\_Lindd 19 11/7/19 2:48 PM

OO SECTION I

### **GUIDE TO EFFICIENT EXAM PREPARATION**

Arrive at the testing center 30 minutes before your scheduled exam time. If you arrive more than half an hour late, you will not be allowed to take the test. that will allow you to remain comfortable and to concentrate. Get to know your testing station, especially if you have never been in a Prometric testing center before. Listen to your proctors regarding any changes in instructions or testing procedures that may apply to your test site.

Finally, remember that it is natural (and even beneficial) to be a little nervous. Focus on being mentally clear and alert. Avoid panic. When you are asked to begin the exam, take a deep breath, focus on the screen, and then begin. Keep an eye on the timer. Take advantage of breaks between blocks to stretch, maybe do some jumping jacks, and relax for a moment with deep breathing or stretching.

# **After the Test**

After you have completed the exam, be sure to have fun and relax regardless of how you may feel. Taking the test is an achievement in itself. Remember, you are much more likely to have passed than not. Enjoy the free time you have before your clerkships. Expect to experience some "reentry" phenomena as you try to regain a real life. Once you have recovered sufficiently from the test (or from partying), we invite you to send us your feedback, corrections, and suggestions for entries, facts, mnemonics, strategies, resource ratings, and the like (see p. xvii, How to Contribute). Sharing your experience will benefit fellow medical students and IMGs.

# ► STUDY MATERIALS

### **Quality Considerations**

Although an ever-increasing number of review books and software are now available on the market, the quality of such material is highly variable. Some common problems are as follows:

- Certain review books are too detailed to allow for review in a reasonable amount of time or cover subtopics that are not emphasized on the exam.
- Many sample question books were originally written years ago and have not been adequately updated to reflect recent trends.
- Some question banks test to a level of detail that you will not find on the exam.

### **Review Books**

In selecting review books, be sure to weigh different opinions against each other, read the reviews and ratings in Section IV of this guide, examine the books closely in the bookstore, and choose carefully. You are investing not only money but also your limited study time. Do not worry about finding the "perfect" book, as many subjects simply do not have one, and different students prefer different formats. Supplement your chosen books with personal notes from other sources, including what you learn from question banks.

If a given review book is not working for you, stop using it no matter how highly rated it may be or how much it costs.

FAS1\_2019\_00\_Section\_Lindd 20 11/7/19 2:48 PM

There are two types of review books: those that are stand-alone titles and those that are part of a series. Books in a series generally have the same style, and you must decide if that style works for you. However, a given style is not optimal for every subject.

You should also find out which books are up to date. Some recent editions reflect major improvements, whereas others contain only cursory changes. Take into consideration how a book reflects the format of the USMLE Step 1.

Charts and diagrams may be the best approach for physiology and biochemistry, whereas tables and outlines may be preferable for microbiology.

# **Apps**

With the explosion of smartphones and tablets, apps are an increasingly popular way to review for the Step 1 exam. The majority of apps are compatible with both iOS and Android. Many popular Step 1 review resources (eg, UWorld, USMLE-Rx) have apps that are compatible with their software. Many popular web references (eg, UpToDate) also now offer app versions. All of these apps offer flexibility, allowing you to study while away from a computer (eg, while traveling).

### **Practice Tests**

Taking practice tests provides valuable information about potential strengths and weaknesses in your fund of knowledge and test-taking skills. Some students use practice examinations simply as a means of breaking up the monotony of studying and adding variety to their study schedule, whereas other students rely almost solely on practice. You should also subscribe to one or more high-quality question banks. In addition, students report that many current practice-exam books have questions that are, on average, shorter and less clinically oriented than those on the current USMLE Step 1.

Additionally, some students preparing for the Step 1 exam have started to incorporate case-based books intended primarily for clinical students on the wards or studying for the Step 2 CK exam. First Aid Cases for the USMLE Step 1 aims to directly address this need.

After taking a practice test, spend time on each question and each answer choice whether you were right or wrong. There are important teaching points in each explanation. Knowing why a wrong answer choice is incorrect is just as important as knowing why the right answer is correct. Do not panic if your practice scores are low as many questions try to trick or distract you to highlight a certain point. Use the questions you missed or were unsure about to develop focused plans during your scheduled catch-up time.

### **Textbooks and Course Syllabi**

Limit your use of textbooks and course syllabi for Step 1 review. Many textbooks are too detailed for high-yield review and include material that is generally not tested on the USMLE Step 1 (eg, drug dosages, complex chemical structures). Syllabi, although familiar, are inconsistent across

► Most practice exams are shorter and less clinical than the real thing.

 Use practice tests to identify concepts and areas of weakness, not just facts that you missed.

FAS1 2019 00 Section Lindd 21 11/7/19 2:48 PM

medical schools and frequently reflect the emphasis of individual faculty, which often does not correspond to that of the USMLE Step 1. Syllabi also tend to be less organized than top-rated books and generally contain fewer diagrams and study questions.

# ► TEST-TAKING STRATEGIES

Practice! Develop your test-taking skills and strategies well before the test date. Your test performance will be influenced by both your knowledge and your test-taking skills. You can strengthen your performance by considering each of these factors. Test-taking skills and strategies should be developed and perfected well in advance of the test date so that you can concentrate on the test itself. We suggest that you try the following strategies to see if they might work for you.

# **Pacing**

You have seven hours to complete up to 280 questions. Note that each one-hour block contains up to 40 questions. This works out to approximately 90 seconds per question. We recommend following the "1 minute rule" to pace yourself. Spend no more than 1 minute on each question. If you are still unsure about the answer after this time, mark the question, make an educated guess, and move on. Following this rule, you should have approximately 20 minutes left after all questions are answered, which you can use to revisit all of your marked questions. Remember that some questions may be experimental and do not count for points (and reassure yourself that these experimental questions are the ones that are stumping you). In the past, pacing errors have been detrimental to the performance of even highly prepared examinees. The bottom line is to keep one eye on the clock at all times!

Time management is an important skill for exam success.

### **Dealing with Each Question**

There are several established techniques for efficiently approaching multiple choice questions; find what works for you. One technique begins with identifying each question as easy, workable, or impossible. Your goal should be to answer all easy questions, resolve all workable questions in a reasonable amount of time, and make quick and intelligent guesses on all impossible questions. Most students read the stem, think of the answer, and turn immediately to the choices. A second technique is to first skim the answer choices to get a context, then read the last sentence of the question (the lead-in), and then read through the passage quickly, extracting only information relevant to answering the question. This can be particularly helpful for questions with long clinical vignettes. Try a variety of techniques on practice exams and see what works best for you. If you get overwhelmed, remember that a 30-second time out to refocus may get you back on track.

FAS1 2019 00 Section Lindd 22 11/7/19 2:48 PM

### Guessing

There is **no penalty** for wrong answers. Thus, **no test block should be left with unanswered questions**. A hunch is probably better than a random guess. If you have to guess, we suggest selecting an answer you recognize over one with which you are totally unfamiliar.

### **Changing Your Answer**

The conventional wisdom is not to change answers that you have already marked unless there is a convincing and logical reason to do so—in other words, go with your "first hunch." Many question banks tell you how many questions you changed from right to wrong, wrong to wrong, and wrong to right. Use this feedback to judge how good a second-guesser you are. If you have extra time, reread the question stem and make sure you didn't misinterpret the question.

► Go with your first hunch, unless you are certain that you are a good second-guesser.

# ► CLINICAL VIGNETTE STRATEGIES

In recent years, the USMLE Step 1 has become increasingly clinically oriented. This change mirrors the trend in medical education toward introducing students to clinical problem solving during the basic science years. The increasing clinical emphasis on Step 1 may be challenging to those students who attend schools with a more traditional curriculum.

Be prepared to read fast and think on your feet!

### What Is a Clinical Vignette?

A clinical vignette is a short (usually paragraph-long) description of a patient, including demographics, presenting symptoms, signs, and other information concerning the patient. Sometimes this paragraph is followed by a brief listing of important physical findings and/or laboratory results. The task of assimilating all this information and answering the associated question in the span of one minute can be intimidating. So be prepared to read quickly and think on your feet. Remember that the question is often indirectly asking something you already know.

Practice questions that include case histories or descriptive vignettes are critical for Step 1 preparation.

# Strategy

Remember that Step 1 vignettes usually describe diseases or disorders in their most classic presentation. So look for cardinal signs (eg, malar rash for SLE or nuchal rigidity for meningitis) in the narrative history. Be aware that the question will contain classic signs and symptoms instead of buzzwords. Sometimes the data from labs and the physical exam will help you confirm or reject possible diagnoses, thereby helping you rule answer choices in or out. In some cases, they will be a dead giveaway for the diagnosis.

 Step 1 vignettes usually describe diseases or disorders in their most classic presentation.

FAS1\_2019\_00\_Section\_Lindd 23 11/7/19 2:48 PM

Making a diagnosis from the history and data is often not the final answer. Not infrequently, the diagnosis is divulged at the end of the vignette, after you have just struggled through the narrative to come up with a diagnosis of your own. The question might then ask about a related aspect of the diagnosed disease. Consider skimming the answer choices and lead-in before diving into a long stem. However, be careful with skimming the answer choices; going too fast may warp your perception of what the vignette is asking.

# ▶ IF YOU THINK YOU FAILED

After the test, many examinees feel that they have failed, and most are at the very least unsure of their pass/fail status. There are several sensible steps you can take to plan for the future in the event that you do not achieve a passing score. First, save and organize all your study materials, including review books, practice tests, and notes. Familiarize yourself with the reapplication procedures for Step 1, including application deadlines and upcoming test dates.

Make sure you know both your school's and the NBME's policies regarding retakes. The NBME allows a maximum of six attempts to pass each Step examination.<sup>18</sup> You may take Step 1 no more than three times within a 12-month period. Your fourth and subsequent attempts must be at least 12 months after your first attempt at that exam and at least six months after your most recent attempt at that exam.

The performance profiles on the back of the USMLE Step 1 score report provide valuable feedback concerning your relative strengths and weaknesses. Study these profiles closely. Set up a study timeline to strengthen gaps in your knowledge as well as to maintain and improve what you already know. Do not neglect high-yield subjects. It is normal to feel somewhat anxious about retaking the test, but if anxiety becomes a problem, seek appropriate counseling.

If you pass Step 1 (score of 194 or above), you are not allowed to retake the exam.

# ▶ TESTING AGENCIES

National Board of Medical Examiners (NBME) / USMLE Secretariat
Department of Licensing Examination Services
3750 Market Street
Philadelphia, PA 19104-3102
(215) 590-9500 (operator) or
(215) 590-9700 (automated information line)
Email: webmail@nbme.org
www.nbme.org

FAS1\_2019\_00\_Section\_Lindd 24 11/7/19 2:48 PM

Educational Commission for Foreign Medical Graduates (ECFMG)

3624 Market Street Philadelphia, PA 19104-2685 (215) 386-5900 Email: info@ecfmg.org

www.ecfmg.org

# **▶** REFERENCES

- 1. United States Medical Licensing Examination. Available from: https:// www.usmle.org/pdfs/step-1/content\_step1.pdf. Accessed October 17, 2019.
- 2. United States Medical Licensing Examination. 2018 Performance Data. Available from: https://www.usmle.org/performance-data/default. aspx#2018\_step-1. Accessed October 17, 2019.
- 3. Prober CG, Kolars JC, First LR, et al. A plea to reassess the role of United States Medical Licensing Examination Step 1 scores in residency selection. Acad Med. 2016;91(1):12–15.
- 4. Roediger HL, Butler AC. The critical role of retrieval practice in long-term retention. Trends Cogn Sci. 2011;15(1):20-27.
- 5. Dunlosky J, Rawson KA, Marsh EJ, et al. Improving students' learning with effective learning techniques: promising directions from cognitive and educational psychology. Psychol Sci Publ Int. 2013;14(1):4–58.
- 6. Larsen DP, Butler AC, Lawson AL, et al. The importance of seeing the patient: test-enhanced learning with standardized patients and written tests improves clinical application of knowledge. Adv Health Sci Educ. 2013;18(3):409-425.
- 7. Panus PC, Stewart DW, Hagemeier NE, et al. A subgroup analysis of the impact of self-testing frequency on examination scores in a pathophysiology course. Am J Pharm Educ. 2014;78(9):165.
- 8. Deng F, Gluckstein JA, Larsen DP. Student-directed retrieval practice is a predictor of medical licensing examination performance. Perspect Med Educ. 2015;4(6):308-313.
- 9. McAndrew M, Morrow CS, Atiyeh L, et al. Dental student study strategies: are self-testing and scheduling related to academic performance? I Dent Educ. 2016;80(5):542-552.
- 10. Augustin M. How to learn effectively in medical school: test yourself, learn actively, and repeat in intervals. Yale I Biol Med. 2014;87(2):207–212.
- 11. Bellezza FS. Mnemonic devices: classification, characteristics, and criteria. Rev Educ Res. 1981;51(2):247-275.
- 12. Dyer J-O, Hudon A, Montpetit-Tourangeau K, et al. Example-based learning: comparing the effects of additionally providing three different integrative learning activities on physiotherapy intervention knowledge. BMC Med Educ. 2015;15:37.
- 13. Chamberland M, Mamede S, St-Onge C, et al. Self-explanation in learning clinical reasoning: the added value of examples and prompts. Med Educ. 2015;49(2):193-202.
- 14. Nesbit JC, Adesope OO. Learning with concept and knowledge maps: a meta-analysis. Rev Educ Res. 2006;76(3):413-448.

FAS1 2019 00 Section Lindd 25 11/7/19 2:48 PM 26

**SECTION I** 

# **GUIDE TO EFFICIENT EXAM PREPARATION**

- 15. Pohl CA, Robeson MR, Hojat M, et al. Sooner or later? USMLE Step 1 performance and test administration date at the end of the second year. *Acad Med.* 2002;77(10):S17–S19.
- 16. Holtman MC, Swanson DB, Ripkey DR, et al. Using basic science subject tests to identify students at risk for failing Step 1. *Acad Med*. 2001;76(10):S48–S51.
- 17. Basco WT, Way DP, Gilbert GE, et al. Undergraduate institutional MCAT scores as predictors of USMLE Step 1 performance. *Acad Med*. 2002;77(10):S13–S16.
- United States Medical Licensing Examination. 2019 USMLE Bulletin of Information. Available from: https://www.usmle.org/pdfs/bulletin/ 2019bulletin.pdf. Accessed July 23, 2018.

FAS1\_2019\_00\_Section\_Lindd 26 11/7/19 2:48 PM

# SECTION I SUPPLEMENT

# **Special Situations**

Please visit www.firstaidteam.com/bonus/ to view this section.

- ▶ First Aid for the International Medical Graduate
- 2
- First Aid for the
  Osteopathic Medical
  Student
  - 13
- ► First Aid for the Podiatric Medical Student 17
- ► First Aid for the Student Requiring Test Accommodations 20

7/

28 SECTION I

SPECIAL SITUATIONS

► NOTES	

FAS1\_2019\_00\_Section\_Lindd 28 11/7/19 2:48 PM

# SECTION I SUPPLEMENT

# **Special Situations**

- ▶ First Aid for the International Medical Graduate
- First Aid for the
  Osteopathic Medical
  Student
- ► First Aid for the Podiatric Medical Student 17
- ► First Aid for the Student Requiring Test Accommodations 20

1

► IMGs make up approximately 25% of the US physician population.

More detailed information can be found in the ECFMG Information Booklet, available at www.ecfmq.org/pubshome.html.

Applicants may apply online for USMLE Step 1, Step 2 CK, or Step 2 CS at www.ecfmg.org.

# ▶ FIRST AID FOR THE INTERNATIONAL MEDICAL GRADUATE

"International medical graduate" (IMG) is the term used to describe any student or graduate of a non-US, non-Canadian, non-Puerto Rican medical school, regardless of whether he or she is a US citizen/resident or not.

### IMG's Steps to Licensure in the United States

To be eligible to take the USMLE Steps, you (the applicant) must be officially enrolled in a medical school located outside the United States and Canada that is listed in the World Directory of Medical Schools (WDOMS; www.wdoms.org) and meet the ECFMG eligibility requirements, both at the time you apply for examination and on your test day. In addition, your "Graduation Year" must be listed as "Current" at the time you apply and on your test day.

If you are an IMG, you must go through the following steps (not necessarily in this order) to apply for residency programs and become licensed to practice in the United States. You must complete these steps even if you are already a practicing physician and have completed a residency program in your own country.

- Pass USMLE Step 1, Step 2 CK, and Step 2 CS, as well as obtain a medical school diploma (not necessarily in this order). All three exams can be taken during medical school. If you have already graduated prior to taking any of the Steps, then you will need to verify your academic credentials (confirmation of enrollment and medical degree) prior to applying for any Step exam.
- You will be certified electronically by the Educational Commission for Foreign Medical Graduates (ECFMG) after above steps are successfully completed. You should receive your formal ECFMG certificate in the mail within the next 1–2 weeks. The ECFMG will not issue a certificate (even if all the USMLE scores are submitted) until it verifies your medical diploma with your medical school.
- You must have a valid ECFMG certificate before entering an accredited residency program in the United States, although you can begin the Electronic Residency Application Service (ERAS) application and interviews before you receive the certificate.
- Apply for residency positions in your fields of interest, either directly or through the ERAS and the National Residency Matching Program (NRMP), otherwise known as "the Match." To be entered into the Match, you need to have passed all the examinations necessary for ECFMG certification (ie, Step 1, Step 2 CK, and Step 2 CS) by the rank order list deadline (usually in late February before the Match). If you do not pass these exams by the deadline, you will be withdrawn from the Match.

- If you are not a US citizen or green-card holder (permanent resident), you will need to obtain a visa that will allow you to enter and work in the United States after you have matched successfully.
- Sign up to receive the ECFMG and ERAS email newsletter to keep up to date with their most current policies and deadlines.
- If required by the state in which your residency program is located, obtain an educational/training/limited medical license. Your residency program may assist you with this application. Note that medical licensing is the prerogative of each individual state, not of the federal government, and that states vary with respect to their laws about licensing.
- Once you have the ECFMG certification, take the USMLE Step 3 during your residency, and then obtain a full medical license. Once you have a state-issued license, you are permitted to practice in federal institutions such as Veterans Affairs (VA) hospitals and Indian Health Service facilities in any state. This can open the door to "moonlighting" opportunities and possibilities for an H1B visa application if relevant. For details on individual state rules, write to the licensing board in the state in question or contact the Federation of State Medical Boards (FSMB). If you need to apply for an H1B visa for starting residency, you need to first take and pass the USMLE Step 3 exam, preferably before you Match. However, you will be able to apply for and take the USMLE Step 3 exam only after you graduate from medical school.
- Complete your residency and then take the appropriate specialty board exams if you wish to become board certified (eg, in internal medicine or surgery). If you already have a specialty certification in another country, some specialty boards may grant you six months' or one year's credit toward your total residency time.
- Currently, most residency programs are accepting applications through ERAS. For more information, see *First Aid for the Match* or contact:

# **ECFMG/ERAS Program**

3624 Market Street Philadelphia, PA 19104-2685 USA (215) 386-5900 Email: eras-support@ecfmg.org www.ecfmg.org/eras

For detailed information on the USMLE Steps, visit the USMLE website at http://www.usmle.org.

# The USMLE and the IMG

The USMLE is a series of standardized exams that give IMGs and US medical graduates a level playing field. The passing marks for IMGs for Step 1, Step 2 CK, and Step 2 CS are determined by a statistical distribution that is based on the scores of US medical school students. For example, to pass Step 1, you will probably have to score higher than the bottom 8–10% of US and Canadian graduates.

▶ Keep informed by signing up for the ECFMG email newsletter at www.ecfmg.org/resources.

► IMGs have a maximum of six attempts to pass any USMLE Step, and must pass the USMLE Steps required for ECFMG certification within a seven-year period. Under USMLE program rules, a maximum of six attempts will be permitted to pass any USMLE Step or component exam. There is a limit of three attempts within a 12-month period for any of the USMLE Steps.

### **Timing of the USMLE**

For an IMG, the timing of a complete application is critical. It is extremely important that you send in your application early if you are to obtain the maximum number of interviews. Complete all exam requirements by August of the year in which you wish to apply. Check the ECFMG website for deadlines to take and pass the various Step exams to be eligible for the NRMP Match.

IMG applicants must pass the USMLE Steps required for ECFMG certification (Step 1, Steps 2 CK and 2 CS) within a seven-year period. The USMLE program recommends, although not all jurisdictions impose, a seven-year limit for completion of the three-step USMLE program.

In terms of USMLE exam order, arguments can be made for taking the Step 1 or the Step 2 CK exam first. For example, you may consider taking the Step 2 CK exam first if you have just graduated from medical school and the clinical topics are still fresh in your mind. However, keep in mind that there is substantial overlap between Step 1 and Step 2 CK topics in areas such as pharmacology, pathophysiology, and biostatistics. You might therefore consider taking the Step 1 and Step 2 CK exams close together to take advantage of this overlap in your test preparation.

# **USMLE Step 1 and the IMG**

**Significance of the Test.** Step 1 is one of the three exams required for the ECFMG certification. Since most US graduates apply to residency with their Step 1 scores only, it may be the only objective tool available with which to compare IMGs with US graduates.

**Signing Up.** We advise that you read the FAQ section on the ECFMG website carefully. Most of the services you will need to use involve either IWA or OASIS. If you have not yet completed medical school, follow these steps to sign up for Step 1:

- Apply and pay for an ECFMG/USMLE ID number on the ECFMG website
- After receiving an email with your ID number, log in to IWA/OASIS, enter your details, and complete the "On-Line part of your USMLE Step 1 application." Choose your test center location and 3-month eligibility period. Additional fees apply if you need to change your eligibility period.
- Pay the Step 1 fee plus any international test surcharges that may apply.
- Access and complete Form 186 (Certification of Identity Form) from IWA as part of the Application for ECFMG Certification.

- Follow the instructions on the form to notarize Form 186 using the online service NotaryCam.com. The fee for this service is included in the ECFMG application fee.
- Once notarized by NotaryCam.com and submitted, Form 186 will remain valid indefinitely. A valid, previously completed Form 186 will remain valid for five years from the date it was accepted.
- After receiving a confirmation email from the ECFMG, you may book an exam date and location on www.prometric.com.

Eligibility Period. A three-month period of your choice.

Fee. The fee for Step 1 is \$940 plus an international test delivery surcharge (if you choose a testing region other than the United States or Canada).

Statistics. In 2018–2019, 80% of IMG examinees passed Step 1 on their first attempt, compared with 96% of MD degree examinees from the United States and Canada.

Tips. Although few if any students feel totally prepared to take Step 1, IMGs in particular require serious study and preparation in order to reach their full potential on this exam. It is also imperative that IMGs do their best on Step 1, as a poor score on Step 1 is a distinct disadvantage in applying for most residencies. Remember that if you pass Step 1, you cannot retake it in an attempt to improve your score. Your goal should thus be to beat the mean, because you can then assert with confidence that you have done better than average for US students (see Table 1). Higher Step 1 scores will also

▶ A higher Step 1 score will improve your chances of getting into a highly competitive specialty.

TABLE 1. USMLE Step 1 Mean Score of Matched Applicants in 2018.

Specialty	<b>US Graduates</b>	US IMGs	Non-US IMGs	
All specialties	233	222	234	
Anesthesiology	232	231	240	
Dermatology	249	<u>-</u>	238	
Diagnostic radiology	240	239	241	
Emergency medicine	233	232	229	
Family medicine	220	211	220	
General surgery	236	237	242	
Internal medicine	233	225	236	
Neurology	231	227	236	
Obstetrics and gynecology	230	229	231	
Pathology	233	226	230	
Pediatrics	227	221	230	
Physical medicine and rehabilitation	225	226	238	
Psychiatry	226	214	222	

Source: www.nrmp.org

lend credibility to your residency application and help you get into highly competitive specialties such as radiology, orthopedics, and dermatology.

Commercial Review Courses. Do commercial review courses help improve your scores? Reports vary, and such courses can be expensive. For some students these programs can provide a more structured learning environment with professional support. However, review courses consume a significant chunk of time away from independent study. Many IMGs participate in review courses as they typically need higher scores to compete effectively with US and Canadian candidates for residency positions. (For more information on review courses, see Section IV in the book.)

### **USMLE Step 2 CK and the IMG**

What Is the Step 2 CK? It is a computerized test of the clinical sciences consisting of up to 318 multiple-choice questions divided into eight blocks. Each block contains a maximum of 40 questions and needs to be completed within 60 minutes. It can be taken at Prometric centers in the United States and several other countries.

Content. The Step 2 CK includes test items in the following content areas:

- Internal medicine
- Obstetrics and gynecology
- Pediatrics
- Preventive medicine
- Psychiatry
- Surgery
- Other areas relevant to the provision of care under supervision

Significance of the Test. The Step 2 CK is required for the ECFMG certificate. It reflects the level of clinical knowledge of the applicant. It tests clinical subjects, primarily internal medicine. Other areas tested are orthopedics, ENT, ophthalmology, safety science, epidemiology, professionalism, and ethics.

Eligibility. Students and graduates from medical schools that are listed in WDOMS and meet the ECFMG eligibility requirement to take the Step 2 CK. Students must have completed at least two years of medical school. This means that students must have completed the basic medical science component of the medical school curriculum by the beginning of the eligibility period selected.

Eligibility Period. A three-month period of your choice.

**Fee.** The fee for the Step 2 CK is \$940 plus an international test delivery surcharge (if you choose a testing region other than the United States or Canada).

► The areas tested on the Step 2 CK relate to the clerkships provided at US medical schools.

Statistics. In 2017–2018, 83% of ECFMG candidates passed the Step 2 CK on their first attempt, compared with 97% of MD degree examinees from US and Canadian schools.

Tips. It's better to take the Step 2 CK after your internal medicine rotation because most of the questions on the exam give clinical scenarios and ask you to make medical diagnoses and clinical decisions. In addition, because this is a clinical sciences exam, cultural and geographic considerations play a greater role than is the case with Step 1. For example, if your medical education gave you ample exposure to malaria, brucellosis, and malnutrition but little to alcohol withdrawal, child abuse, and cholesterol screening, you must work to familiarize yourself with topics that are more heavily emphasized in US medicine. You must also have a basic understanding of the legal and social aspects of US medicine, because you will be asked questions about communicating with and advising patients.

▶ Be familiar with topics that are heavily emphasized in US medicine, such as cholesterol screening.

# **USMLE Step 2 CS and the IMG**

What Is the Step 2 CS? The Step 2 CS is a test of clinical and communication skills administered as a one-day, eight-hour exam. It includes 12 encounters with standardized patients (15 minutes each, with 10 minutes to write a note after each encounter).

Content. The Step 2 CS tests the ability to communicate in English as well as interpersonal skills, data-gathering skills, the ability to perform a physical exam, and the ability to formulate a brief note, a differential diagnosis, and a list of diagnostic tests. The areas that are covered in the exam are as follows:

- Internal medicine
- Surgery
- Obstetrics and gynecology
- Pediatrics
- Psychiatry
- Family medicine

Unlike the USMLE Step 1, Step 2 CK, or Step 3, there are no numerical grades for the Step 2 CS—it's simply either a "pass" or a "fail." To pass, a candidate must attain a passing performance in each of the following three components:

- Integrated Clinical Encounter (ICE): includes Data Gathering, Physical Exam, and the electronic Patient Note
- Spoken English Proficiency (SEP)
- Communication and Interpersonal Skills (CIS)

According to the NBME, the most commonly failed component for IMGs is the CIS.

▶ The Step 2 CS is graded as pass/fail.

Significance of the Test. The Step 2 CS assesses spoken English language proficiency and is required for the ECFMG certificate. The Test of English as a Foreign Language (TOEFL) is no longer required.

Eligibility. Students must have completed at least two years of medical school in order to take the test. That means students must have completed the basic medical science component of the medical school curriculum at the time they apply for the exam.

Fee. The fee for the Step 2 CS is \$1580.

**Statistics.** In 2017–2018, 75% of ECFMG candidates passed the Step 2 CS on their first attempt, compared with 95% of MD degree examinees from US and Canadian schools.

Scheduling. You must schedule the Step 2 CS within four months of the date indicated on your notification of registration. You must take the exam within 12 months of the date indicated on your notification of registration. It is generally advisable to take the Step 2 CS as soon as possible in the year before your Match, as often the results either come in late or arrive too late to allow you to retake the test and pass it before the Match.

**Test Site Locations.** The Step 2 CS is currently administered at the following five locations:

- Philadelphia, PA
- Atlanta, GA
- Los Angeles, CA
- Chicago, IL
- Houston, TX

For more information about the Step 2 CS exam, please refer to *First Aid for the Step* 2 CS.

# **USMLE Step 3 and the IMG**

What Is the USMLE Step 3? It is a two-day computerized test in clinical medicine consisting of 413 multiple-choice questions and 13 computer-based case simulations (CCS). The exam aims to test your knowledge and its application to patient care and clinical decision making (ie, this exam tests if you can safely practice medicine independently and without supervision). Please go to the USMLE website to learn more about recent changes to the exam.

**Significance of the Test.** Taking Step 3 before residency is critical for IMGs seeking an H1B visa and is also a bonus that can be added to the residency application. Step 3 is also required to obtain a full medical license in the United States and can be taken during residency for this purpose.

Fee. The fee for Step 3 is \$895.

▶ Try to take the Step 2 CS the year

before you plan to Match.

▶ Complete the Step 3 exam before

you apply for an H1B visa.

Eligibility. Examinees are no longer required to apply to the Step 3 exam under the eligibility requirements of a specific medical licensing authority. Those wishing to sit for the Step 3 exam, independent of the place of residence, must meet the following requirements:

- Have completed an MD or DO degree from an LCME- or AOAaccredited US or Canadian medical school, or from a medical school outside the US and Canada listed in the World Directory of Medical Schools.
- Have taken and passed the Step 1, Step 2 CK, and Step 2 CS exams.
- If an IMG, be certified by the ECFMG.

The Step 3 exam is not available outside the United States. Applications can be found online at www.fsmb.org and must be submitted to the FSMB.

Statistics. In 2018, 90% of IMC candidates passed the Step 3 on their first attempt, compared with 98% of MD degree examinees from US and Canadian schools.

### Residencies and the IMG

In the Match, the number of US-citizen IMG applications has grown over the past few years, while the percentage accepted has remained constant (see Table 2). More information about residency programs can be obtained at www.ama-assn.org.

## The Match and the IMG

Given the growing number of IMG candidates with strong applications, you should bear in mind that good USMLE scores are not the only way to gain a competitive edge. However, USMLE Step 1 and Step 2 CK scores continue to be used as the initial screening mechanism when candidates are being considered for interviews.

TABLE 2. IMGs in the Match.

Applicants	2016	2017	2018	2019
US-citizen IMGs	5,323	5,069	5,075	5,080
% US-citizen IMGs accepted	53.9	54.8	57.1	59
Non-US-citizen IMGs	7,460	7,284	7,067	6,869
% non-US-citizen IMGs accepted	50.5	52.4	56.1	58.6
US seniors (non-IMGs)	18,187	18,539	18,818	18,925
% US seniors accepted	93.8	94.3	94.3	93.9
DO graduates		3,590	4,617	6,001
% DO graduates accepted		81.7	81.7	84.6

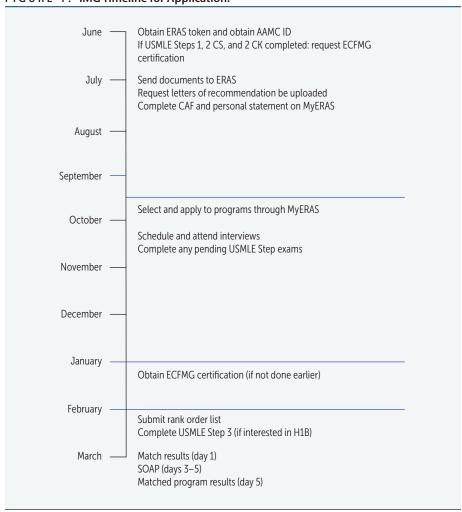
Source: www.nrmp.org.

Based on accumulated IMG Match experiences over recent years, here are a few pointers to help IMGs maximize their chances for a residency interview:

- Apply early. Programs offer a limited number of interviews and often select candidates on a first-come, first-served basis. Because of this, you should aim to complete the entire process of applying for the ERAS token, registering with the Association of American Medical Colleges (AAMC), mailing necessary documents to ERAS, and completing the ERAS application by mid-September (see Figure 1). Community programs usually send out interview offers earlier than do university and university-affiliated programs.
- LS clinical experience helps. Externships and observerships in a US hospital setting have emerged as an important credential on an IMG application. Externships are like short-term medical school internships and offer hands-on clinical experience. Observerships, also called "shadowing," involve following a physician and observing how he or she manages patients. Some programs require students to have participated in an externship or observership before applying. It is best to gain such an experience before or at the time you apply to various programs so that you can mention it on your

 All US hospitals allow externship only when the applicant is actively enrolled in a medical school, so plan ahead.

FIGURE 1. IMG Timeline for Application.



ERAS application. If such an experience or opportunity comes up after you apply, be sure to inform the programs accordingly.

- Clinical research helps. University programs are attracted to candidates who show a strong interest in clinical research and academics. They may even relax their application criteria for individuals with unique backgrounds and strong research experience. Publications in well-known journals are an added bonus.
- Time the Step 2 CS well. ECFMG has published the new Step 2 CS score-reporting schedule for 2019–2020 at http://www.ecfmg.org. Most program directors would like to see a passing score on the Step 1, Step 2 CK, and Step 2 CS exams before they rank an IMG on their rank order list in mid-February. There have been many instances in which candidates have lost a potential Match—either because of delayed CS results or because they have been unable to retake the exam on time following a failure. It is difficult to predict a result on the Step 2 CS, since the grading process is not very transparent. Therefore, it is advisable to take the Step 2 CS as early as possible in the application year.
- US letters of recommendation help. Letters of recommendation from clinicians practicing in the United States carry more weight than recommendations from home countries.
- Step up the Step 3. If H1B visa sponsorship is desired, aim to have Step 3 results by January of the Match year. In addition to the visa advantage you will gain, an early and good Step 3 score may benefit IMGs who have been away from clinical medicine for a while as well as those who have low scores on Step 1 and the Step 2 CK. Note that the Step 3 can be taken only after medical school graduation.
- Verify medical credentials in a timely manner. Do not overlook the medical school credential verification process. The ECFMG certificate arrives only after credentials have been verified and after you have passed Step 1, the Step 2 CK, and the Step 2 CS, so you should keep track of the process and check their application status online using IWA/OASIS.
- Don't count on a pre-Match. Programs participating in NRMP Match can no longer offer a pre-Match.

### What if You Do Not Match?

For applicants who do not Match into a residency program, there's SOAP (Supplemental Offer and Acceptance Program). Under SOAP, unmatched applicants will have access to the list of unfilled programs at noon Eastern time on the Monday of Match week. The unfilled programs electing to participate in SOAP will offer positions to unmatched applicants through the Registration, Ranking, and Results (R3) system. A series of "rounds" will begin at noon Eastern time on Wednesday of Match week until 5:00 pm Eastern time on Friday of Match week. Detailed information about SOAP can be found at the NRMP website at http://www.nrmp.org.

▶ A good score on the Step 3 may help offset poorer scores on the Step 1 or 2 CK exams.

**SECTION I** 

# Educational Commission for Foreign Medical Graduates (ECFMG)

3624 Market Street

Philadelphia, PA 19104-2685

(215) 386-5900

Fax: (215) 386-9196

Email: info@ecfmg.org

www.ecfmg.org

The ECFMG telephone number is answered only between 9:00 AM—5:00 PM Monday through Friday EST. The ECFMG often takes a long time to answer the phone, which is frequently busy at peak times of the year, and then gives you a long voice-mail message—so it is better to email early than to rely on a last-minute phone call. When contacting the ECFMG by email, include your USMLE/ECFMG Identification Number and use the email address that you registered with the ECFMG. Do not contact the NBME, as all IMG exam matters are conducted by the ECFMG. The ECFMG also publishes an information booklet on ECFMG certification and the USMLE program, which gives details on the dates and locations of forthcoming Step tests for IMGs together with application forms. The *Information Booklet* is available to view and download on the ECFMG's website at www.ecfmg.org, where they also have a complete list of fees for certification posted (see Table 3).

TABLE 3. Estimated Costs for IMGs (as of 2019).

<b>Exams and Services</b>	Fee(s)	
USMLE Step 1	\$940 + international surcharge (eg, \$195 in all European countries offering the exam)	
USMLE Step 2 CK	\$940 + international surcharge (eg, \$220 in all European countries offering the exam)	
USMLE Step 2 CS	\$1580	
USMLE Step 3	\$895	
ERAS	\$130 registration fee (ECFMG token fee) \$80 USMLE transcript assessment \$99 for programs 1–10 \$15 each for programs 11–20 \$19 each for programs 21–30 \$26 each for programs 31+	
NRMP \$85 registration fee (for ranking 20 program \$30 per additional program ranked \$35 per partner (couples match only) \$50 late registration fee (sign up before November 30 to avoid paying this fee)		
J-1 visa application fee	\$160 visa application fee \$340 annual ECFMG application fee \$220 payable to Homeland Security (SEVIS fee)	

# Federation of State Medical Boards (FSMB)

400 Fuller Wiser Road, Suite 300 Euless, TX 76039-3856 (817) 868-4041 Email: usmle@fsmb.org www.fsmb.org

The FSMB has a number of publications available, including free policy documents. All of these documents are available to view and download for free on the FSMB's website at www.fsmb.org. For Step 3 inquiries, the telephone number is (817) 868-4041.

The AMA has dedicated a portion of its website to information on IMG demographics, residencies, immigration, and the like. This information can be found at www.ama-assn.org.

# ▶ FIRST AID FOR THE OSTEOPATHIC MEDICAL STUDENT

### What Is the COMLEX-USA Level 1?

The National Board of Osteopathic Medical Examiners (NBOME) administers the Comprehensive Osteopathic Medical Licensing Examination, or COMLEX-USA. Like the USMLE, the COMLEX-USA is administered over three levels.

The COMLEX-USA series assesses osteopathic medical knowledge and clinical skills using clinical presentations and physician tasks. A description of the COMLEX-USA Written Examination Blueprints for each level, which outline the various clinical presentations and physician tasks that examinees will encounter, is given on the NBOME website. Another stated goal of the COMLEX-USA Level 1 is to create a more primary careoriented exam that integrates osteopathic principles into clinical situations.

To be eligible to take the COMLEX-USA Level 1, you must be on track to satisfactorily complete your first two years in an AOA-accredited medical school. The office of the dean at each school informs the NBOME that the student will complete the first two years of medical school and is in good standing. At this point, the NBOME sends out an email with detailed instructions on how to register for the exam.

For all three levels of the COMLEX-USA, raw scores are converted to a percentile score and a score ranging from 5 to 800. For Levels 1 and 2, a score of 400 is required to pass; for Level 3, a score of 350 is needed. COMLEX-USA scores are posted at the NBOME website 4–6 weeks after the test and usually mailed within 8 weeks after the test. The mean score is always 500.

If you pass a COMLEX-USA examination, you are not allowed to retake it to improve your grade. Currently, if you fail, there is no specific limit to the number of times you can retake it in order to pass. However, a student may not take the exam more than four times in one year. Levels 2 and 3 exams must be passed in sequential order within seven years of passing Level 1.

Note that candidates taking COMLEX-USA examinations will be limited to a total of six attempts for each examination.

### What Is the Structure of the COMLEX-USA Level 1?

The COMLEX-USA Level 1 is a computer-based examination consisting of 400 questions over an eight-hour period in a single day (nine hours counting breaks). Most of the questions are in one-best-answer format, but a small number are matching-type questions. Some one-best-answer questions are bundled together around a common question stem that usually takes the form of a clinical scenario. Every section of the COMLEX-USA Level 1 ends with either matching questions, multiple questions around a single stem, or both. New question formats may gradually be introduced, but candidates will be notified if this occurs. Multimedia questions are also included on the exam.

Questions are grouped into eight subsections of 50 questions each in a manner similar to that of the USMLE. The individual subsections are not timed, but the exam is divided into two blocks consisting of four subsections. Each subsection consists of 200 questions to be completed within four hours. Reviewing and changing answers may be done only in the current subsection. A "review page" is presented for each subsection in order to advise test takers of questions completed, questions marked for further review, and incomplete questions for which no answer has been given.

Breaks are even more structured with COMLEX-USA than they are with the USMLE. Students are allowed to take an optional 10-minute break at the end of the second and sixth subsections. After subsection 4, students are given a 40-minute lunch break. These are the only times a student is permitted a break. Any unused break time will not be added to the time allotted for taking the examination. More information about the computer-based COMLEX-USA examinations can be obtained from www.nbome.org.

### What Is the Difference Between the USMLE and the COMLEX-USA?

According to the NBOME, the COMLEX-USA Level 1 focuses broadly on the following categories, with osteopathic principles and practices integrated into each section:

- Health promotion and disease prevention
- The history and physical
- Diagnostic technologies

- Management
- Scientific understanding of mechanisms
- Health care delivery

Although the COMLEX-USA and the USMLE are similar in scope, content, and emphasis, some differences are worth noting. For example, the interface is different; you cannot search for lab values. Instead, lab values and reference ranges (where appropriate) are included directly in the clinical vignette or test question. Fewer details are given about a patient's condition, so a savvy student needs to know how to differentiate between similar pathologies. Also, age, gender, and race are key factors for diagnosis on the COMLEX-USA. Images or videos are embedded in the question stem and the examinee has to click an attachment button to see the image. If you don't read the question carefully, the attachment buttons are very easy to miss. A standard calculator feature is embedded in the examination interface.

COMLEX-USA Level 1 tests osteopathic principles in addition to basic science materials but does not emphasize lab techniques. Although both exams often require that you apply and integrate knowledge over several areas of basic science to answer a given question, many students who took both tests reported that the questions differed somewhat in style. Students reported, for example, that USMLE questions generally required that the test taker reason and draw from the information given (often a two-step process), whereas those on the COMLEX-USA exam tended to be more straightforward and that multiple different questions are asked pertaining to one question stem.

COMLEX-USA test takers can expect to have only a few questions on biochemistry, molecular biology, or lab technique. On the other hand, microbiology is very heavily tested by clinical presentation and by lab identification. The COMLEX-USA exam also focuses more on disease management, specific legal principles (eg, Tarasoff case and the Emergency Treatment Act) and more detailed ethical principles (eg, res ipsa loquitur) than the USMLE Step 1. Another main difference is that the COMLEX-USA exam stresses osteopathic manipulative medicine. Therefore, question banks specific to the USMLE will not be adequate, and supplementation with a question bank specific to the COMLEX-USA is highly recommended. The most commonly used are COMBANK or COMQUEST.

Students also commented that the COMLEX-USA utilized "buzzwords," although limited in their use (eg, "rose spots" in typhoid fever), whereas the USMLE avoided buzzwords in favor of descriptions of clinical findings or symptoms (eg, rose-colored papules on the abdomen rather than rose spots). Finally, USMLE appeared to have more photographs than did the COMLEX-USA. In general, the overall impression was that the USMLE was a more "thought-provoking" exam, while the COMLEX-USA was more of a "knowledge-based" exam.

▶ The test interface for the COMLEX-USA Level 1 is not the same as the USMLE Step 1 interface. ▶ If you're not sure whether you need to take either the COMLEX-USA Level 1 or the USMLE Step 1, consider taking both to keep your Match options open.

### Who Should Take Both the USMLE and the COMLEX-USA?

Aside from facing the COMLEX-USA Level 1, you must decide if you will also take the USMLE Step 1. We recommend that you consider taking both the USMLE and the COMLEX-USA under the following circumstances:

- If you are applying to allopathic residencies. Although there is growing acceptance of COMLEX-USA certification on the part of allopathic residencies, some allopathic programs prefer or even require passage of the USMLE Step 1. These include many academic programs, programs in competitive specialties (eg, orthopedics, ophthalmology, or dermatology), and programs in competitive geographic areas (eg, Vermont, Utah, and California). Fourth-year osteopathic medical students who have already Matched may be a good source of information about which programs and specialties look for USMLE scores. It is also a good idea to contact program directors at the institutions you are interested in to ask about their policy regarding the COMLEX-USA versus the USMLE.
- If you are unsure about your postgraduate training plans. Successful passage of both the COMLEX-USA Level 1 and the USMLE Step 1 is certain to provide you with the greatest possible range of options when you are applying for internship and residency training.

In addition, the COMLEX-USA Level 1 has in recent years placed increasing emphasis on questions related to primary care medicine and prevention. Having a strong background in family or primary care medicine can help test takers when they face questions on prevention.

# **How Do I Prepare for the COMLEX-USA Level 1?**

Student experience suggests that you should start studying for the COMLEX-USA four to six months before the test is given, as an early start will allow you to spend up to a month on each subject. The recommendations made in Section I regarding study and testing methods, strategies, and resources, as well as the books suggested in Section IV for the USMLE Step 1, hold true for the COMLEX-USA as well.

Another important source of information is in the *Examination Guidelines* and *Sample Exam*, a booklet that discusses the breakdown of each subject while also providing sample questions and corresponding answers. Many students, however, felt that this breakdown provided only a general guideline and was not representative of the level of difficulty of the actual COMLEX-USA. The sample questions did not provide examples of clinical vignettes, which made up approximately 25% of the exam. You will receive this publication with registration materials for the COMLEX-USA Level 1, but you can also receive a copy and additional information by writing:

# **NBOME**

8765 W. Higgins Road, Suite 200 Chicago, IL 60631-4174 (773) 714-0622 www.nbome.org The NBOME developed the Comprehensive Osteopathic Medical Self-Assessment Examination (COMSAE) series to fill the need for selfassessment on the part of osteopathic medical students. Many students take the COMSAE exam before the COMLEX-USA in addition to using testbank questions and board review books. Students can purchase a copy of this exam at www.nbome.org/comsae.asp.

In recent years, students have reported an emphasis in certain areas. For example:

- There was an increased emphasis on upper limb anatomy/brachial
- Specific topics were repeatedly tested on the exam. These included cardiovascular physiology and pathology, acid-base physiology, diabetes, benign prostatic hyperplasia, sexually transmitted diseases, measles, and rubella. Thyroid and adrenal function, neurology (head injury), specific drug treatments for bacterial infection, migraines/cluster headaches, and drug mechanisms also received heavy emphasis.
- Behavioral science questions were based on psychiatry.
- High-yield osteopathic manipulative technique (OMT) topics included an emphasis on the sympathetic and parasympathetic innervations of viscera and nerve roots, rib mechanics/diagnosis, and basic craniosacral theory. Students who spend time reviewing basic anatomy, studying nerve and dermatome innervations, and understanding how to perform basic OMT techniques (eg, muscle energy or counterstrain) can improve their scores.

The COMLEX-USA Level 1 also includes multimedia-based questions. Such questions test the student's ability to perform a good physical exam and to elicit various physical diagnostic signs (eg, Murphy sign).

# ▶ FIRST AID FOR THE PODIATRIC MEDICAL STUDENT

The National Board of Podiatric Medical Examiners (NBPME) offers the American Podiatric Medical Licensing Examinations (APMLE), which are designed to assess whether a candidate possesses the knowledge required to practice as a minimally competent entry-level podiatric surgeon. The APMLE is used as part of the licensing process governing the practice of podiatric medicine and surgery. The APMLE is recognized by all 50 states and the District of Columbia, the US Army, the US Navy, and the Canadian provinces of Alberta, British Columbia, and Ontario. Individual states use the examination scores differently; therefore, doctor of podiatric medicine (DPM) candidates should refer to the NBPME Part I and Part II Information Bulletin 2019.

- You must know the Chapman reflex points and the obscure names of physical exam signs.
- ► COMLEX is heavy on "bugs and drugs."

- ▶ Areas tested on the NBPME Part I:
- General anatomy
- Lower extremity anatomy
- Biochemistry
- Physiology
- Medical microbiology & immunology
- Pathology
- Pharmacology

The APMLE Part I is generally taken after the completion of the second year of podiatric medical education. Unlike the USMLE Step 1, there is no behavioral science section, nor is biomechanics tested. The exam samples seven basic science disciplines: general anatomy (13%); lower extremity anatomy (25%); biochemistry (10%); physiology (13%); microbiology and immunology (13%); pathology (13%); and pharmacology (13%). A detailed outline of topics and subtopics covered on the exam can be found in the *Candidate Information Bulletin Part I Examination*, available at www.apmle.org.

# **Your APMLE Appointment**

Applicants have to register for the exam online at www.prometric.com/NBPME. Once registration is completed, you will receive an Authorization to Test (ATT) email notification that allows you to schedule your exam online. This should be done promptly to secure the testing location and exam date of your choice. The exam will be offered at an independent Prometric testing facility. Test centers within a 50-mile radius of a podiatric medicine school specifically reserve a number of seats on each APMLE Part I exam date. You may take the exam at any Prometric site regardless of which school you attend. Specific instructions about exam dates and registration deadlines can be found in the Candidate Information Bulletin.

### **Exam Format**

The APMLE Part I is a written exam consisting of 205 questions. The test consists exclusively of one-best-answer multiple choice questions with four options per question. A review screen showing all answered, unanswered, and marked questions will be available at the end. Students are encouraged to mark questions and return to these for review at the end of the exam if time allows. Examinees have four hours in which to complete the exam and are given scratch paper that must be turned in at the end of the exam. Some questions on the exam will be "trial questions." These questions are evaluated as future board questions but are not counted in your score.

### **Interpreting Your Score**

Exam results are emailed to examinees approximately four weeks after the exam date, and are also available online via the Prometric dashboard. APMLE scores are reported as pass/fail, with a scaled score of at least 75 needed to pass. Historically, 85% of first-time test takers pass the APMLE Part I. Failing candidates receive a report with a score between 55 and 74 in addition to diagnostic messages intended to help identify strengths or weaknesses in specific content areas. If you fail the APMLE Part I, you must retake the entire examination at a later date. There is no limit to the number of times you can retake the exam.

# **Preparation for the APMLE Part I**

Begin studying for the APMLE Part I at least three months prior to the test date. The suggestions made in Section I regarding study and testing methods for the USMLE Step 1 can be applied to the APMLE as well. This book should, however, be used as a supplement and not as the sole source of information. Neither you nor your school or future residency will ever see your actual passing numerical score. Competing with colleagues should not be an issue, and study groups are beneficial to many.

A study method that helps many students is to copy the outline of the material to be tested from the *Candidate Information Bulletin*. Check off each topic during your study, because doing so will ensure that you have engaged each topic. If you are pressed for time, prioritize subjects on the basis of their weight on the exam. A full 25% of the APMLE Part I focuses on lower extremity anatomy. In this area, students should rely on the notes and material that they received from their class. Remember, lower extremity anatomy is the podiatric physician's specialty—so everything about it is important. Do not forget to study osteology. Keep your old tests and look through old lower extremity class exams, since each of the podiatric colleges submits questions from its faculty. This strategy will give you an understanding of the types of questions that may be asked. On the APMLE Part I, you will see some of the same classic lower extremity anatomy questions you were tested on in school.

The APMLE, like the USMLE, requires that you apply and integrate knowledge over several areas of basic science in order to answer exam questions. Students report that many questions emphasize clinical presentations; however, the facts in this book are very useful in helping students recall the various diseases and organisms. DPM candidates should expand on the high-yield pharmacology section and study antifungal drugs and treatments for *Pseudomonas*, methicillin-resistant *S aureus*, candidiasis, and erythrasma. The high-yield section focusing on pathology is very useful; however, additional emphasis on diabetes mellitus and all its secondary manifestations, particularly peripheral neuropathy, should not be overlooked. Students should also focus on renal physiology and drug elimination, the biochemistry of gout, and neurophysiology, all of which have been noted to be important topics on the APMLE Part I exam.

A sample set of questions is found on the APMLE website www.apmle.org. These samples are somewhat similar in difficulty to actual board questions. If you have any questions regarding registration, fees, test centers, authorization forms, or score reports, please contact your college registrar or:

### Prometric

877-302-8952

Email: nbpmeinquiry@prometric.com

www.prometric.com

► Know the anatomy of the lower extremity!

# ▶ FIRST AID FOR THE STUDENT REQUIRING TEST ACCOMMODATIONS

The USMLE provides accommodations for students with documented disabilities. The basis for such accommodations is the Americans with Disabilities Act (ADA) of 1990. The ADA defines a disability as "a significant limitation in one or more major life activities." This includes both "observable/physical" disabilities (eg, blindness, hearing loss, narcolepsy) and "hidden/mental disabilities" (eg, attention-deficit hyperactivity disorder, chronic fatigue syndrome, learning disabilities).

 US students seeking ADA-compliant accommodations must contact the NBME directly; IMGs, contact the ECFMG. To provide appropriate support, the administrators of the USMLE must be informed of both the nature and the severity of an examinee's disability. Such documentation is required for an examinee to receive testing accommodations. Accommodations include extra time on tests, low-stimulation environments, extra or extended breaks, and zoom text.

# Who Can Apply for Accommodations?

Students or graduates of a school in the United States or Canada that is accredited by the Liaison Committee on Medical Education (LCME) or the AOA may apply for test accommodations directly from the NBME. Requests are granted only if they meet the ADA definition of a disability. If you are a disabled student or a disabled graduate of a foreign medical school, you must contact the ECFMG (see the following page).

### Who Is Not Eligible for Accommodations?

Individuals who do not meet the ADA definition of disabled are not eligible for test accommodations. Difficulties not eligible for test accommodations include test anxiety, slow reading without an identified underlying cognitive deficit, English as a second language, and learning difficulties that have not been diagnosed as a medically recognized disability.

# **Understanding the Need for Documentation**

Although most learning-disabled medical students are all too familiar with the often exhausting process of providing documentation of their disability, you should realize that applying for USMLE accommodation is different from these previous experiences. This is because the NBME determines whether an individual is disabled solely on the basis of the guidelines set by the ADA. Previous accommodation does not in itself justify provision of an accommodation for the USMLE, so be sure to review the NBME guidelines carefully.

# **Getting the Information**

The first step in applying for USMLE special accommodations is to contact the NBME and obtain a guidelines and questionnaire booklet. For the Step 1, Step 2 CK, and Step 2 CS exams, this can be obtained by calling or writing to:

# **Disability Services**

National Board of Medical Examiners 3750 Market Street Philadelphia, PA 19104-3102 (215) 590-9509 Email: disabilityservices@nbme.org www.usmle.org/test-accommodations

Internet access to this information is also available at www.nbme.org. This information is also relevant for IMGs, since the information is the same as that sent by the ECFMG.

Foreign graduates should contact the ECFMG to obtain information on special accommodations by calling or writing to:

# **ECFMG**

3624 Market Street Philadelphia, PA 19104-2685 (215) 386-5900 www.ecfmg.org

When you get this information, take some time to read it carefully. The guidelines are clear and explicit about what you need to do to obtain accommodations.

### SECTION II

## High-Yield General Principles

"There comes a time when for every addition of knowledge you forget something that you knew before. It is of the highest importance, therefore, not to have useless facts elbowing out the useful ones."

—Sir Arthur Conan Doyle, A Study in Scarlet

"Never regard study as a duty, but as the enviable opportunity to learn."

—Albert Einstein

"Live as if you were to die tomorrow. Learn as if you were to live forever."

—Gandle

▶ How to Use the Database	30
▶Biochemistry	33
▶Immunology	95
<b>▶</b> Microbiology	123
▶ Pathology	205
▶ Pharmacology	229
▶ Public Health Sciences	255

FAS1\_2019\_01-Biochem.indd 29 11/7/19 3:16 PM

#### ► HOW TO USE THE DATABASE

The 2020 edition of *First Aid for the USMLE Step 1* contains a revised and expanded database of basic science material that students, student authors, and faculty authors have identified as high yield for board review. The information is presented in a partially organ-based format. Hence, Section III is devoted to the foundational principles of biochemistry, microbiology, immunology, basic pathology, basic pharmacology, and public health sciences. Section III focuses on organ systems, with subsections covering the embryology, anatomy and histology, physiology, clinical pathology, and clinical pharmacology relevant to each. Each subsection is then divided into smaller topic areas containing related facts. Individual facts are generally presented in a three-column format, with the **Title** of the fact in the first column, the **Description** of the fact in the second column, and the **Mnemonic** or **Special Note** in the third column. Some facts do not have a mnemonic and are presented in a two-column format. Others are presented in list or tabular form in order to emphasize key associations.

The database structure used in Sections II and III is useful for reviewing material already learned. These sections are **not** ideal for learning complex or highly conceptual material for the first time.

The database of high-yield facts is not comprehensive. Use it to complement your core study material and not as your primary study source. The facts and notes have been condensed and edited to emphasize the essential material, and as a result, each entry is "incomplete" and arguably "over-simplified." Often, the more you research a topic, the more complex it becomes, with certain topics resisting simplification. Work with the material, add your own notes and mnemonics, and recognize that not all memory techniques work for all students.

We update the database of high-yield facts annually to keep current with new trends in boards emphasis, including clinical relevance. However, we must note that inevitably many other high-yield topics are not yet included in our database.

We actively encourage medical students and faculty to submit high-yield topics, well-written entries, diagrams, clinical images, and useful mnemonics so that we may enhance the database for future students. We also solicit recommendations of alternate tools for study that may be useful in preparing for the examination, such as charts, flash cards, apps, and online resources (see How to Contribute, p. xix).

FAS1\_2019\_01-Biochem.indd 30 11/7/19 3:16 PM

#### **Image Acknowledgments**

All images and diagrams marked with ☑ are © USMLE-Rx.com (MedIQ Learning, LLC) and reproduced here by special permission. All images marked with ☑ are © Dr. Richard P. Usatine, author of *The Color Atlas of Family Medicine*, *The Color Atlas of Internal Medicine*, and *The Color Atlas of Pediatrics*, and are reproduced here by special permission (www. usatinemedia.com). Images and diagrams marked with ☑ are adapted or reproduced with permission of other sources as listed on page 727. Images and diagrams with no acknowledgment are part of this book.

#### **Disclaimer**

The entries in this section reflect student opinions of what is high yield. Because of the diverse sources of material, no attempt has been made to trace or reference the origins of entries individually. We have regarded mnemonics as essentially in the public domain. Errata will gladly be corrected if brought to the attention of the authors, either through our online errata submission form at www.firstaidteam.com or directly by email to firstaid@scholarrx.com.

FAS1\_2019\_01-Biochem.indd 31 11/7/19 3:16 PM

32 **SECTI** 

## SECTION II HIGH-YIELD GENERAL PRINCIPLES

<b>▶</b> NOTES	

FAS1\_2019\_01-Biochem.indd 32 11/7/19 3:16 PM

### HIGH-YIELD PRINCIPLES IN

## **Biochemistry**

"Biochemistry is the study of carbon compounds that crawl."

-Mike Adams

"We think we have found the basic mechanism by which life comes from life."

-Francis H. C. Crick

"The biochemistry and biophysics are the notes required for life; they conspire, collectively, to generate the real unit of life, the organism."

-Ursula Goodenough

This high-yield material includes molecular biology, genetics, cell biology, and principles of metabolism (especially vitamins, cofactors, minerals, and single-enzyme-deficiency diseases). When studying metabolic pathways, emphasize important regulatory steps and enzyme deficiencies that result in disease, as well as reactions targeted by pharmacologic interventions. For example, understanding the defect in Lesch-Nyhan syndrome and its clinical consequences is higher yield than memorizing every intermediate in the purine salvage pathway.

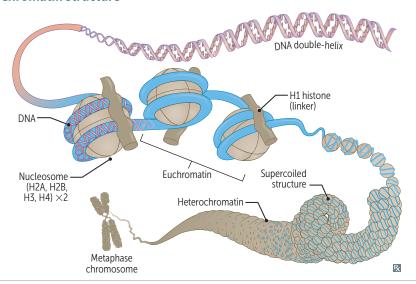
Do not spend time learning details of organic chemistry, mechanisms, or physical chemistry. Detailed chemical structures are infrequently tested; however, many structures have been included here to help students learn reactions and the important enzymes involved. Familiarity with the biochemical techniques that have medical relevance—such as ELISA, immunoelectrophoresis, Southern blotting, and PCR—is useful. Review the related biochemistry when studying pharmacology or genetic diseases as a way to reinforce and integrate the material.

▶Molecular	34
▶ Cellular	46
▶ Laboratory Technic	ques 52
▶ Genetics	56
Nutrition	65
▶ Metabolism	

FAS1\_2019\_01-Biochem.indd 33 11/7/19 3:16 PM

#### ▶ BIOCHEMISTRY—MOLECULAR

#### **Chromatin structure**



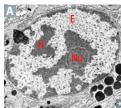
DNA exists in the condensed, chromatin form to fit into the nucleus. DNA loops twice around a histone octamer to form a nucleosome ("beads on a string"). H1 binds to the nucleosome and to "linker DNA," thereby stabilizing the chromatin fiber.

Phosphate groups give DNA a  $\ominus$  charge. Lysine and arginine give histones a  $\oplus$  charge.

In mitosis, DNA condenses to form chromosomes. DNA and histone synthesis occurs during S phase.

Mitochondria have their own DNA, which is circular and does not utilize histones.

#### Heterochromatin



Condensed, appears darker on EM (labeled H in ♠; Nu, nucleolus). Sterically inaccessible, thus transcriptionally inactive. ↑ methylation, ↓ acetylation.

HeteroChromatin = Highly Condensed.
Barr bodies (inactive X chromosomes) may be visible on the periphery of nucleus.

British Co. Section Section 19 (1997)		
Euchromatin	Less condensed, appears lighter on EM (labeled E in A). Transcriptionally active, sterically accessible.	Eu = true, "truly transcribed." Euchromatin is Expressed.
DNA methylation	Changes the expression of a DNA segment without changing the sequence. Involved with aging, carcinogenesis, genomic imprinting, transposable element repression, and inactivation of the X chromosome.	DNA is methylated in imprinting.  Methylation within gene promoter (CpG islands) typically represses (silences) gene transcription.  CpG Methylation Makes DNA Mute.
Histone methylation	Usually causes reversible transcriptional suppression, but can also cause activation depending on location of methyl groups.	Histone Methylation Mostly Makes DNA Mute.
Histone acetylation	Removal of histone's ⊕ charge → relaxed DNA coiling → ↑ transcription.	Histone Acetylation makes DNA Active.
Histone deacetylation	Removal of acetyl groups → tightened DNA coiling → ↓ transcription.	

FAS1\_2019\_01-Biochem.indd 34 11/7/19 3:16 PM

#### **Nucleotides**

NucleoSide = base + (deoxy)ribose (Sugar). NucleoTide = base + (deoxy)ribose + phosphaTe; 5' end of incoming nucleotide bears the

linked by 3'-5' phosphodiester bond.

PURines (A,G)—2 rings. PYrimidines (C,U,T)—1 ring.

Deamination reactions:

Cytosine → uracil

Adenine → hypoxanthine

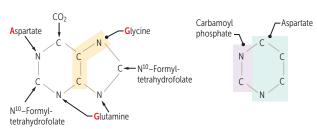
Guanine → xanthine

5-methylcytosine → thymine

Uracil found in RNA; thymine in DNA. Methylation of uracil makes thymine.

Purine (A, G)

Pyrimidine (C, U, T)



5' end of incoming nucleotide bears the triphosphate (energy source for the bond). Triphosphate bond is target of 3' hydroxyl attack.

PURe As Gold.

CUT the PY (pie).

Thymine has a methyl.

C-G bond (3 H bonds) stronger than A-T bond (2 H bonds). ↑ C-G content → ↑ melting temperature of DNA. "C-G bonds are like Crazy Glue."

Amino acids necessary for **pur**ine synthesis (cats **pur**r until they **GAG**):

Glycine

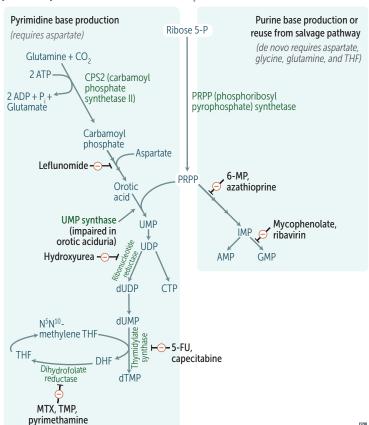
Aspartate

Glutamine

FAS1\_2019\_01-Biochem.indd 35 11/7/19 3:16 PM

## De novo pyrimidine and purine synthesis

Various immunosuppressive, antineoplastic, and antibiotic drugs function by interfering with nucleotide synthesis:



#### **Pyrimidine synthesis:**

- Leflunomide: inhibits dihydroorotate dehydrogenase
- 5-fluorouracil (5-FU) and its prodrug capecitabine: form 5-F-dUMP, which inhibits thymidylate synthase (↓ dTMP)

#### **Purine synthesis:**

- 6-mercaptopurine (6-MP) and its prodrug azathioprine: inhibit de novo purine synthesis
- Mycophenolate and ribavirin: inhibit inosine monophosphate dehydrogenase

#### Purine and pyrimidine synthesis:

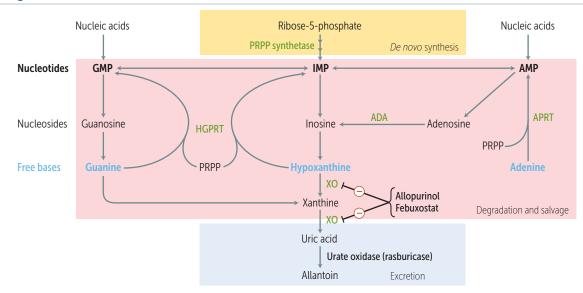
- Hydroxyurea: inhibits ribonucleotide reductase
- Methotrexate (MTX), trimethoprim (TMP), and pyrimethamine: inhibit dihydrofolate reductase (↓ deoxythymidine monophosphate [dTMP]) in humans, bacteria, and protozoa, respectively

CPS1 = m1tochondria (urea cycle) CPS2 = cyTWOsol

Ŗ

FAS1\_2019\_01-Biochem.indd 36 11/7/19 3:16 PM

#### **Purine salvage deficiencies**



ADA, adenosine deaminase; APRT, adenine phosphoribosyltransferase; HGPRT, hypoxanthine guanine phosphoribosyltransferase; XO, xanthine oxidase.

Adenosine deaminase deficiency

ADA is required for degradation of adenosine and deoxyadenosine. ↓ ADA → ↑ dATP

- → ↓ ribonucleotide reductase activity
- → lymphotoxicity.

One of the major causes of autosomal recessive SCID.

Ŗ

Lesch-Nyhan syndrome

Defective purine salvage due to absent HGPRT, which converts hypoxanthine to IMP and guanine to GMP. Results in excess uric acid production and de novo purine synthesis. X-linked recessive.

Findings: intellectual disability, self-mutilation, aggression, hyperuricemia (orange "sand" [sodium urate crystals] in diaper), gout, dystonia, macrocytosis.

Treatment: allopurinol or febuxostat (2nd line).

#### **HGPRT**

**H**yperuricemia

Gout

Pissed off (aggression, self-mutilation)

Retardation (intellectual disability)

DysTonia

#### **Genetic code features**

Unambiguous	Each codon specifies only 1 amino acid.	
Degenerate/ redundant	Most amino acids are coded by multiple codons.  Wobble—codons that differ in 3rd ("wobble") position may code for the same tRNA/amino acid. Specific base pairing is usually required only in the first 2 nucleotide positions of mRNA codon.	Exceptions: methionine (AUG) and tryptophan (UGG) encoded by only 1 codon.
Commaless, nonoverlapping	Read from a fixed starting point as a continuous sequence of bases.	Exceptions: some viruses.
Universal	Genetic code is conserved throughout evolution.	Exception in humans: mitochondria.

FAS1\_2019\_01-Biochem.indd 37 11/7/19 3:16 PM

DNA replication	Eukaryotic DNA replication is more complex than in prokaryotes but uses many enzymes analogous to those listed below. In both prokaryotes and eukaryotes, DNA replication is semiconservative, involves continuous and discontinuous (Okazaki fragment) synthesis, and occurs in the $5' \rightarrow 3'$ direction.		
Origin of replication A	Particular consensus sequence in genome where DNA replication begins. May be single (prokaryotes) or multiple (eukaryotes).	AT-rich sequences (such as TATA box regions) are found in promoters and origins of replication.	
Replication fork B	Y-shaped region along DNA template where leading and lagging strands are synthesized.		
Helicase C	Unwinds DNA template at replication fork.	Helicase Halves DNA. Deficient in Bloom syndrome (BLM gene mutation).	
Single-stranded binding proteins D	Prevent strands from reannealing.		
DNA topoisomerases <b>E</b>	Create a single- or double-stranded break in the helix to add or remove supercoils.	In eukaryotes: irinotecan/topotecan inhibit topoisomerase (TOP) I, etoposide/teniposide inhibit TOP II.	
		In prokaryotes: fluoroquinolones inhibit TOP II (DNA gyrase) and TOP IV.	
Primase F	Makes an RNA primer on which DNA polymerase III can initiate replication.		
DNA polymerase III G	Prokaryotes only. Elongates leading strand by adding deoxynucleotides to the 3′ end. Elongates lagging strand until it reaches primer of preceding fragment.  DNA polymerase III has 5′ → 3′ synthest proofreads with 3′ → 5′ exonuclease. Drugs blocking DNA replication often modified 3′ OH, thereby preventing at the next nucleotide ("chain termination").		
DNA polymerase I H	Prokaryotes only. Degrades RNA primer; replaces it with DNA.	Same functions as DNA polymerase III, also excises RNA primer with 5' → 3' exonuclease.	
DNA ligase 🚺	Catalyzes the formation of a phosphodiester bond within a strand of double-stranded DNA.	Joins Okazaki fragments. Ligase Links DNA.	
Telomerase	Eukaryotes only. A reverse transcriptase (RNA-dependent DNA polymerase) that adds DNA (TTAGGG) to 3' ends of chromosomes to avoid loss of genetic material with every duplication.	Often dysregulated in cancer cells, allowing unlimited replication.  Telomerase TAGs for Greatness and Glory.	
	Topoisomerase Helicase Replica	DNA polymerase III  Leading strand  Lagging strand  Okazaki fragment	
Area of interest Leading strand Fork movent	Origin of replication Lagging strand  Capture Company	RNA primer  A polymerase III  DNA polymerase I	

FAS1\_2019\_01-Biochem.indd 38 11/7/19 3:16 PM

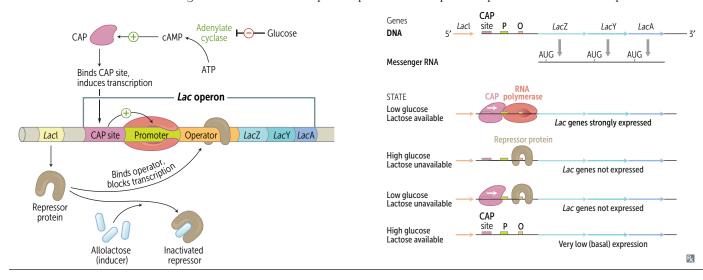
#### Severity of damage: silent << missense < nonsense < frameshift. **Mutations in DNA** Types of single nucleotide (point) mutations: • Transition—purine to purine (eg, A to G) or pyrimidine to pyrimidine (eg, C to T). **Transversion**—purine to pyrimidine (eg, A to T) or pyrimidine to purine (eg, C to G). Single nucleotide substitutions **Silent mutation** Nucleotide substitution codes for same (synonymous) amino acid; often base change in 3rd position of codon (tRNA wobble). Missense mutation Nucleotide substitution results in changed amino acid (called conservative if new amino acid has similar chemical structure). Examples include sickle cell disease (substitution of glutamic acid with valine). Nucleotide substitution results in early stop codon (UGA, UAA, UAG). Usually results in **Nonsense mutation** nonfunctional protein. Stop the nonsense! Other mutations **Frameshift mutation** Deletion or insertion of a number of nucleotides not divisible by 3 → misreading of all nucleotides downstream. Protein may be shorter or longer, and its function may be disrupted or altered. Examples include Duchenne muscular dystrophy, Tay-Sachs disease. **Splice site mutation** Retained intron in mRNA → protein with impaired or altered function. Examples include rare causes of cancers, dementia, epilepsy, some types of β-thalassemia, Gaucher disease, Marfan syndrome. Original Silent Missense Nonsense Frameshift Frameshift sequence mutation mutation mutation deletion insertion Coding DNA mRNA codon Glu Glu Val Amino acid Stop Asp Asp Altered amino acids Ŗ

FAS1\_2019\_01-Biochem.indd 39 11/7/19 3:16 PM

#### Lac operon

Classic example of a genetic response to an environmental change. Glucose is the preferred metabolic substrate in *E coli*, but when glucose is absent and lactose is available, the *lac* operon is activated to switch to lactose metabolism. Mechanism of shift:

- Low glucose → ↑ adenylate cyclase activity → ↑ generation of cAMP from ATP → activation of catabolite activator protein (CAP) → ↑ transcription.
- High lactose → unbinds repressor protein from repressor/operator site → † transcription.

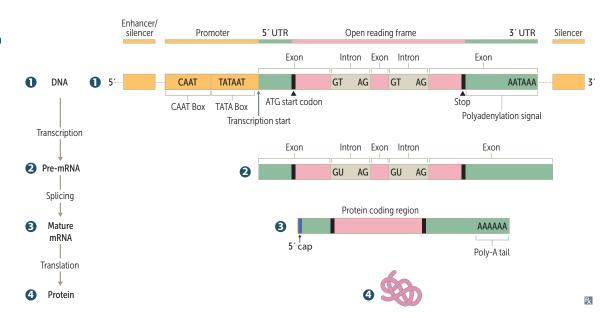


#### **DNA** repair

Single strand		
Nucleotide excision repair	Specific endonucleases release the oligonucleotides containing damaged bases; DNA polymerase and ligase fill and reseal the gap, respectively. Repairs bulky helix-distorting lesions. Occurs in G <sub>1</sub> phase of cell cycle.	Defective in xeroderma pigmentosum (inability to repair DNA pyrimidine dimers caused by UV exposure). Findings: dry skin, extreme light sensitivity, skin cancer.
Base excision repair	Base-specific Glycosylase removes altered base and creates AP site (apurinic/apyrimidinic).  One or more nucleotides are removed by AP-Endonuclease, which cleaves 5′ end.  AP-Lyase cleaves 3′ end. DNA Polymerase-β fills the gap and DNA Ligase seals it. Occurs throughout cell cycle.	Important in repair of spontaneous/toxic deamination.  "GEL PLease"
Mismatch repair	Mismatched nucleotides in newly synthesized (unmethylated) strand are removed and gap is filled and resealed. Occurs predominantly in S phase of cell cycle.	Defective in Lynch syndrome (hereditary nonpolyposis colorectal cancer [HNPCC]).
Double strand		
Nonhomologous end joining	Brings together 2 ends of DNA fragments to repair double-stranded breaks.	Defective in ataxia-telangiectasia. No requirement for homology. Some DNA may be lost.
Homologous recombination	Requires 2 homologous DNA duplexes. A strand from damaged dsDNA is repaired using a complementary strand from intact homologous dsDNA as a template.	Defective in breast/ovarian cancers with BRCA1 mutation and in Fanconi anemia. Restores duplexes accurately without loss of nucleotides.

FAS1\_2019\_01-Biochem.indd 40 11/7/19 3:16 PM

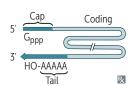
# Functional organization of a eukaryotic gene



### **Regulation of gene expression**

Promoter	Site where RNA polymerase II and multiple other transcription factors bind to DNA upstream from gene locus (AT-rich upstream sequence with TATA and CAAT boxes).	Promoter mutation commonly results in dramatic ↓ in level of gene transcription.
Enhancer	DNA locus where regulatory proteins ("activators") bind, increasing expression of a gene on the same chromosome.	Enhancers and silencers may be located close to, far from, or even within (in an intron) the gene whose expression they regulate.
Silencer	DNA locus where regulatory proteins ("repressors") bind, decreasing expression of a gene on the same chromosome.	

## RNA processing (eukaryotes)



Initial transcript is called heterogeneous nuclear RNA (hnRNA). hnRNA is then modified and becomes mRNA.

The following processes occur in the nucleus:

- Capping of 5' end (addition of 7-methylguanosine cap)
- Polyadenylation of 3′ end (≈ 200 As)
- Splicing out of introns

Capped, tailed, and spliced transcript is called mRNA.

mRNA is transported out of nucleus to be translated in cytosol.

mRNA quality control occurs at cytoplasmic processing bodies (P-bodies), which contain exonucleases, decapping enzymes, and microRNAs; mRNAs may be degraded or stored in P-bodies for future translation.

Poly-A polymerase does not require a template. AAUAAA = polyadenylation signal.

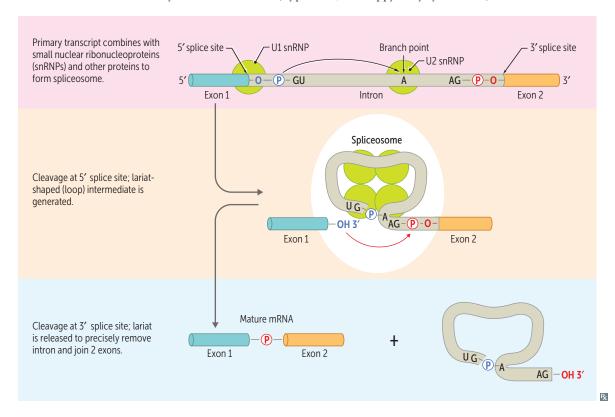
FAS1\_2019\_01-Biochem.indd 41 11/7/19 3:16 PM

#### **RNA** polymerases

Eukaryotes	RNA polymerase I makes rRNA, the most common (rampant) type; present only in nucleolus.  RNA polymerase II makes mRNA (massive), microRNA (miRNA), and small nuclear RNA (snRNA).  RNA polymerase III makes 5S rRNA, tRNA (tiny).  No proofreading function, but can initiate chains. RNA polymerase II opens DNA at promoter site.	I, II, and III are numbered in the same order that their products are used in protein synthesis: rRNA, mRNA, then tRNA. α-amanitin, found in Amanita phalloides (death cap mushrooms), inhibits RNA polymerase II. Causes severe hepatotoxicity if ingested. Actinomycin D, also called dactinomycin, inhibits RNA polymerase in both prokaryotes and eukaryotes.
Prokaryotes	1 RNA polymerase (multisubunit complex) makes all 3 kinds of RNA.	Rifampin inhibits DNA-dependent RNA polymerase in prokaryotes.

#### Splicing of pre-mRNA

Part of process by which precursor mRNA (pre-mRNA) is transformed into mature mRNA. Alterations in snRNP assembly can cause clinical disease; eg, in spinal muscular atrophy, snRNP assembly is affected due to ↓ SMN protein → congenital degeneration of anterior horns of spinal cord → symmetric weakness (hypotonia, or "floppy baby syndrome").



FAS1\_2019\_01-Biochem.indd 42 11/7/19 3:16 PM

#### Introns vs exons

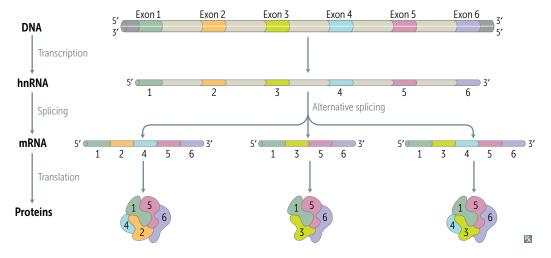
Exons contain the actual genetic information coding for protein.

Introns do not code for protein, but are important in regulation of gene expression.

Different exons are frequently combined by alternative splicing to produce a larger number of unique proteins.

Alternative splicing can produce a variety of protein products from a single hnRNA sequence (eg, transmembrane vs secreted Ig, tropomyosin variants in muscle, dopamine receptors in the brain).

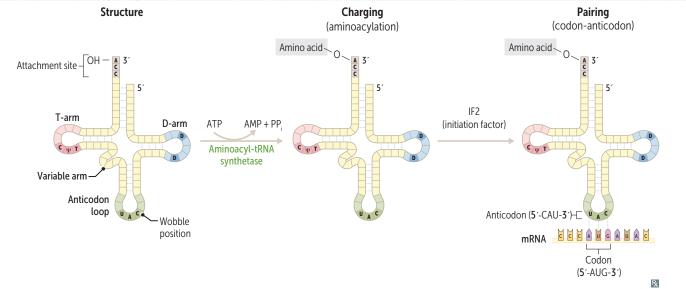
Introns are intervening sequences and stay in the nucleus, whereas exons exit and are expressed.



FAS1\_2019\_01-Biochem.indd 43 11/7/19 3:16 PM

#### **tRNA**

#### 75–90 nucleotides, 2° structure, cloverleaf form, anticodon end is opposite 3' aminoacyl end. All **Structure** tRNAs, both eukaryotic and prokaryotic, have CCA at 3' end along with a high percentage of chemically modified bases. The amino acid is covalently bound to the 3' end of the tRNA. CCA Can Carry Amino acids. T-arm: contains the TΨC (ribothymidine, pseudouridine, cytidine) sequence necessary for tRNAribosome binding. **T**-arm **T**ethers tRNA molecule to ribosome. D-arm: contains Dihydrouridine residues necessary for tRNA recognition by the correct aminoacyltRNA synthetase. **D**-arm allows **D**etection of the tRNA by aminoacyl-tRNA synthetase. Attachment site: the 5'-CCA-3' is the amino acid acceptor site. Charging Aminoacyl-tRNA synthetase (uses ATP; 1 unique enzyme per respective amino acid) and binding of charged tRNA to the codon are responsible for the accuracy of amino acid selection. Aminoacyl-tRNA synthetase matches an amino acid to the tRNA by scrutinizing the amino acid before and after it binds to tRNA. If an incorrect amino acid is attached, the bond is hydrolyzed. A mischarged tRNA reads the usual codon but inserts the wrong amino acid.



Start	and	stop	cod	ons
-------	-----	------	-----	-----

mRNA start codons	AUG (or rarely GUG).	AUG in AUG urates protein synthesis.
Eukaryotes	Codes for methionine, which may be removed before translation is completed.	1 ,
Prokaryotes	Codes for N-formylmethionine (fMet).	fMet stimulates neutrophil chemotaxis
mRNA stop codons	UGA, UAA, UAG.	UGA = U Go Away.
•		$\mathbf{UAA} = \mathbf{U} \mathbf{A} \mathbf{re} \mathbf{A} \mathbf{way}.$
		UAG = U Are Gone.

FAS1\_2019\_01-Biochem.indd 44 11/7/19 3:16 PM

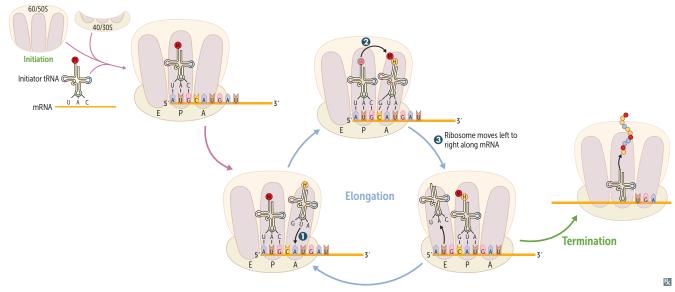
#### **Protein synthesis**

#### Initiation 1. Eukaryotic initiation factors (eIFs) identify the 5' cap. 2. eIFs help assemble the 40S ribosomal subunit with the initiator tRNA. C-terminus. 3. eIFs released when the mRNA and the ribosomal 60S subunit assemble with the complex. Requires GTP. (translocation). Aminoacyl-tRNA binds to A site (except for **Elongation** Think of "going APE": initiator methionine, which binds the P site), requires an elongation factor and GTP. 2 rRNA ("ribozyme") catalyzes peptide bond formation, transfers growing polypeptide to amino acid in A site. 3 Ribosome advances 3 nucleotides toward 3' end of mRNA, moving peptidyl tRNA to P site (translocation). **Termination** Eukaryotic release factors (eRFs) recognize the stop codon and halt translation → completed polypeptide is released from ribosome. Requires GTP.

Eukaryotes:  $40S + 60S \rightarrow 80S$  (Even). Prokaryotes:  $30S + 50S \rightarrow 70S$  (Prime). Synthesis occurs from N-terminus to

ATP—tRNA Activation (charging). GTP—tRNA Gripping and Going places

- $\mathbf{A}$  site = incoming  $\mathbf{A}$ minoacyl-tRNA.
- **P** site = accommodates growing **P**eptide.
- **E** site = holds **E**mpty tRNA as it **E**xits.



#### **Posttranslational modifications**

Trimming	Removal of N- or C-terminal propeptides from zymogen to generate mature protein (eg, trypsinogen to trypsin).
Covalent alterations	Phosphorylation, glycosylation, hydroxylation, methylation, acetylation, and ubiquitination.
Chaperone protein	Intracellular protein involved in facilitating and maintaining protein folding. In yeast, heat shock proteins (eg, HSP60) are expressed at high temperatures to prevent protein denaturing/misfolding.

FAS1\_2019\_01-Biochem.indd 45 11/7/19 3:16 PM

#### ▶ BIOCHEMISTRY—CELLULAR Cell cycle phases Checkpoints control transitions between phases of cell cycle. This process is regulated by cyclins, cyclin-dependent kinases (CDKs), and tumor suppressors. M phase (shortest phase of cell cycle) includes mitosis (prophase, prometaphase, metaphase, anaphase, telophase) and cytokinesis (cytoplasm splits in two). $G_1$ and $G_0$ are of variable duration. REGULATION OF CELL CYCLE Constitutively expressed but inactive when not Cyclin-dependent kinases bound to cyclin. **Cyclins** Regulatory proteins that control cell cycle events; phase specific; activate CDKs. **Cyclin-CDK complexes** Phosphorylate other proteins to coordinate cell cycle progression; must be activated and inactivated at appropriate times for cell cycle to progress. INTERPHASE **Tumor suppressors** p53 $\rightarrow$ p21 induction $\rightarrow$ CDK inhibition $\rightarrow$ Rb hypophosphorylation (activation) $\rightarrow$ G<sub>1</sub>-S progression inhibition. Mutations in tumor suppressor genes can result in unrestrained Rb, p53 modulate cell division (eg, Li-Fraumeni syndrome). Ŗ G, restriction point Growth factors (eg, insulin, PDGF, EPO, EGF) bind tyrosine kinase receptors to transition the cell from G<sub>1</sub> to S phase. **CELL TYPES** Neurons, skeletal and cardiac muscle, RBCs. **Permanent** Remain in $G_0$ , regenerate from stem cells. Stable (quiescent) Enter $G_1$ from $G_0$ when stimulated. Hepatocytes, lymphocytes, PCT, periosteal cells. Labile Never go to $G_0$ , divide rapidly with a short $G_1$ . Bone marrow, gut epithelium, skin, hair follicles, Most affected by chemotherapy. germ cells. **Rough endoplasmic** Site of synthesis of secretory (exported) proteins Mucus-secreting goblet cells of the small reticulum and of N-linked oligosaccharide addition to intestine and antibody-secreting plasma cells lysosomal and other proteins. are rich in RER. Nissl bodies (RER in neurons)—synthesize Proteins within organelles (eg, ER, Golgi bodies, peptide neurotransmitters for secretion. lysosomes) are formed in RER. Free ribosomes—unattached to any membrane; site of synthesis of cytosolic, peroxisomal, and mitochondrial proteins. **Smooth endoplasmic** Site of steroid synthesis and detoxification of Liver hepatocytes and steroid hormonereticulum drugs and poisons. Lacks surface ribosomes. producing cells of the adrenal cortex and Location of glucose-6-phosphatase (last step of gonads are rich in SER. glycogenolysis).

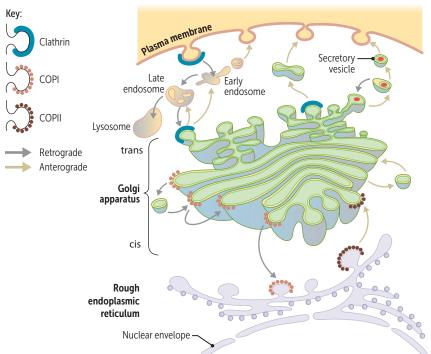
FAS1\_2019\_01-Biochem.indd 46 11/7/19 3:16 PM

#### **Cell trafficking**

Golgi is distribution center for proteins and lipids from ER to vesicles and plasma membrane. Posttranslational events in Golgi include modifying N-oligosaccharides on asparagine, adding O-oligosaccharides on serine and threonine, and adding mannose-6-phosphate to proteins for lysosomal trafficking.

Endosomes are sorting centers for material from outside the cell or from the Golgi, sending it to lysosomes for destruction or back to the membrane/Golgi for further use.

**I-cell disease** (inclusion cell disease/mucolipidosis type II)—inherited lysosomal storage disorder (autosomal recessive); defect in N-acetylglucosaminyl-1-phosphotransferase → failure of the Golgi to phosphorylate mannose residues (↓ mannose-6-phosphate) on glycoproteins → proteins are secreted extracellularly rather than delivered to lysosomes. Results in coarse facial features, gingival hyperplasia, clouded corneas, restricted joint movements, claw hand deformities, kyphoscoliosis, and high plasma levels of lysosomal enzymes. Often fatal in childhood.



#### Signal recognition particle (SRP)

Abundant, cytosolic ribonucleoprotein that traffics polypeptide-ribosome complex from the cytosol to the RER. Absent or dysfunctional SRP → accumulation of protein in cytosol.

#### Vesicular trafficking proteins

COPI: Golgi → Golgi (retrograde); *cis*-Golgi → ER.

COPII: ER  $\rightarrow$  cis-Golgi (anterograde).

"Two (COPII) steps forward (anterograde); one (COPI) step back (retrograde)."

Clathrin: *trans*-Golgi → lysosomes; plasma membrane → endosomes (receptor-mediated endocytosis [eg, LDL receptor activity]).

#### Peroxisome

Membrane-enclosed organelle involved in:

- β-oxidation of very-long-chain fatty acids (VLCFA) (strictly peroxisomal process)
- α-oxidation of branched-chain fatty acids (strictly peroxisomal process)
- Catabolism of amino acids and ethanol
- Synthesis of cholesterol, bile acids, and plasmalogens (important membrane phospholipid, especially in white matter of brain)

**Zellweger syndrome**—autosomal recessive disorder of peroxisome biogenesis due to mutated *PEX* genes. Hypotonia, seizures, hepatomegaly, early death.

Refsum disease—autosomal recessive disorder of  $\alpha$ -oxidation  $\rightarrow$  phytanic acid not metabolized to pristanic acid. Scaly skin, ataxia, cataracts/night blindness, shortening of 4th toe, epiphyseal dysplasia. Treatment: diet, plasmapheresis.

Adrenoleukodystrophy—X-linked recessive disorder of  $\beta$ -oxidation due to mutation in ABCDI gene  $\rightarrow$  VLCFA buildup in adrenal glands, white (leuko) matter of brain, testes. Progressive disease that can lead to adrenal gland crisis, coma, and death.

FAS1\_2019\_01-Biochem.indd 47 11/7/19 3:16 PM

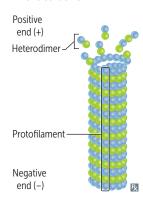
#### **Proteasome**

Barrel-shaped protein complex that degrades damaged or ubiquitin-tagged proteins. Defects in the ubiquitin-proteasome system have been implicated in some cases of Parkinson disease.

**Cytoskeletal elements** A network of protein fibers within the cytoplasm that supports cell structure, cell and organelle movement, and cell division.

	movement, und cen division.	
TYPE OF FILAMENT	PREDOMINANT FUNCTION	EXAMPLES
Microfilaments	Muscle contraction, cytokinesis	Actin, microvilli.
Intermediate filaments	Maintain cell structure	Vimentin, desmin, cytokeratin, lamins, glial fibrillary acidic protein (GFAP), neurofilaments.
Microtubules	Movement, cell division	Cilia, flagella, mitotic spindle, axonal trafficking, centrioles.

#### Microtubule



Cylindrical outer structure composed of a helical array of polymerized heterodimers of  $\alpha$ - and  $\beta$ -tubulin. Each dimer has 2 GTP bound. Incorporated into flagella, cilia, mitotic spindles. Grows slowly, collapses quickly. Also involved in slow axoplasmic transport in

Molecular motor proteins—transport cellular cargo toward opposite ends of microtubule.

- **RE**trograde to microtubule  $(+ \rightarrow -)$ —**DY**nein.
- Anterograde to microtubule  $(- \rightarrow +)$ —Kinesin.

Clostridium tetani, herpes simplex virus, poliovirus, and rabies virus use dynein for retrograde transport to the neuronal cell body. Drugs that act on microtubules (Microtubules

Get Constructed Very Poorly):

- Mebendazole (antihelminthic)
- Griseofulvin (antifungal)
- Colchicine (antigout)
- Vincristine/Vinblastine (anticancer)
- Paclitaxel (anticancer)

Negative end Near Nucleus.

Positive end Points to Periphery.

REaDY? AttacK!

FAS1\_2019\_01-Biochem.indd 48 11/7/19 3:16 PM

#### Cilia structure

9 doublet + 2 singlet arrangement of microtubules A.

Basal body (base of cilium below cell membrane) consists of 9 microtubule triplets **B** with no central microtubules.

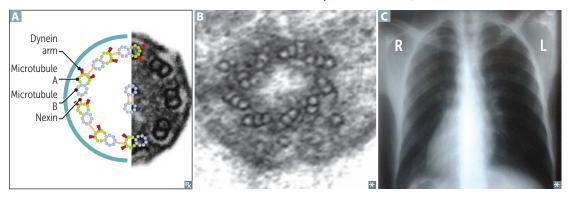
Axonemal dynein—ATPase that links peripheral

9 doublets and causes bending of cilium by differential sliding of doublets.

Gap junctions enable coordinated ciliary movement.

#### Kartagener syndrome (1° ciliary dyskinesia)—

immotile cilia due to a dynein arm defect. Autosomal recessive. Results in ↓ male and female fertility due to immotile sperm and dysfunctional fallopian tube cilia, respectively; ↑ risk of ectopic pregnancy. Can cause bronchiectasis, recurrent sinusitis, chronic ear infections, conductive hearing loss, and situs inversus (eg, dextrocardia on CXR ). ↓ nasal nitric oxide (used as screening test). (Kartagener's restaurant: take-out only; there's no dynein "dine-in".)



## Sodium-potassium pump

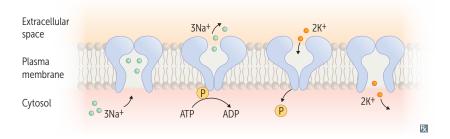
Na<sup>+</sup>-K<sup>+</sup> ATPase is located in the plasma membrane with ATP site on cytosolic side. For each ATP consumed, 3 Na<sup>+</sup> leave the cell (pump phosphorylated) and 2 K<sup>+</sup> enter the cell (pump dephosphorylated).

Plasma membrane is an asymmetric lipid bilayer containing cholesterol, phospholipids, sphingolipids, glycolipids, and proteins.

#### Pumpkin = pump $K^+$ in.

Ouabain (a cardiac glycoside) inhibits by binding to K<sup>+</sup> site.

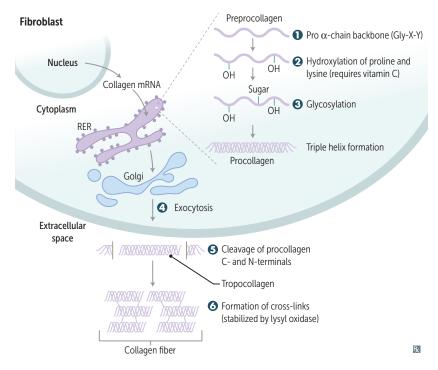
Cardiac glycosides (digoxin and digitoxin) directly inhibit the Na<sup>+</sup>-K<sup>+</sup> ATPase, which leads to indirect inhibition of Na<sup>+</sup>/Ca<sup>2+</sup> exchange → ↑ [Ca<sup>2+</sup>]<sub>i</sub> → ↑ cardiac contractility.



FAS1\_2019\_01-Biochem.indd 49 11/7/19 3:16 PM

Collagen	Most abundant protein in the human body. Extensively modified by posttranslational modification. Organizes and strengthens extracellular matrix.	Be So Totally Cool, Read Books.
Type I	Most common (90%)—Bone (made by osteoblasts), Skin, Tendon, dentin, fascia, cornea, late wound repair.	Type <b>I</b> : bone.  ↓ production in osteogenesis imperfecta type I.
Type II	Cartilage (including hyaline), vitreous body, nucleus pulposus.	Type <b>II</b> : car <mark>two</mark> lage.
Type III	Reticulin—skin, blood vessels, uterus, fetal tissue, early wound repair.	Type III: deficient in the uncommon, vascular type of Ehlers-Danlos syndrome (ThreE D).
Type IV	Basement membrane (basal lamina), lens.	Type <b>IV</b> : under the <b>floor</b> (basement membrane). Defective in Alport syndrome; targeted by autoantibodies in Goodpasture syndrome.

#### Collagen synthesis and structure



- Synthesis—translation of collagen α chains (preprocollagen)—usually Gly-X-Y (X and Y are proline or lysine). Collagen is ½ glycine; glycine content of collagen is less variable than that of lysine and proline. Hydroxyproline is used for lab quantification of collagen.
- 2 Hydroxylation—hydroxylation of specific proline and lysine residues. Requires vitamin C; deficiency → scurvy.
- 3 Glycosylation—glycosylation of pro-α-chain hydroxylysine residues and formation of procollagen via hydrogen and disulfide bonds (triple helix of 3 collagen α chains). Problems forming triple helix → osteogenesis imperfecta.
- **②** Exocytosis—exocytosis of procollagen into extracellular space.
- Proteolytic processing—cleavage of disulfide-rich terminal regions of procollagen
   → insoluble tropocollagen.
- 6 Cross-linking—reinforcement of many staggered tropocollagen molecules by covalent lysine-hydroxylysine cross-linkage (by copper-containing lysyl oxidase) to make collagen fibrils. Problems with cross-linking
  - → Menkes disease.

FAS1\_2019\_01-Biochem.indd 50 11/7/19 3:16 PM

## Osteogenesis imperfecta



Genetic bone disorder (brittle bone disease) caused by a variety of gene defects (most commonly *COL1A1* and *COL1A2*).

Most common form is autosomal dominant with ↓ production of otherwise normal type I collagen. Manifestations include:

- Multiple fractures and bone deformities after minimal trauma (eg, during birth)
- Blue sclerae B due to the translucent connective tissue over choroidal veins
- Some forms have tooth abnormalities, including opalescent teeth that wear easily due to lack of dentin (dentinogenesis imperfecta)
- Conductive hearing loss (abnormal ossicles)

May be confused with child abuse.

Treat with bisphosphonates to ↓ fracture risk. Patients can't **BITE**:

Bones = multiple fractures

I (eye) = blue sclerae

Teeth = dental imperfections

 $\mathbf{E}$ ar = hearing loss



## **Ehlers-Danlos syndrome**

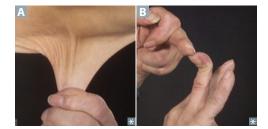
Faulty collagen synthesis causing hyperextensible skin A, hypermobile joints B, and tendency to bleed (easy bruising).

Multiple types. Inheritance and severity vary. Can be autosomal dominant or recessive. May be associated with joint dislocation, berry and aortic aneurysms, organ rupture.

Hypermobility type (joint instability): most common type.

Classical type (joint and skin symptoms): caused by a mutation in type V collagen (eg, COL5A1, COL5A2).

Vascular type (fragile tissues including vessels [eg, aorta], muscles, and organs that are prone to rupture [eg, gravid uterus]): mutations in type III procollagen (eg, COL3A1).

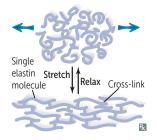


#### Menkes disease

X-linked recessive connective tissue disease caused by impaired copper absorption and transport due to defective Menkes protein (ATP7A, vs ATP7B in Wilson disease). Low copper levels (vs high levels in Wilson disease). Leads to ↓ activity of lysyl oxidase (copper is a necessary cofactor) → defective collagen. Results in brittle, "kinky" hair, growth retardation, hypotonia, † risk of cerebral aneurysms.

FAS1\_2019\_01-Biochem.indd 51 11/7/19 3:16 PM

#### **Elastin**



Stretchy protein within skin, lungs, large arteries, elastic ligaments, vocal cords, ligamenta flava (connect vertebrae → relaxed and stretched conformations).

Rich in nonhydroxylated proline, glycine, and lysine residues, vs the hydroxylated residues of collagen.

Tropoelastin with fibrillin scaffolding.

Cross-linking takes place extracellularly and gives elastin its elastic properties.

Broken down by elastase, which is normally inhibited by  $\alpha_l$ -antitrypsin.

 $\alpha_{l}$ -Antitrypsin deficiency results in unopposed elastase activity, which can cause COPD.

Changes with aging: ↓ dermal collagen and elastin, ↓ synthesis of collagen fibrils; cross-linking remains normal.

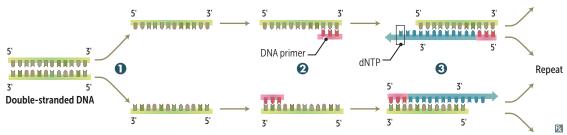


Marfan syndrome—autosomal dominant (with variable expression) connective tissue disorder affecting skeleton, heart, and eyes. *FBN1* gene mutation on chromosome 15 (fifteen) results in defective fibrillin, a glycoprotein that forms a sheath around elastin. Findings: tall with long extremities; pectus carinatum (more specific) or pectus excavatum A; hypermobile joints; long, tapering fingers and toes (arachnodactyly); cystic medial necrosis of aorta; aortic root aneurysm rupture or dissection (most common cause of death); mitral valve prolapse. Subluxation of lenses, typically upward and temporally (vs downward and medially in homocystinuria).

#### ▶ BIOCHEMISTRY—LABORATORY TECHNIQUES

## Polymerase chain reaction

Molecular biology lab procedure used to amplify a desired fragment of DNA. Useful as a diagnostic tool (eg, neonatal HIV, herpes encephalitis).



- **1 Denaturation**—DNA is heated to ~95°C to separate the strands.
- ② Annealing—Sample is cooled to ~55°C. DNA primers, a heat-stable DNA polymerase (*Taq*), and deoxynucleotide triphosphates (dNTPs) are added. DNA primers anneal to the specific sequence to be amplified on each strand.
- **3 Elongation**—Temperature is increased to ~72°C. DNA polymerase attaches dNTPs to the strand to replicate the sequence after each primer.

Heating and cooling cycles continue until the DNA sample size is sufficient.

# Reverse transcriptase polymerase chain reaction

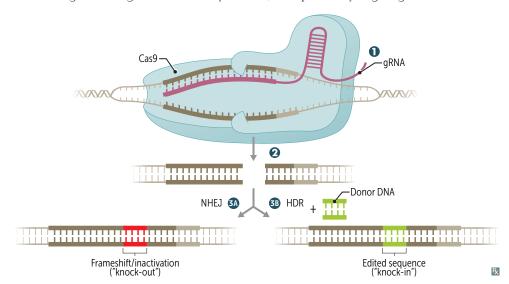
Detects and quantifies mRNA levels in a sample. Uses reverse transcription to create a complementary DNA template that is amplified via standard PCR procedure.

FAS1 2019 01-Biochem.indd 52 11/7/19 3:16 PM

#### CRISPR/Cas9

A genome editing tool derived from bacteria. Consists of a guide RNA (gRNA) ①, which is complementary to a target DNA sequence, and an endonuclease (Cas9), which makes a single-or double-strand break at the target site ②. Break imperfectly repaired by nonhomologous end joining (NHEJ) → accidental frameshift mutations ("knock-out") ③, or a donor DNA sequence can be added to fill in the gap using homology-directed repair (HDR) ③.

Not used clinically. Potential applications include removing virulence factors from pathogens, replacing disease-causing alleles of genes with healthy variants, and specifically targeting tumor cells.



#### **Blotting procedures**

Southern blot	1. <b>DNA</b> sample is enzymatically cleaved into smaller pieces, which are separated on a gel by electrophoresis, and then transferred to a filter.		PEDIGREE				I: Parents II: Children	
	<ol> <li>Filter is exposed to radiolabeled DNA probe that recognizes and anneals to its complementary strand.</li> <li>Resulting double-stranded, labeled piece of DNA is visualized when filter is exposed to film.</li> </ol>	SOUTHERN BLOT	Aa	Aa	aa	Aa	AA	Genotype  Mutant  Normal
Northern blot	Similar to Southern blot, except that an RNA sample is electrophoresed. Useful for studying mRNA levels, which are reflective of gene expression.		: thern	= DN				
Western blot	Sample protein is separated via gel electrophoresis and transferred to a membrane. Labeled antibody is used to bind to relevant <b>protein</b> .			= RNA = Prote				
Southwestern blot	Identifies <b>DNA-binding proteins</b> (eg, c-Jun, c-Fos [leucine zipper motif]) using labeled double-stranded DNA probes.							

FAS1\_2019\_01-Biochem.indd 53 11/7/19 3:16 PM

#### Flow cytometry

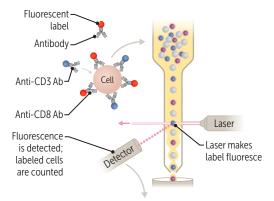
Laboratory technique to assess size, granularity, and protein expression (immunophenotype) of individual cells in a sample.

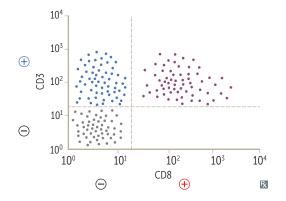
Cells are tagged with antibodies specific to surface or intracellular proteins. Antibodies are then tagged with a unique fluorescent dye. Sample is analyzed one cell at a time by focusing a laser on the cell and measuring light scatter and intensity of fluorescence.

Data are plotted either as histogram (one measure) or scatter plot (any two measures, as shown). In illustration:

- Cells in right lower quadrant ⊕ for CD8 and ⊝ for CD3. In this example, right lower quadrant is empty because all CD8-expressing cells also express CD3.
- Cells in left upper quadrant ⊕ for CD3 and ⊕ for CD8.
- Cells in right upper quadrant ⊕ for both CD8 and CD3.

Commonly used in workup of hematologic abnormalities (eg, leukemia, paroxysmal nocturnal hemoglobinuria, fetal RBCs in mother's blood) and immunodeficiencies (eg, CD4<sup>+</sup> cell count in HIV).





#### Microarrays

Thousands of nucleic acid sequences are arranged in grids on glass or silicon. DNA or RNA probes are hybridized to the chip, and a scanner detects the relative amounts of complementary binding. Used to profile gene expression levels of thousands of genes simultaneously to study certain diseases and treatments. Able to detect single nucleotide polymorphisms (SNPs) and copy number variations (CNVs) for a variety of applications including genotyping, clinical genetic testing, forensic analysis, cancer mutations, and genetic linkage analysis.

## Enzyme-linked immunosorbent assay

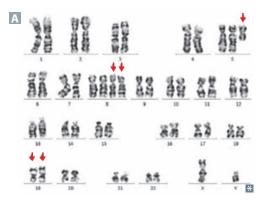
Immunologic test used to detect the presence of either a specific antigen or antibody in a patient's blood sample. Detection involves the use of an antibody linked to an enzyme. Added substrate reacts with enzyme, producing a detectable signal. Can have high sensitivity and specificity, but is less specific than Western blot.

FAS1\_2019\_01-Biochem.indd 54 11/7/19 3:16 PM

#### **Karyotyping**

Colchicine is added to cultured cells to halt chromosomes in metaphase. Chromosomes are stained, ordered, and numbered according to morphology, size, arm-length ratio, and banding pattern (arrows in A point to extensive abnormalities in a cancer cell).

Can be performed on a sample of blood, bone marrow, amniotic fluid, or placental tissue. Used to diagnose chromosomal imbalances (eg, autosomal trisomies, sex chromosome disorders).

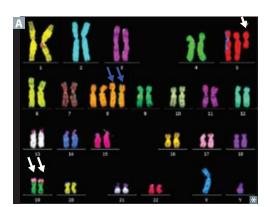


## Fluorescence in situ hybridization

Fluorescent DNA or RNA probe binds to specific gene site of interest on chromosomes (arrows in A point to abnormalities in a cancer cell, whose karyotype is seen above; each fluorescent color represents a chromosomespecific probe).

Used for specific localization of genes and direct visualization of chromosomal anomalies at the molecular level.

- Microdeletion—no fluorescence on a chromosome compared to fluorescence at the same locus on the second copy of that chromosome.
- Translocation—fluorescence signal that corresponds to one chromosome is found in a different chromosome (two white arrows in A show fragments of chromosome 17 that have translocated to chromosome 19).
- Duplication—a second copy of a chromosome, resulting in a trisomy or tetrasomy (two blue arrows show duplicated chromosomes 8, resulting in a tetrasomy).



#### **Molecular cloning**

Production of a recombinant DNA molecule in a bacterial host.

- 1. Isolate eukaryotic mRNA (post-RNA processing) of interest.
- 2. Add reverse transcriptase (an RNA-dependent DNA polymerase) to produce complementary DNA (cDNA, lacks introns).
- 3. Insert cDNA fragments into bacterial plasmids containing antibiotic resistance genes.
- 4. Transform (insert) recombinant plasmid into bacteria.
- 5. Surviving bacteria on antibiotic medium produce cloned DNA (copies of cDNA).

FAS1\_2019\_01-Biochem.indd 55

56

SECTION II

## BIOCHEMISTRY → BIOCHEMISTRY—GENETICS

Gene expression modifications	<ul> <li>Transgenic strategies in mice involve:</li> <li>Random insertion of gene into mouse genome</li> <li>Targeted insertion or deletion of gene through homologous recombination with mouse gene</li> </ul>	Knock-out = removing a gene, taking it out. Knock-in = inserting a gene.  Random insertion—constitutive expression. Targeted insertion—conditional expression.
Cre-lox system	Can inducibly manipulate genes at specific develonable deletion causes embryonic death).	opmental points (eg, to study a gene whose
RNA interference	Process whereby small non-coding RNA molecule	es target mRNAs to inhibit gene expression.
MicroRNA (miRNA)	Naturally produced by the cell as hairpin structures. Loose nucleotide pairing allows broader targeting of related mRNAs, blocking translation and accelerating mRNA degradation.	Abnormal expression of miRNAs contributes to certain malignancies (eg, by silencing an mRNA from a tumor suppressor gene).
Small interfering RNA (siRNA)	Usually derived from exogenous dsRNA source (eg, virus). Once inside a cell, siRNA requires complete nucleotide pairing, leading to highly specific mRNA targeting. Results in mRNA cleavage prior to translation.	Can be produced by in vitro transcription for gene "knockdown" experiments.

### ▶ BIOCHEMISTRY—GENETICS

#### **Genetic terms**

TERM	DEFINITION	EXAMPLE
Codominance	Both alleles contribute to the phenotype of the heterozygote.	Blood groups A, B, AB; $\alpha_l$ -antitrypsin deficiency; HLA groups.
Variable expressivity	Patients with the same genotype have varying phenotypes.	2 patients with neurofibromatosis type 1 (NF1) may have varying disease severity.
Incomplete penetrance	Not all individuals with a mutant genotype show the mutant phenotype.  % penetrance × probability of inheriting genotype = risk of expressing phenotype.	BRCA1 gene mutations do not always result in breast or ovarian cancer.
Pleiotropy	One gene contributes to multiple phenotypic effects.	Untreated phenylketonuria (PKU) manifests with light skin, intellectual disability, and musty body odor.
Anticipation	Increased severity or earlier onset of disease in succeeding generations.	Trinucleotide repeat diseases (eg, Huntington disease).
Loss of heterozygosity	If a patient inherits or develops a mutation in a tumor suppressor gene, the complementary allele must be deleted/mutated before cancer develops. This is not true of oncogenes.	Retinoblastoma and the "two-hit hypothesis," Lynch syndrome (HNPCC), Li-Fraumeni syndrome.

FAS1\_2019\_01-Biochem.indd 56 11/7/19 3:16 PM

#### **Genetic terms (continued)**

TERM	DEFINITION	EXAMPLE
Dominant negative mutation	Exerts a dominant effect. A heterozygote produces a nonfunctional altered protein that also prevents the normal gene product from functioning.	A single mutated <i>p53</i> tumor suppressor gene results in a protein that is able to bind DNA and block the nonmutated p53 from binding to the promoter.
Linkage disequilibrium	Tendency for certain alleles at 2 linked loci to occur together more or less often than expected by chance. Measured in a population, not in a family, and often varies in different populations.	
Mosaicism	Presence of genetically distinct cell lines in the same individual.  Somatic mosaicism—mutation arises from mitotic errors after fertilization and propagates through multiple tissues or organs.  Gonadal mosaicism—mutation only in egg or sperm cells. If parents and relatives do not have the disease, suspect gonadal (or germline) mosaicism.	<b>McCune-Albright syndrome</b> —due to G <sub>s</sub> -protein activating mutation. Presents with unilateral café-au-lait spots A with ragged edges, polyostotic fibrous dysplasia (bone is replaced by collagen and fibroblasts), and at least one endocrinopathy (eg, precocious puberty). Lethal if mutation occurs before fertilization (affecting all cells), but survivable in patients with mosaicism.
Locus heterogeneity	Mutations at different loci can produce a similar phenotype.	Albinism.
Allelic heterogeneity	Different mutations in the same locus produce the same phenotype.	β-thalassemia.
Heteroplasmy	Presence of both normal and mutated mtDNA, resulting in variable expression in mitochondrially inherited disease.	mtDNA passed from mother to all children.
Uniparental disomy	Offspring receives 2 copies of a chromosome from 1 parent and no copies from the other parent. HeterodIsomy (heterozygous) indicates a meiosis I error. IsodIsomy (homozygous) indicates a meiosis II error or postzygotic chromosomal duplication of one of a pair of chromosomes, and loss of the other of the original pair.	Uniparental is euploid (correct number of chromosomes). Most occurrences of uniparental disomy (UPD) → normal phenotype. Consider isodisomy in an individual manifesting a recessive disorder when only one parent is a carrier. Examples: Prader-Willi and Angelman syndromes.

## Hardy-Weinberg population genetics

	A (p)	a ( <b>q</b> )
A (p)	AA (p²)	Aa ( <mark>pq</mark> )
a (q)	Aa ( <mark>pq</mark> )	aa (q²)

If **p** and **q** represent the frequencies of alleles A and a, respectively, in a population, then  $\mathbf{p} + \mathbf{q} = 1$ :

- $\mathbf{p}^2$  = frequency of homozygosity for allele A
- $\mathbf{q}^2$  = frequency of homozygosity for allele a
- 2pq = frequency of heterozygosity (carrier frequency, if an autosomal recessive disease)

Therefore, the sum of the frequencies of these genotypes is  $\mathbf{p}^2 + 2\mathbf{p}\mathbf{q} + \mathbf{q}^2 = 1$ .

The frequency of an X-linked recessive disease in males = q and in females =  $q^2$ .

Hardy-Weinberg law assumptions include:

- No mutation occurring at the locus
- Natural selection is not occurring
- Completely random mating
- No net migration
- Large population

If a population is in Hardy-Weinberg equilibrium, then the values of p and q remain constant from generation to generation.

FAS1\_2019\_01-Biochem.indd 57 11/7/19 3:16 PM

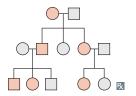
## SECTION II BIOCHEMISTRY → BIOCHEMISTRY—GENETICS

Disorders of imprinting	Imprinting—one gene copy is silenced by methylation, and only the other copy is expressed → parent-of-origin effects.			
	Prader-Willi syndrome	Angel Man syndrome		
WHICH GENE IS SILENT?	Maternally derived genes are silenced Disease occurs when the Paternal allele is deleted or mutated	Paternally derived <i>UBE3A</i> is silenced  Disease occurs when the Maternal allele is deleted or mutated		
SIGNS AND SYMPTOMS	Hyperphagia, obesity, intellectual disability, hypogonadism, hypotonia	Seizures, Ataxia, severe Intellectual disability, inappropriate Laughter ("happy puppet") Set SAIL for Angel Island		
CHROMOSOMES INVOLVED	Chromosome 15 of paternal origin	UBE3A on maternal copy of chromosome 15		
NOTES	25% of cases are due to maternal uniparental disomy	5% of cases are due to paternal uniparental disomy		
	Prader has no Dad (Paternal Deletion)	MDs are angels (Maternal Deletion)		

FAS1\_2019\_01-Biochem.indd 58

#### **Modes of inheritance**

#### **Autosomal dominant**

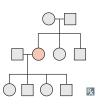


Often due to defects in structural genes. Many generations, both males and females are affected.



Often pleiotropic (multiple apparently unrelated effects) and variably expressive (different between individuals). Family history crucial to diagnosis. With one affected (heterozygous) parent, on average, ½ of children affected.

#### **Autosomal recessive**



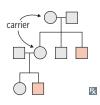
With 2 carrier (heterozygous) parents, on average: 1/4 of children will be affected (homozygous), ½ of children will be carriers, and ¼ of children will be neither affected nor carriers.

	Α	a
Α	AA	Aa
a	Aa	aa

Often due to enzyme deficiencies. Usually seen in only 1 generation. Commonly more severe than dominant disorders; patients often present in childhood.

† risk in consanguineous families. Unaffected individual with affected sibling has 2/3 probability of being a carrier.

#### X-linked recessive

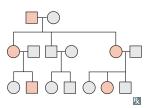


Sons of heterozygous mothers have a 50% chance of being affected. No male-to-male transmission. Skips generations.

	Χ	Χ		Χ	Χ
Χ	XX	XX	Χ	XX	XX
Υ	XY	XY	Υ	XY	XY

Commonly more severe in males. Females usually must be homozygous to be affected.

#### X-linked dominant

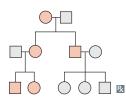


Transmitted through both parents. Mothers transmit to 50% of daughters and sons; fathers transmit to all daughters but no sons.

	Χ	Χ		Χ	Χ	
	XX	XX	Χ	XX	XX	
,	XY	XY	Υ	XY	XY	

Examples: fragile X syndrome, Alport syndrome, hypophosphatemic rickets (also called X-linked hypophosphatemia)—phosphate wasting at proximal tubule → rickets-like presentation.

#### Mitochondrial inheritance



Transmitted only through the mother. All offspring of affected females may show signs of disease.

Variable expression in a population or even within a family due to heteroplasmy.

Mitochondrial myopathies—rare disorders; often present with myopathy, lactic acidosis, and CNS disease, eg, MELAS syndrome (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes). 2° to failure in oxidative phosphorylation. Muscle biopsy often shows "ragged red fibers" (due to accumulation of diseased mitochondria in the subsarcolemma of the muscle fiber).

Leber hereditary optic neuropathy—cell

death in optic nerve neurons → subacute bilateral vision loss in teens/young adults, 90% males. Usually permanent.





FAS1 2019 01-Biochem.indd 59 11/7/19 3:16 PM

## Autosomal dominant diseases

Achondroplasia, autosomal dominant polycystic kidney disease, familial adenomatous polyposis, familial hypercholesterolemia, hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu syndrome), hereditary spherocytosis, Huntington disease, Li-Fraumeni syndrome, Marfan syndrome, multiple endocrine neoplasias, myotonic muscular dystrophy, neurofibromatosis type 1 (von Recklinghausen disease), neurofibromatosis type 2, tuberous sclerosis, von Hippel-Lindau disease.

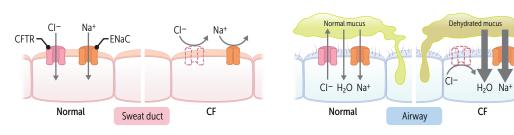
## Autosomal recessive diseases

Oculocutaneous albinism, autosomal recessive polycystic kidney disease (ARPKD), cystic fibrosis, Friedreich ataxia, glycogen storage diseases, hemochromatosis, Kartagener syndrome, mucopolysaccharidoses (except Hunter syndrome), phenylketonuria, sickle cell anemia, sphingolipidoses (except Fabry disease), thalassemias, Wilson disease.

#### **Cystic fibrosis**

GENETICS	Autosomal recessive; defect in CFTR gene on chromosome 7; commonly a deletion of Phe508. Most common lethal genetic disease in Caucasian population.
PATHOPHYSIOLOGY	CFTR encodes an ATP-gated Cl <sup>-</sup> channel that secretes Cl <sup>-</sup> in lungs and GI tract, and reabsorbs Cl <sup>-</sup> in sweat glands. Most common mutation → misfolded protein → protein retained in RER and not transported to cell membrane, causing ↓ Cl <sup>-</sup> (and H <sub>2</sub> O) secretion; ↑ intracellular Cl <sup>-</sup> results in compensatory ↑ Na <sup>+</sup> reabsorption via epithelial Na <sup>+</sup> channels (ENaC) → ↑ H <sub>2</sub> O reabsorption → abnormally thick mucus secreted into lungs and GI tract. ↑ Na <sup>+</sup> reabsorption also causes more negative transepithelial potential difference.
DIAGNOSIS	↑ Cl <sup>-</sup> concentration in pilocarpine-induced sweat test is diagnostic. Can present with contraction alkalosis and hypokalemia (ECF effects analogous to a patient taking a loop diuretic) because of ECF H <sub>2</sub> O/Na <sup>+</sup> losses via sweating and concomitant renal K <sup>+</sup> /H <sup>+</sup> wasting. ↑ immunoreactive trypsinogen (newborn screening).
COMPLICATIONS	Recurrent pulmonary infections (eg, <i>S aureus</i> [infancy and early childhood], <i>P aeruginosa</i> [adulthood], allergic bronchopulmonary aspergillosis [ABPA]), chronic bronchitis and bronchiectasis → reticulonodular pattern on CXR, opacification of sinuses.  Pancreatic insufficiency, malabsorption with steatorrhea, fat-soluble vitamin deficiencies (A, D, E, K), biliary cirrhosis, liver disease. Meconium ileus in newborns.  Infertility in men (absence of vas deferens, spermatogenesis may be unaffected) and subfertility in women (amenorrhea, abnormally thick cervical mucus).  Nasal polyps, clubbing of nails.
TREATMENT	Multifactorial: chest physiotherapy, albuterol, aerosolized dornase alfa (DNase), and hypertonic

Multifactorial: chest physiotherapy, albuterol, aerosolized dornase alfa (DNase), and hypertonic saline facilitate mucus clearance. Azithromycin used as anti-inflammatory agent. Ibuprofen slows disease progression. Pancreatic enzyme replacement therapy for pancreatic insufficiency. In patients with Phe508 deletion: combination of lumacaftor (corrects misfolded proteins and improves their transport to cell surface) and ivacaftor (opens Cl⁻ channels → improved chloride transport).



Ŗ

FAS1\_2019\_01-Biochem.indd 60 11/7/19 3:16 PM

## X-linked recessive disorders

Ornithine transcarbamylase deficiency, Fabry disease, Wiskott-Aldrich syndrome, Ocular albinism, G6PD deficiency, Hunter syndrome, Bruton agammaglobulinemia, Hemophilia A and B, Lesch-Nyhan syndrome, Duchenne (and Becker) muscular dystrophy.

X-inactivation (lyonization)—one copy of female X chromosome forms a transcriptionally inactive Barr body. Female carriers variably affected depending on the pattern of inactivation of the X chromosome carrying the mutant vs normal gene.

Oblivious Female Will Often Give Her Boys Her x-Linked Disorders

Females with Turner syndrome (45,XO) are more likely to have an X-linked recessive disorder.

### **Muscular dystrophies**

#### **Duchenne**



X-linked disorder typically due to **frameshift** deletions or nonsense mutations → truncated or absent dystrophin protein → progressive myofiber damage. Weakness begins in pelvic girdle muscles and progresses superiorly. Pseudohypertrophy of calf muscles due to fibrofatty replacement of muscle A. Waddling gait.

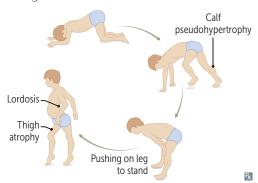
Onset before 5 years of age. Dilated cardiomyopathy is common cause of death.

**Gowers sign**—patient uses upper extremities to help stand up. Classically seen in Duchenne muscular dystrophy, but also seen in other muscular dystrophies and inflammatory myopathies (eg, polymyositis).

Duchenne = deleted dystrophin.

Dystrophin gene (*DMD*) is the largest protein-coding human gene  $\rightarrow \uparrow$  chance of spontaneous mutation. Dystrophin helps anchor muscle fibers, primarily in skeletal and cardiac muscle. It connects the intracellular cytoskeleton (actin) to the transmembrane proteins  $\alpha$ - and  $\beta$ -dystroglycan, which are connected to the extracellular matrix (ECM). Loss of dystrophin  $\rightarrow$  myonecrosis.

† CK and aldolase; genetic testing confirms diagnosis.



#### **Becker**

X-linked disorder typically due to **non-frameshift** deletions in dystrophin gene (partially functional instead of truncated).

Less severe than Duchenne (**B**ecker is **b**etter).

Onset in adolescence or early adulthood.

Deletions can cause both Duchenne and Becker muscular dystrophies. 3/3 of cases have large deletions spanning one or more exons.

#### Myotonic dystrophy

Autosomal dominant. **CTG** trinucleotide repeat expansion in the *DMPK* gene → abnormal expression of myotonin protein kinase → myotonia (eg, difficulty releasing hand from handshake), muscle wasting, cataracts, testicular atrophy, frontal balding, arrhythmia.

Autosomal dominant. CTG trinucleotide repeat cataracts, Toupee (early balding in men), Gonadal expansion in the *DMPK* gene → abnormal atrophy.

FAS1\_2019\_01-Biochem.indd 61 11/7/19 3:16 PM

#### **Rett syndrome**

Sporadic disorder seen almost exclusively in girls (affected males die in utero or shortly after birth). Most cases are caused by de novo mutation of *MECP2* on X chromosome. Symptoms of **Rett** syndrome usually appear between ages 1–4 and are characterized by regression (**Rett**urn) in motor, verbal, and cognitive abilities; ataxia; seizures; growth failure; and stereotyped handwringing.

#### Fragile X syndrome

X-linked dominant inheritance. Trinucleotide repeat in *FMR1* gene → hypermethylation → ↓ expression. Most common inherited cause of intellectual disability (Down syndrome is the most common genetic cause, but most cases occur sporadically).

Findings: post-pubertal macroorchidism (enlarged testes), long face with a large jaw, large everted ears, autism, mitral valve prolapse, hypermobile joints.

Trinucleotide repeat expansion  $[(CGG)_n]$  occurs during oogenesis.

## Trinucleotide repeat expansion diseases

Huntington disease, myotonic dystrophy, fragile X syndrome, and Friedreich ataxia.

May show genetic anticipation (disease severity

↑ and age of onset ↓ in successive generations).

Try (trinucleotide) hunting for my fragile cagefree eggs (X).

DISEASE	TRINUCLEOTIDE REPEAT	MODE OF INHERITANCE	MNEMONIC
<b>Huntington disease</b>	$(CAG)_n$	AD	Caudate has ↓ ACh and GABA
Myotonic dystrophy	(CTG) <sub>n</sub>	AD	Cataracts, Toupee (early balding in men), Gonadal atrophy in men, reduced fertility in women
Fragile X syndrome	$(\mathbf{CGG})_{n}$	XD	Chin (protruding), Giant Gonads
Friedreich ataxia	(GAA) <sub>n</sub>	AR	Ataxic <b>GAA</b> it

FAS1\_2019\_01-Biochem.indd 62 11/7/19 3:16 PM

#### **Autosomal trisomies**

## Down syndrome (trisomy 21)



Single palmar crease

Findings: intellectual disability, flat facies, prominent epicanthal folds, single palmar crease, incurved 5th finger, gap between 1st 2 toes, duodenal atresia, Hirschsprung disease, congenital heart disease (eg, ASD), Brushfield spots. Associated with early-onset Alzheimer disease (chromosome 21 codes for amyloid precursor protein), † risk of AML/ALL.

95% of cases due to meiotic nondisjunction († with advanced maternal age; from 1:1500 in women < 20 to 1:25 in women > 45 years old).

4% of cases due to unbalanced Robertsonian translocation, most typically between chromosomes 14 and 21. Only 1% of cases are due to postfertilization mitotic error.

Incidence 1:700.

Drinking age (21).

Most common viable chromosomal disorder and most common cause of genetic intellectual disability.

First-trimester ultrasound commonly shows

† nuchal translucency and hypoplastic nasal
bone. Markers for Down syndrome are HI up:
† hCG, † inhibin.

The **5 A**'s of Down syndrome:

- Advanced maternal age
- Atresia (duodenal)
- Atrioventricular septal defect
- Alzheimer disease (early onset)
- AML/ALL

Edwards syndrome (trisomy 18)



Overlapping fingers 🛚

Findings: PRINCE Edward—Prominent occiput, Rocker-bottom feet, Intellectual disability, Nondisjunction, Clenched fists with overlapping fingers, low-set Ears, micrognathia (small jaw), congenital heart disease, omphalocele, myelomeningocele. Death usually occurs by age 1 year.

Incidence 1:8000.

Election age (18).

2nd most common autosomal trisomy resulting in live birth (most common is Down syndrome).

## Patau syndrome (trisomy 13)



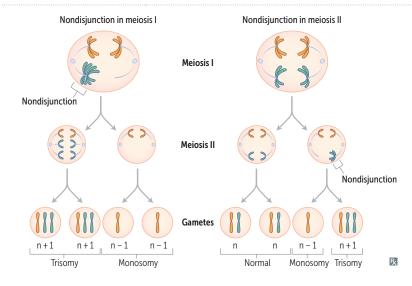
Cutis aplasia

Findings: severe intellectual disability, rockerbottom feet, microphthalmia, microcephaly, cleft liP/Palate, holoProsencephaly, Polydactyly, cutis aPlasia, congenital heart (Pump) disease, Polycystic kidney disease, omphalocele. Death usually occurs by age 1. Incidence 1:15,000.

Puberty (13).

Defect in fusion of prechordal mesoderm

→ midline defects.



1st trimester screening				
Trisomy	β-hCG	PAPP-A		
21	t	1		
18	<b>1</b>	1		
13	1	1		

2nd trim	2nd trimester screening				
Trisomy	β-hCG	Inhibin A	Estriol	AFP	
21	t	t	1	ţ	
18	1	— or ↓	1	ţ	
13	_	_	_	_	

FAS1\_2019\_01-Biochem.indd 63 11/7/19 3:16 PM

## Genetic disorders by chromosome

CHROMOSOME	SELECTED EXAMPLES	
3	von Hippel-Lindau disease, renal cell carcinoma	
4	ADPKD (PKD2), achondroplasia, Huntington disease	
5	Cri-du-chat syndrome, familial adenomatous polyposis	
6	Hemochromatosis (HFE)	
7	Williams syndrome, cystic fibrosis	
9	Friedreich ataxia, tuberous sclerosis (TSCl)	
11	Wilms tumor, $\beta$ -globin gene defects (eg, sickle cell disease, $\beta$ -thalassemia), MEN1	
13	Patau syndrome, Wilson disease, retinoblastoma (RB1), BRCA2	
15	Prader-Willi syndrome, Angelman syndrome, Marfan syndrome	
16	ADPKD (PKD1), $\alpha$ -globin gene defects (eg, $\alpha$ -thalassemia), tuberous sclerosis (TSC2)	
17	Neurofibromatosis type 1, BRCA1, TP53	
18	Edwards syndrome	
21	Down syndrome	
22	Neurofibromatosis type 2, DiGeorge syndrome (22q11)	
X	Fragile X syndrome, X-linked agammaglobulinemia, Klinefelter syndrome (XXY)	

## Robertsonian translocation

Chromosomal translocation that commonly involves chromosome pairs 21, 22, 13, 14, and 15. One of the most common types of translocation. Occurs when the long arms of 2 acrocentric chromosomes (chromosomes with centromeres near their ends) fuse at the centromere and the 2 short arms are lost.

Balanced translocations normally do not cause any abnormal phenotype. Unbalanced translocations can result in miscarriage, stillbirth, and chromosomal imbalance (eg, Down syndrome, Patau syndrome).

#### **Cri-du-chat syndrome**

*Cri du chat* = **cry** of the **cat**. Congenital deletion on short arm of chromosome 5 (46,XX or XY, 5p–).

Findings: microcephaly, moderate to severe intellectual disability, high-pitched **cry**ing/**meow**ing, epicanthal folds, cardiac abnormalities (VSD).

#### Williams syndrome



Congenital microdeletion of long arm of chromosome 7 (deleted region includes elastin gene). Findings: distinctive "elfin" facies A, intellectual disability, hypercalcemia, well-developed verbal skills, extreme friendliness with strangers, cardiovascular problems (eg, supravalvular aortic stenosis, renal artery stenosis). Think Will Ferrell in Elf.

FAS1\_2019\_01-Biochem.indd 64 11/7/19 3:16 PM

#### ▶ BIOCHEMISTRY—NUTRITION

#### Vitamins: fat soluble

A, D, E, K. Absorption dependent on ileum and pancreas. Toxicity more common than for water-soluble vitamins because fat-soluble vitamins accumulate in fat.

Malabsorption syndromes with steatorrhea (eg, cystic fibrosis and celiac disease) or mineral oil intake can cause fat-soluble vitamin deficiencies.

#### Vitamins: water soluble

B<sub>1</sub> (thiamine: TPP)

B<sub>2</sub> (riboflavin: FAD, FMN)

B<sub>3</sub> (niacin: NAD<sup>+</sup>)

B<sub>5</sub> (pantothenic acid: CoA) B<sub>6</sub> (pyridoxine: PLP)

B<sub>7</sub> (biotin) B<sub>9</sub> (folate)  $B_{12}$  (cobalamin) C (ascorbic acid) All wash out easily from body except B<sub>12</sub> and B<sub>9</sub> (folate).  $B_{12}$  stored in liver for  $\sim 3-4$  years.  $B_9$ stored in liver for  $\sim 3-4$  months.

B-complex deficiencies often result in dermatitis, glossitis, and diarrhea. Can be coenzymes (eg, ascorbic acid) or precursors to coenzymes (eg, FAD, NAD+).

FAS1\_2019\_01-Biochem.indd 65 11/7/19 3:16 PM **SECTION II** 

#### **BIOCHEMISTRY** ▶ BIOCHEMISTRY—NUTRITION

#### **Vitamin A**

Includes retinal, retinol, retinoic acid.

FUNCTION

Antioxidant; constituent of visual pigments (retinal); essential for normal differentiation of epithelial cells into specialized tissue (pancreatic cells, mucus-secreting cells); prevents squamous metaplasia. Used to treat measles and acute promyelocytic leukemia (APL).

Retinol is vitamin A, so think retin-A (used topically for wrinkles and Acne).
Found in liver and leafy vegetables.
Supplementation in vitamin A-deficient measles patients may improve outcomes.
Use oral isotretinoin to treat severe cystic acne.
Use all-trans retinoic acid to treat acute

#### DEFICIENCY



Night blindness (nyctalopia); dry, scaly skin (xerosis cutis); corneal squamous metaplasia → Bitot spots (keratin debris; foamy appearance on conjunctiva A); corneal degeneration (keratomalacia); immunosuppression.

**EXCESS** 

Acute toxicity—nausea, vomiting, vertigo, and blurred vision.

Chronic toxicity—alopecia, dry skin (eg, scaliness), hepatic toxicity and enlargement, arthralgias, and idiopathic intracranial hypertension.

Teratogenic (cleft palate, cardiac abnormalities), therefore a ⊖ pregnancy test and two forms of contraception are required before isotretinoin (vitamin A derivative) is prescribed.

Isotretinoin is teratogenic.

promyelocytic leukemia.

#### Vitamin B<sub>1</sub>

Also called thiamine.

FUNCTION

In thiamine pyrophosphate (TPP), a cofactor for several dehydrogenase enzyme reactions:

- Branched-chain ketoacid dehydrogenase
- α-ketoglutarate dehydrogenase (TCA cycle)
- Pyruvate dehydrogenase (links glycolysis to TCA cycle)
- Transketolase (HMP shunt)

DEFICIENCY

Impaired glucose breakdown → ATP depletion worsened by glucose infusion; highly aerobic tissues (eg, brain, heart) are affected first. In alcoholic or malnourished patients, give thiamine before dextrose to ↓ risk of precipitating Wernicke encephalopathy. Diagnosis made by ↑ in RBC transketolase activity following vitamin B₁ administration.

Be APT.

Spell beriberi as BerlBerl to remember vitamin B<sub>1</sub>.

Wernicke encephalopathy—acute, lifethreatening, neurologic condition; classic triad of confusion, ophthalmoplegia, ataxia.

Korsakoff syndrome—amnestic disorder due to chronic alcohol consumption; presents with confabulation, personality changes, memory loss (permanent).

Wernicke-Korsakoff syndrome—damage to medial dorsal nucleus of thalamus, mammillary bodies. Presentation is combination of Wernicke encephalopathy and Korsakoff syndrome.

**Dry beriberi**—polyneuropathy, symmetric muscle wasting.

Wet beriberi—high-output cardiac failure (dilated cardiomyopathy), edema.

FAS1\_2019\_01-Biochem.indd 66 11/7/19 3:16 PM

Vitamin B₂	Also called riboflavin.	
FUNCTION	Component of flavins FAD and FMN, used as cofactors in redox reactions, eg, the succinate dehydrogenase reaction in the TCA cycle.	FAD and FMN are derived from riboFlavin (B <sub>2</sub> $\approx$ 2 ATP).
DEFICIENCY	Cheilosis (inflammation of lips, scaling and fissures at the corners of the mouth), Corneal vascularization.	The 2 C's of B <sub>2</sub> .
Vitamin B₃	Also called niacin, nicotinic acid.	
FUNCTION	Constituent of NAD <sup>+</sup> , NADP <sup>+</sup> (used in redox reactions). Derived from tryptophan. Synthesis requires vitamins B <sub>2</sub> and B <sub>6</sub> . Used to treat dyslipidemia; lowers levels of VLDL and raises levels of HDL.	NAD derived from Niacin ( $B_3 \approx 3$ ATP).
DEFICIENCY	Glossitis. Severe deficiency leads to pellagra, which can also be caused by Hartnup disease, malignant carcinoid syndrome († tryptophan metabolism), and isoniazid (‡ vitamin B <sub>6</sub> ). Symptoms of pellagra: Diarrhea, Dementia (also hallucinations), Dermatitis (C3/C4 dermatome circumferential "broad collar" rash [Casal necklace], hyperpigmentation of sunexposed limbs A).	The 3 D's of B <sub>3</sub> .  Hartnup disease—autosomal recessive.  Deficiency of neutral amino acid (eg, tryptophan) transporters in proximal renal tubular cells and on enterocytes → neutral aminoaciduria and ↓ absorption from the gut → ↓ tryptophan for conversion to niacin → pellagra-like symptoms. Treat with highprotein diet and nicotinic acid.  Deficiency of vitamin B <sub>3</sub> → pellagra.
EXCESS	Facial flushing (induced by prostaglandin, not histamine; can avoid by taking aspirin with niacin), hyperglycemia, hyperuricemia.	Excess of vitamin $B_3 \rightarrow \mathbf{pod}$ agra.
Vitamin B₅	Also called pantothenic acid.	
FUNCTION	Essential component of coenzyme A (CoA, a cofactor for acyl transfers) and fatty acid synthase.	B <sub>5</sub> is "pento" thenic acid.
DEFICIENCY	Dermatitis, enteritis, alopecia, adrenal insufficiency.	
Vitamin B <sub>6</sub>	Also called pyridoxine.	
FUNCTION	Converted to pyridoxal phosphate (PLP), a cofactor used in transamination (eg, ALT and AST), decarboxylation reactions, glycogen phosphorylase. Synthesis of glutathione, cystathionine, heme, niacin, histamine, and neurotransmitters including serotonin, epinephrine, norepinephrine (NE), dopamine, and GABA.	
DEFICIENCY	Convulsions, hyperirritability, peripheral neuropathy (deficiency inducible by isoniazid and oral contraceptives), sideroblastic anemia (due to impaired hemoglobin synthesis and iron excess).	

11/7/19 3:16 PM FAS1\_2019\_01-Biochem.indd 67

68 SECTION II

### BIOCHEMISTRY → BIOCHEMISTRY—NUTRITION

Vitamin B <sub>7</sub> Also called biotin.		
FUNCTION	Cofactor for carboxylation enzymes (which add a 1-carbon group):  ■ Pyruvate carboxylase: pyruvate (3C)  → oxaloacetate (4C)  ■ Acetyl-CoA carboxylase: acetyl-CoA (2C)  → malonyl-CoA (3C)  ■ Propionyl-CoA carboxylase: propionyl-CoA (3C) → methylmalonyl-CoA (4C)	
DEFICIENCY	Relatively rare. Dermatitis, enteritis, alopecia.  Caused by long-term antibiotic use or excessive ingestion of raw egg whites.	"Avidin in egg whites avidly binds biotin."
Vitamin B <sub>9</sub>	Also called folate.	
FUNCTION	Converted to tetrahydrofolic acid (THF), a coenzyme for 1-carbon transfer/methylation reactions.  Important for the synthesis of nitrogenous bases in DNA and RNA.	Found in leafy green vegetables. Absorbed in jejunum. Folate from foliage. Small reserve pool stored primarily in the liver.
DEFICIENCY	Macrocytic, megaloblastic anemia; hypersegmented polymorphonuclear cells (PMNs); glossitis; no neurologic symptoms (as opposed to vitamin B₁₂ deficiency). Labs: ↑ homocysteine, normal methylmalonic acid levels. Seen in alcoholism and pregnancy.	Deficiency can be caused by several drugs (eg, phenytoin, sulfonamides, methotrexate).  Supplemental maternal folic acid at least 1 month prior to conception and during early pregnancy to \$\frac{1}{2}\$ risk of neural tube defects. Give vitamin B <sub>9</sub> for the 9 months of pregnancy.

FAS1\_2019\_01-Biochem.indd 68 11/7/19 3:16 PM

Vitamin B <sub>12</sub>	Also called cobalamin.		
FUNCTION	Cofactor for methionine synthase (transfers CH <sub>3</sub> groups as methylcobalamin) and methylmalonyl-CoA mutase. Important for DNA synthesis.	Found in animal products.  Synthesized only by microorganisms. Very larger reserve pool (several years) stored primarily in the liver. Deficiency caused by malabsorption	
DEFICIENCY	Macrocytic, megaloblastic anemia; hypersegmented PMNs; paresthesias and subacute combined degeneration (degeneration of dorsal columns, lateral corticospinal tracts, and spinocerebellar tracts) due to abnormal myelin. Associated with ↑ serum homocysteine and methylmalonic acid levels, along with 2° folate deficiency. Prolonged deficiency → irreversible nerve damage.	(eg, sprue, enteritis, <i>Diphyllobothrium latum</i> , achlorhydria, bacterial overgrowth, alcohol excess), lack of intrinsic factor (eg, pernicious anemia, gastric bypass surgery), absence of terminal ileum (surgical resection, eg, for Crohn disease), certain drugs (eg, metformin), or insufficient intake (eg, veganism).  Anti-intrinsic factor antibodies diagnostic for pernicious anemia.  Folate supplementation can mask the hematologic symptoms of B <sub>12</sub> deficiency, but not the neurologic symptoms.	
	Protein	Fatty acids with odd number of carbons, branched-chain amino acids	
	THF-CH <sub>3</sub> Methionine $\longrightarrow$ SAM  Methionine synthase  Homocysteine $B_6$ Adenosin	CH <sub>3</sub> to anabolic pathways  S-adenosyl homocysteine  Methylmalonyl-CoA mutase  Succinyl-CoA  Heme  TCA	
	Cysteine	B	

Vitamin C	Also called ascorbic acid.	
FUNCTION	Antioxidant; also facilitates iron absorption by reducing it to Fe <sup>2+</sup> state. Necessary for hydroxylation of proline and lysine in collagen synthesis. Necessary for dopamine β-hydroxylase, which converts dopamine to NE.	Found in fruits and vegetables. Pronounce "absorbic" acid. Ancillary treatment for methemoglobinemia by reducing Fe <sup>3+</sup> to Fe <sup>2+</sup> .
DEFICIENCY	Scurvy—swollen gums, easy bruising, petechiae, hemarthrosis, anemia, poor wound healing, perifollicular and subperiosteal hemorrhages, "corkscrew" hair.  Weakened immune response.	Vitamin C deficiency causes sCurvy due to a Collagen synthesis defect.
EXCESS	Nausea, vomiting, diarrhea, fatigue, calcium oxalate nephrolithiasis. Can † iron toxicity in predisposed individuals by increasing dietary iron absorption (ie, can worsen hereditary hemochromatosis or transfusion-related iron overload).	

FAS1\_2019\_01-Biochem.indd 69 11/7/19 3:16 PM

#### 70

### SECTION II

### **BIOCHEMISTRY** ► BIOCHEMISTRY—NUTRITION

Vitamin D	<ul> <li>D<sub>3</sub> (cholecalciferol) from exposure of skin (stratum basale) to sun, ingestion of fish, milk, plants.</li> <li>D<sub>2</sub> (ergocalciferol) from ingestion of plants, fungi, yeasts.</li> <li>Both converted to 25-OH D<sub>3</sub> (storage form) in liver and to the active form 1,25-(OH)<sub>2</sub> D<sub>3</sub> (calcitriol) in kidney.</li> </ul>
FUNCTION	† intestinal absorption of Ca <sup>2+</sup> and PO <sub>4</sub> <sup>3-</sup> .  † bone mineralization at low levels.  † bone resorption at higher levels.
REGULATION	<ul> <li>↑ PTH, ↓ Ca<sup>2+</sup>, ↓ PO<sub>4</sub><sup>3-</sup> → ↑ 1,25-(OH)<sub>2</sub>D<sub>3</sub> production.</li> <li>1,25-(OH)<sub>2</sub>D<sub>3</sub> feedback inhibits its own production.</li> <li>↑ PTH → ↑ Ca<sup>2+</sup> reabsorption and ↓ PO<sub>4</sub><sup>3-</sup> reabsorption in the kidney.</li> </ul>
DEFICIENCY	Disloste in children (defermite such as gone yarum "handasa" 🐧 actes malacia in adulte (hana

#### DEFICIENCY



Rickets in children (deformity, such as genu varum "bowlegs" A), osteomalacia in adults (bone pain and muscle weakness), hypocalcemic tetany.

Caused by malabsorption, ↓ sun exposure, poor diet, chronic kidney disease (CKD), advanced liver disease.

Give oral vitamin D to breastfed infants.

Deficiency is exacerbated by pigmented skin, premature birth.

EXCESS

Hypercalcemia, hypercalciuria, loss of appetite, stupor. Seen in granulomatous diseases († activation of vitamin D by epithelioid macrophages).

Vitamin E	Includes tocopherol, tocotrienol.	
FUNCTION	Antioxidant (protects RBCs and membranes from free radical damage).	
DEFICIENCY	Hemolytic anemia, acanthocytosis, muscle weakness, demyelination of posterior columns (‡ position and vibration sensation) and spinocerebellar tract (ataxia).	Neurologic presentation may appear similar to vitamin B <sub>12</sub> deficiency, but without megaloblastic anemia, hypersegmented neutrophils, or † serum methylmalonic acid levels.
EXCESS	Risk of enterocolitis in infants.	High-dose supplementation may alter metabolism of vitamin K → enhanced anticoagulant effects of warfarin.

FAS1\_2019\_01-Biochem.indd 70 11/7/19 3:16 PM

Vitamin K	Includes phytomenadione, phylloquinone, phytonadione, menaquinone.	
FUNCTION	Activated by epoxide reductase to the reduced form, which is a cofactor for the γ-carboxylation of glutamic acid residues on various proteins required for blood clotting. Synthesized by intestinal flora.	K is for Koagulation. Necessary for the maturation of clotting factors II, VII, IX, X, and proteins C and S. Warfarin inhibits vitamin K–dependent synthesis of these factors and proteins.
DEFICIENCY	Neonatal hemorrhage with † PT and † aPTT but normal bleeding time (neonates have sterile intestines and are unable to synthesize vitamin K). Can also occur after prolonged use of broad-spectrum antibiotics.	Not in breast milk; neonates are given vitamin K injection at birth to prevent hemorrhagic disease of the newborn.

#### **Zinc**

FUNCTION

Mineral essential for the activity of 100+ enzymes. Important in the formation of zinc fingers (transcription factor motif).

#### DEFICIENCY



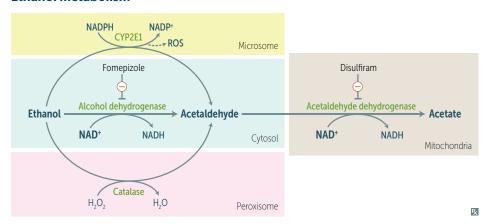
Delayed wound healing, suppressed immunity, male hypogonadism, \$\dagger\$ adult hair (axillary, facial, pubic), dysgeusia, anosmia. Associated with acrodermatitis enteropathica (\$\bar{A}\$, defect in intestinal zinc absorption). May predispose to alcoholic cirrhosis.

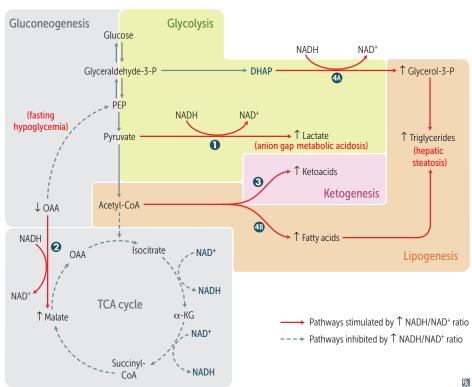
#### **Protein-energy malnutrition**

Kwashiorkor	Protein malnutrition resulting in skin lesions, edema due to ↓ plasma oncotic pressure, liver malfunction (fatty change due to ↓ apolipoprotein synthesis). Clinical picture is small child with swollen abdomen ♣.  Kwashiorkor results from protein- deficient MEALS: Malnutrition Edema Anemia Liver (fatty) Skin lesions (eg, hyperkeratosis, dyspigmentation)	A CONTRACTOR OF THE PARTY OF TH	B
Marasmus	Malnutrition not causing edema. Diet is deficient in calories but no nutrients are entirely absent.  Marasmus results in Muscle wasting B.		

FAS1\_2019\_01-Biochem.indd 71 11/7/19 3:16 PM

#### **Ethanol metabolism**





Fomepizole—blocks alcohol
DH; antidote For Overdoses of
Methanol or Ethylene glycol.
Disulfiram— blocks acetaldehyde
dehydrogenase → ↑ acetaldehyde
→ ↑ hangover symptoms
→ discouraging drinking.
NAD+ is the limiting reagent.

Alcohol dehydrogenase operates via

zero-order kinetics.

Ethanol metabolism † NADH/ NAD+ ratio in liver, causing:

- Lactic acidosis—† pyruvate conversion to lactate
- Fasting hypoglycemia— ↓ gluconeogenesis due to ↑ conversion of OAA to malate
- **3** Ketoacidosis—diversion of acetyl-CoA into ketogenesis rather than TCA cycle
- ◆ Hepatosteatosis— ↑ conversion of DHAP to glycerol-3-P
   ♠; acetyl-CoA diverges into fatty acid synthesis
   ♠, which combines with glycerol-3-P to synthesize triglycerides
- ↑ NADH/NAD<sup>+</sup> ratio inhibits TCA cycle → ↑ acetyl-CoA used in ketogenesis (→ ketoacidosis), lipogenesis (→ hepatosteatosis).

#### ▶ BIOCHEMISTRY—METABOLISM

#### **Metabolism sites**

Mitochondria	Fatty acid oxidation (β-oxidation), acetyl- CoA production, TCA cycle, oxidative phosphorylation, ketogenesis.	
Cytoplasm	Glycolysis, HMP shunt, and synthesis of cholesterol (SER), proteins (ribosomes, RER), fatty acids, and nucleotides.	
Both	Heme synthesis, Urea cycle, Gluconeogenesis. HUGs take two (both).	

FAS1\_2019\_01-Biochem.indd 72 11/7/19 3:16 PM

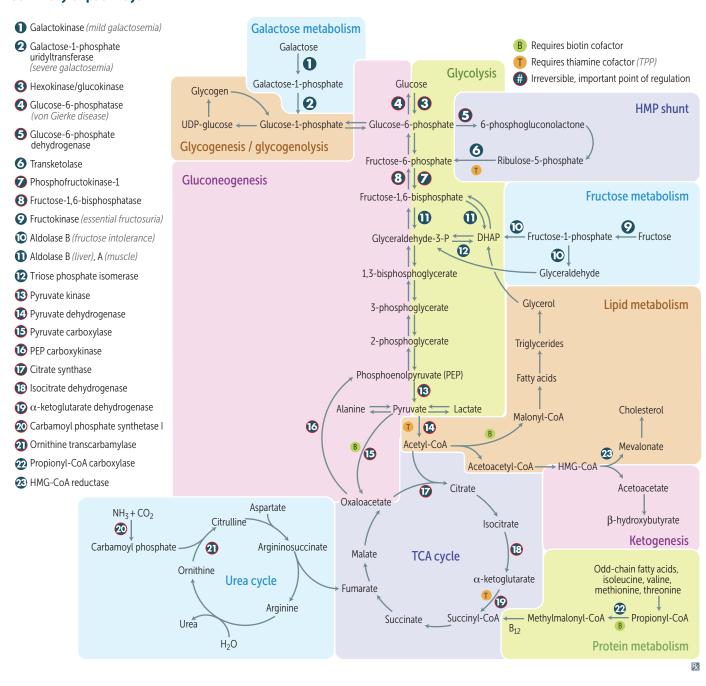
Enzyme terminology	An enzyme's name often describes its function. For example, glucokinase is an enzyme that catalyzes the phosphorylation of glucose using a molecule of ATP. The following are commonly used enzyme descriptors.	
Kinase	Catalyzes transfer of a phosphate group from a high-energy molecule (usually ATP) to a substrate (eg, phosphofructokinase).	
Phosphorylase	Adds inorganic phosphate onto substrate without using ATP (eg, glycogen phosphorylase).	
Phosphatase	Removes phosphate group from substrate (eg, fructose-1,6-bisphosphatase).	
Dehydrogenase	Catalyzes oxidation-reduction reactions (eg, pyruvate dehydrogenase).	
Hydroxylase	Adds hydroxyl group (-OH) onto substrate (eg, tyrosine hydroxylase).	
Carboxylase	Transfers CO <sub>2</sub> groups with the help of biotin (eg, pyruvate carboxylase).	
Mutase	Relocates a functional group within a molecule (eg, vitamin $B_{12}$ –dependent methylmalonyl-CoA mutase).	
Synthase/synthetase	Joins two molecules together using a source of energy (eg, ATP, acetyl-CoA, nucleotide sugar).	

#### Rate-determining enzymes of metabolic processes

PROCESS	ENZYME	REGULATORS
Glycolysis	Phosphofructokinase-l (PFK-l)	AMP $\oplus$ , fructose-2,6-bisphosphate $\oplus$ ATP $\ominus$ , citrate $\ominus$
Gluconeogenesis	Fructose-1,6-bisphosphatase	$AMP \ominus$ , fructose-2,6-bisphosphate $\ominus$
TCA cycle	Isocitrate dehydrogenase	ADP ⊕ ATP ⊝, NADH ⊝
Glycogenesis	Glycogen synthase	Glucose-6-phosphate ⊕, insulin ⊕, cortisol ⊕ Epinephrine ⊝, glucagon ⊝
Glycogenolysis	Glycogen phosphorylase	Epinephrine $\oplus$ , glucagon $\oplus$ , AMP $\oplus$ Glucose-6-phosphate $\ominus$ , insulin $\ominus$ , ATP $\ominus$
HMP shunt	Glucose-6-phosphate dehydrogenase (G6PD)	NADP⁺ ⊕ NADPH ⊝
De novo pyrimidine synthesis	Carbamoyl phosphate synthetase II	ATP ⊕, PRPP ⊕ UTP ⊝
De novo purine synthesis	Glutamine-phosphoribosylpyrophosphate (PRPP) amidotransferase	AMP $\ominus$ , inosine monophosphate (IMP) $\ominus$ , GMP $\ominus$
Urea cycle	Carbamoyl phosphate synthetase I	N-acetylglutamate ⊕
Fatty acid synthesis	Acetyl-CoA carboxylase (ACC)	Insulin ⊕, citrate ⊕ Glucagon ⊝, palmitoyl-CoA ⊝
Fatty acid oxidation	Carnitine acyltransferase I	Malonyl-CoA ⊝
Ketogenesis	HMG-CoA synthase	
Cholesterol synthesis	HMG-CoA reductase	Insulin ⊕, thyroxine ⊕, estrogen ⊕ Glucagon ⊝, cholesterol ⊝

11/7/19 3:16 PM FAS1\_2019\_01-Biochem.indd 73

#### **Summary of pathways**



#### **ATP production**

Aerobic metabolism of one glucose molecule produces 32 net ATP via malate-aspartate shuttle (heart and liver), 30 net ATP via glycerol-3-phosphate shuttle (muscle).

Anaerobic glycolysis produces only 2 net ATP per glucose molecule.

ATP hydrolysis can be coupled to energetically unfavorable reactions.

Arsenic causes glycolysis to produce zero net ATP.

FAS1\_2019\_01-Biochem.indd 74 11/7/19 3:16 PM

#### **Activated carriers**

CARRIER MOLECULE	CARRIED IN ACTIVATED FORM
ATP	Phosphoryl groups
NADH, NADPH, FADH <sub>2</sub>	Electrons
CoA, lipoamide	Acyl groups
Biotin	$CO_2$
Tetrahydrofolates	l-carbon units
S-adenosylmethionine (SAM)	CH₃ groups
TPP	Aldehydes

## Universal electron acceptors

Nicotinamides (NAD<sup>+</sup>, NADP<sup>+</sup> from vitamin B<sub>3</sub>) and flavin nucleotides (FAD from vitamin B<sub>2</sub>).

NAD<sup>+</sup> is generally used in **catabolic** processes to carry reducing equivalents away as NADH.

NADPH is used in **anabolic** processes (eg, steroid and fatty acid synthesis) as a supply of reducing equivalents.

NADPH is a product of the HMP shunt. NADPH is used in:

- Anabolic processes
- Respiratory burst
- Cytochrome P-450 system
- Glutathione reductase

### Hexokinase vs glucokinase

Phosphorylation of glucose to yield glucose-6-phosphate is catalyzed by glucokinase in the liver and hexokinase in other tissues. Hexokinase sequesters glucose in tissues, where it is used even when glucose concentrations are low. At high glucose concentrations, glucokinase helps to store glucose in liver.

	Hexokinase	Glucokinase
Location	Most tissues, except liver and pancreatic $\beta$ cells	Liver, $\beta$ cells of pancreas
K <sub>m</sub>	Lower († affinity)	Higher (↓ affinity)
V <sub>max</sub>	Lower (‡ capacity)	Higher († capacity)
Induced by insulin	No	Yes
Feedback inhibition by	Glucose-6-phosphate	Fructose-6-phosphate

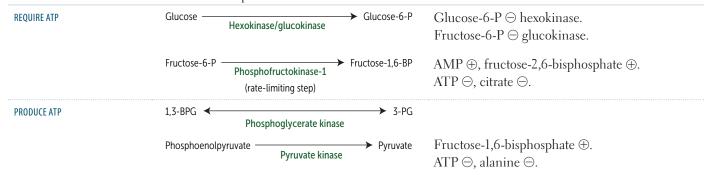
FAS1\_2019\_01-Biochem.indd 75 11/7/19 3:16 PM

## Glycolysis regulation, key enzymes

Net glycolysis (cytoplasm):

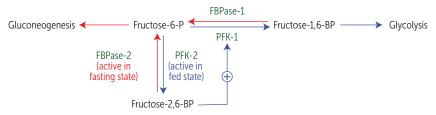
Glucose + 2  $P_i$  + 2 ADP + 2  $NAD^+$   $\rightarrow$  2 pyruvate + 2 ATP + 2 NADH + 2  $H^+$  + 2  $H_2O$ .

Equation not balanced chemically, and exact balanced equation depends on ionization state of reactants and products.



# Regulation by fructose-2,6-bisphosphate

Fructose bisphosphatase-2 (FBPase-2) and phosphofructokinase-2 (PFK-2) are the same bifunctional enzyme whose function is reversed by phosphorylation by protein kinase A.



Fasting state: ↑ glucagon → ↑ cAMP → ↑ protein kinase A → ↑ FBPase-2, ↓ PFK-2, less glycolysis, more gluconeogenesis.

FaBian the Peasant (FBP) has to work hard when starving.

Fed state: ↑ insulin → ↓ cAMP → ↓ protein kinase A → ↓ FBPase-2, ↑ PFK-2, more glycolysis, less gluconeogenesis.

Prince FredericK (PFK) works only when fed.

# Pyruvate dehydrogenase complex

Mitochondrial enzyme complex linking glycolysis and TCA cycle. Differentially regulated in fed (active)/fasting (inactive) states. Reaction: pyruvate + NAD+ + CoA → acetyl-CoA + CO<sub>2</sub> + NADH.

Contains 3 enzymes requiring 5 cofactors:

- 1. Thiamine pyrophosphate (B<sub>1</sub>)
- 2. Lipoic acid
- 3. CoA (B<sub>5</sub>, pantothenic acid)
- 4. FAD (B<sub>2</sub>, riboflavin)
- 5. NAD<sup>+</sup> (B<sub>3</sub>, niacin)

Activated by: ↑ NAD+/NADH ratio, ↑ ADP ↑ Ca<sup>2+</sup>.

The complex is similar to the α-ketoglutarate dehydrogenase complex (same cofactors, similar substrate and action), which converts α-ketoglutarate → succinyl-CoA (TCA cycle).

The Lovely Coenzymes For Nerds.

Arsenic inhibits lipoic acid. Arsenic poisoning clinical findings: imagine a vampire (pigmentary skin changes, skin cancer), vomiting and having diarrhea, running away from a cutie (QT prolongation) with garlic breath.

FAS1\_2019\_01-Biochem.indd 76 11/7/19 3:16 PM

#### Pyruvate dehydrogenase complex deficiency

Causes a buildup of pyruvate that gets shunted to lactate (via LDH) and alanine (via ALT). X-linked.

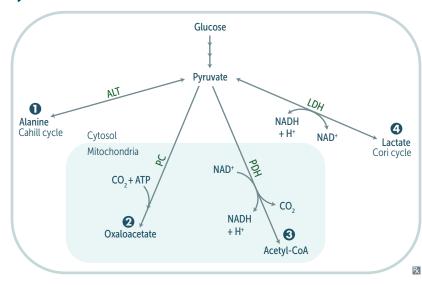
FINDINGS

Neurologic defects, lactic acidosis, † serum alanine starting in infancy.

TREATMENT

† intake of ketogenic nutrients (eg, high fat content or † lysine and leucine).

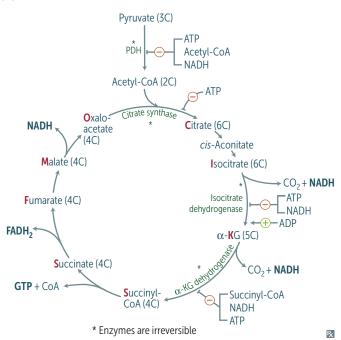
#### **Pyruvate metabolism**



Functions of different pyruvate metabolic pathways (and their associated cofactors):

- ◆ Alanine aminotransferase (B<sub>6</sub>): alanine carries amino groups to the liver from muscle
- 2 Pyruvate carboxylase (biotin): oxaloacetate can replenish TCA cycle or be used in gluconeogenesis
- 3 Pyruvate dehydrogenase (B<sub>1</sub>, B<sub>2</sub>, B<sub>3</sub>, B<sub>5</sub>, lipoic acid): transition from glycolysis to the TCA cycle
- 4 Lactic acid dehydrogenase (B<sub>3</sub>): end of anaerobic glycolysis (major pathway in RBCs, WBCs, kidney medulla, lens, testes, and cornea)

#### **TCA cycle**



Also called Krebs cycle. Pyruvate → acetyl-CoA produces 1 NADH, 1 CO<sub>2</sub>.

The TCA cycle produces 3 NADH, 1 FADH<sub>2</sub>, 2 CO<sub>2</sub>, 1 GTP per acetyl-CoA = 10 ATP/ acetyl-CoA (2× everything per glucose). TCA cycle reactions occur in the mitochondria.

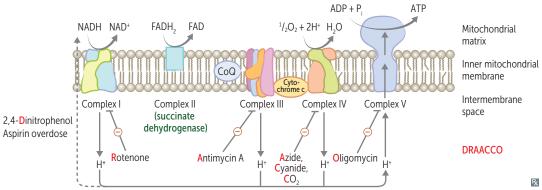
 $\alpha$ -ketoglutarate dehydrogenase complex requires the same cofactors as the pyruvate dehydrogenase complex (vitamins  $B_1$ ,  $B_2$ ,  $B_3$ ,  $B_5$ , lipoic acid).

Citrate Is Krebs' Starting Substrate For Making Oxaloacetate.

FAS1\_2019\_01-Biochem.indd 77 11/7/19 3:16 PM

# Electron transport chain and oxidative phosphorylation

NADH electrons from glycolysis enter mitochondria via the malate-aspartate or glycerol-3-phosphate shuttle. FADH<sub>2</sub> electrons are transferred to complex II (at a lower energy level than NADH). The passage of electrons results in the formation of a proton gradient that, coupled to oxidative phosphorylation, drives the production of ATP.



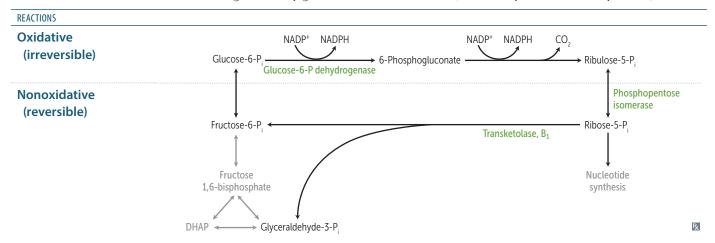
ATP PRODUCED VIA ATP SYNTHASE		
	1 NADH → 2.5 ATP; 1 FADH <sub>2</sub> → 1.5 ATP.	
OXIDATIVE PHOSPHORYLATION POISON	S	
Electron transport inhibitors	Directly inhibit electron transport, causing a ↓ proton gradient and block of ATP synthesis.	Rotenone: complex one inhibitor.  "An-3-mycin" (antimycin) A: complex 3 inhibitor.  Cyanide, carbon monoxide, azide (the -ides, 4 letters) inhibit complex IV.
ATP synthase inhibitors	Directly inhibit mitochondrial ATP synthase, causing an † proton gradient. No ATP is produced because electron transport stops.	Oligomycin.
Uncoupling agents	↑ permeability of membrane, causing a ↓ proton gradient and ↑ O <sub>2</sub> consumption. ATP synthesis stops, but electron transport continues. Produces heat.	2,4-Dinitrophenol (used illicitly for weight loss), aspirin (fevers often occur after overdose), thermogenin in brown fat (has more mitochondria than white fat).
Gluconeogenesis, rreversible enzymes		Pathway Produces Fresh Glucose.
Pyruvate carboxylase	In mitochondria. Pyruvate → oxaloacetate.	Requires biotin, ATP. Activated by acetyl-CoA.
Phosphoenolpyruvate carboxykinase	In cytosol. Oxaloacetate  → phosphoenolpyruvate.	Requires GTP.
Fructose-1,6- bisphosphatase	In cytosol. Fructose-1,6-bisphosphate  → fructose-6-phosphate.	Citrate $\oplus$ , AMP $\ominus$ , fructose 2,6-bisphosphate $\ominus$ .
		Citrate ⊕, AMP ⊝, fructose 2,6-bisphosphate ⊝

FAS1\_2019\_01-Biochem.indd 78 11/7/19 3:16 PM

### Pentose phosphate pathway

Also called HMP shunt. Provides a source of NADPH from abundantly available glucose-6-P (NADPH is required for reductive reactions, eg, glutathione reduction inside RBCs, fatty acid and cholesterol biosynthesis). Additionally, this pathway yields ribose for nucleotide synthesis. Two distinct phases (oxidative and nonoxidative), both of which occur in the cytoplasm. No ATP is used or produced.

Sites: lactating mammary glands, liver, adrenal cortex (sites of fatty acid or steroid synthesis), RBCs.

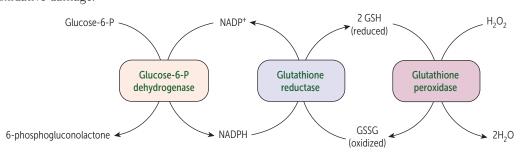


#### Glucose-6-phosphate dehydrogenase deficiency

NADPH is necessary to keep glutathione reduced, which in turn detoxifies free radicals and peroxides. ↓ NADPH in RBCs leads to hemolytic anemia due to poor RBC defense against oxidizing agents (eg, fava beans, sulfonamides, nitrofurantoin, primaquine/ chloroquine, antituberculosis drugs). Infection (most common cause) can also precipitate hemolysis; inflammatory response produces free radicals that diffuse into RBCs, causing oxidative damage.

X-linked recessive disorder; most common human enzyme deficiency; more prevalent among African Americans. † malarial resistance.

Heinz bodies—denatured globin chains precipitate within RBCs due to oxidative stress. Bite cells—result from the phagocytic removal of Heinz bodies by splenic macrophages. Think, "Bite into some Heinz ketchup."



FAS1\_2019\_01-Biochem.indd 79 11/7/19 3:16 PM

#### **Disorders of fructose metabolism**

#### **Essential fructosuria**

Involves a defect in **fructokinase**. Autosomal recessive. A benign, asymptomatic condition (fructokinase deficiency is **kin**der), since fructose is not trapped in cells. Hexokinase becomes 1° pathway for converting fructose to fructose-6-phosphate.

Symptoms: fructose appears in blood and urine.

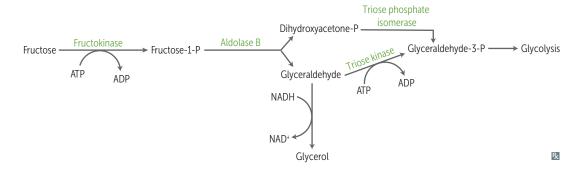
Disorders of fructose metabolism cause milder symptoms than analogous disorders of galactose metabolism.

### Hereditary fructose intolerance

Hereditary deficiency of **aldolase B**. Autosomal recessive. Fructose-1-phosphate accumulates, causing a ↓ in available phosphate, which results in inhibition of glycogenolysis and gluconeogenesis. Symptoms present following consumption of fruit, juice, or honey. Urine dipstick will be ⊝ (tests for glucose only); reducing sugar can be detected in the urine (nonspecific test for inborn errors of carbohydrate metabolism).

Symptoms: hypoglycemia, jaundice, cirrhosis, vomiting.

Treatment: 1 intake of fructose, sucrose (glucose + fructose), and sorbitol (metabolized to fructose).



#### **Disorders of galactose metabolism**

## Galactokinase deficiency

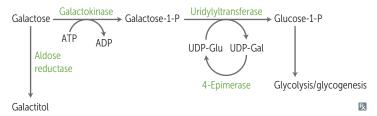
Hereditary deficiency of **galactokinase**. Galactitol accumulates if galactose is present in diet. Relatively mild condition. Autosomal recessive.

Symptoms: galactose appears in blood (galactosemia) and urine (galactosuria); infantile cataracts. May present as failure to track objects or to develop a social smile. Galactokinase deficiency is kinder (benign condition).

#### Classic galactosemia

Absence of **galactose-1-phosphate uridyltransferase**. Autosomal recessive. Damage is caused by accumulation of toxic substances (including galactitol, which accumulates in the lens of the eye). Symptoms develop when infant begins feeding (lactose present in breast milk and routine formula) and include failure to thrive, jaundice, hepatomegaly, infantile cataracts, intellectual disability. Can predispose to *E coli* sepsis in neonates.

Treatment: exclude galactose and lactose (galactose + glucose) from diet.



Fructose is to Aldolase B as Galactose is to UridylTransferase (FAB GUT).

The more serious defects lead to PO<sub>4</sub><sup>3-</sup> depletion.

FAS1\_2019\_01-Biochem.indd 80 11/7/19 3:16 PM

#### **Sorbitol**

An alternative method of trapping glucose in the cell is to convert it to its alcohol counterpart, sorbitol, via aldose reductase. Some tissues then convert sorbitol to fructose using sorbitol dehydrogenase; tissues with an insufficient amount/activity of this enzyme are at risk of intracellular sorbitol accumulation, causing osmotic damage (eg, cataracts, retinopathy, and peripheral neuropathy seen with chronic hyperglycemia in diabetes).

High blood levels of galactose also result in conversion to the osmotically active galactitol via aldose reductase.

Liver, Ovaries, and Seminal vesicles have both enzymes (they LOSe sorbitol).



Lens has primarily aldose reductase. Retina, Kidneys, and Schwann cells have only aldose reductase (LuRKS).

#### **Lactase deficiency**

Insufficient lactase enzyme → dietary lactose intolerance. Lactase functions on the intestinal brush border to digest lactose (in milk and milk products) into glucose and galactose.

Primary: age-dependent decline after childhood (absence of lactase-persistent allele), common in people of Asian, African, or Native American descent.

Secondary: loss of intestinal brush border due to gastroenteritis (eg, rotavirus), autoimmune disease. Congenital lactase deficiency: rare, due to defective gene.

Stool demonstrates \( \dagger pH and breath shows \( \dagger hydrogen content with lactose hydrogen breath test. Intestinal biopsy reveals normal mucosa in patients with hereditary lactose intolerance.

**FINDINGS** 

Bloating, cramps, flatulence, osmotic diarrhea.

TREATMENT

Avoid dairy products or add lactase pills to diet; lactose-free milk.

#### **Amino acids**

Only L-amino acids are found in proteins.

#### Essential

PVT TIM HaLL: Phenylalanine, Valine, Tryptophan, Threonine, Isoleucine, Methionine, Histidine, Leucine, Lysine.

Glucogenic: Methionine, histidine, valine. We met his valentine, she is so sweet (glucogenic). Glucogenic/ketogenic: Isoleucine, phenylalanine, threonine, tryptophan.

Ketogenic: Leucine, Lysine. The onLy pureLy ketogenic amino acids.

#### Acidic

Aspartic acid, glutamic acid.

Negatively charged at body pH.

#### Basic

**Arginine**, **his**tidine, **lys**ine.

Arginine is most **basic**. Histidine has no charge at body pH. Arginine and histidine are required during periods of growth.

Arginine and lysine are † in histones which bind negatively charged DNA.

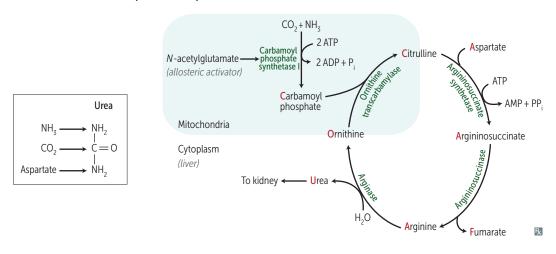
His lys (lies) are basic.

FAS1\_2019\_01-Biochem.indd 81 11/7/19 3:16 PM

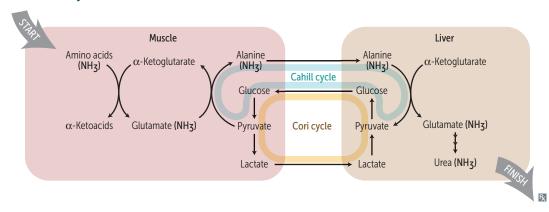
#### **Urea cycle**

Amino acid catabolism results in the formation of common metabolites (eg, pyruvate, acetyl-CoA), which serve as metabolic fuels. Excess nitrogen generated by this process is converted to urea and excreted by the kidneys.

Ordinarily, Careless Crappers Are Also Frivolous About Urination.



#### Transport of ammonia by alanine



#### Hyperammonemia



Can be acquired (eg, liver disease) or hereditary (eg, urea cycle enzyme deficiencies).

Presents with flapping tremor (eg, asterixis), slurring of speech, somnolence, vomiting, cerebral edema, blurring of vision.

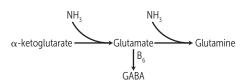
↑ NH<sub>3</sub> changes relative amounts of α-ketoglutarate, glutamate, GABA, and glutamine to favor ↑ glutamine. CNS toxicity may involve ↓ GABA, ↓ α-ketoglutarate, TCA cycle inhibition, and cerebral edema due to glutamine-induced osmotic shifts.

Treatment: limit protein in diet.

May be given to ↓ ammonia levels:

- Lactulose to acidify GI tract and trap NH<sub>4</sub><sup>+</sup> for excretion.
- Antibiotics (eg, rifaximin, neomycin) to

   ‡ ammoniagenic bacteria.
- Benzoate, phenylacetate, or phenylbutyrate react with glycine or glutamine, forming products that are excreted renally.



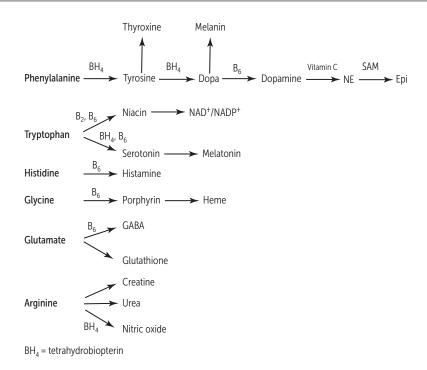
FAS1\_2019\_01-Biochem.indd 82 11/7/19 3:16 PM

#### Ornithine transcarbamylase deficiency

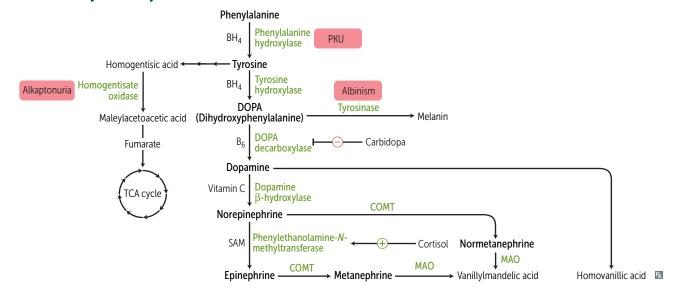
Most common urea cycle disorder. X-linked recessive (vs other urea cycle enzyme deficiencies, which are autosomal recessive). Interferes with the body's ability to eliminate ammonia. Often evident in the first few days of life, but may present later. Excess carbamoyl phosphate is converted to orotic acid (part of the pyrimidine synthesis pathway).

Findings: † orotic acid in blood and urine, ‡ BUN, symptoms of hyperammonemia. No megaloblastic anemia (vs orotic aciduria).

#### **Amino acid derivatives**



#### Catecholamine synthesis/tyrosine catabolism



FAS1\_2019\_01-Biochem.indd 83 11/7/19 3:16 PM

#### **Phenylketonuria**

Due to ↓ phenylalanine hydroxylase or ↓ tetrahydrobiopterin (BH<sub>4</sub>) cofactor (malignant PKU). Tyrosine becomes essential. ↑ phenylalanine → ↑ phenyl ketones in urine. Findings: intellectual disability, growth

Findings: intellectual disability, growth retardation, seizures, fair complexion, eczema, musty body odor.

Treatment: ↓ phenylalanine and ↑ tyrosine in diet, tetrahydrobiopterin supplementation.

Maternal PKU—lack of proper dietary therapy during pregnancy. Findings in infant: microcephaly, intellectual disability, growth retardation, congenital heart defects.

Autosomal recessive. Incidence ≈ 1:10,000.

Screening occurs 2–3 days after birth (normal at birth because of maternal enzyme during fetal life)

Phenyl ketones—phenylacetate, phenyllactate, and phenylpyruvate.

Disorder of **aromatic** amino acid metabolism → musty body **odor**.

PKU patients must avoid the artificial sweetener aspartame, which contains phenylalanine.

### Maple syrup urine disease

Blocked degradation of **branched** amino acids (**I**soleucine, **L**eucine, **V**aline) due to ↓ branched-chain α-ketoacid dehydrogenase (B<sub>1</sub>). Causes ↑ α-ketoacids in the blood, especially those of leucine.

Treatment: restriction of isoleucine, leucine, valine in diet, and thiamine supplementation.

Autosomal recessive.

Presentation: vomiting, poor feeding, urine smells like maple syrup/burnt sugar. Causes severe CNS defects, intellectual disability, death.

I Love Vermont maple syrup from maple trees (with B<sub>1</sub>ranches).

#### **Alkaptonuria**



Congenital deficiency of homogentisate oxidase in the degradative pathway of tyrosine to fumarate → pigment-forming homogentisic acid builds up in tissue A. Autosomal recessive. Usually benign. Findings: bluish-black connective tissue, ear cartilage, and sclerae (ochronosis); urine turns black on prolonged exposure to air. May have debilitating arthralgias (homogentisic acid toxic to cartilage).

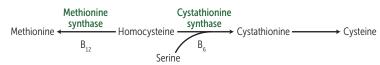
#### Homocystinuria

Causes (all autosomal recessive):

- Cystathionine synthase deficiency (treatment: ↓ methionine, ↑ cysteine, ↑ B<sub>6</sub>, B<sub>12</sub>, and folate in diet)
- I affinity of cystathionine synthase for pyridoxal phosphate (treatment: 11 B<sub>6</sub> and 1 cysteine in diet)
- Methionine synthase (homocysteine methyltransferase) deficiency (treatment: † methionine in diet)
- Methylenetetrahydrofolate reductase (MTHFR) deficiency (treatment: † folate in diet)

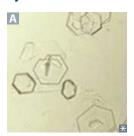
All forms result in excess homocysteine.

HOMOCYstinuria: ↑↑ Homocysteine in urine, Osteoporosis, Marfanoid habitus,
Ocular changes (downward and inward lens subluxation), Cardiovascular effects (thrombosis and atherosclerosis → stroke and MI), kYphosis, intellectual disability, fair complexion. In homocystinuria, lens subluxes "down and in" (vs Marfan, "up and fans out").



FAS1 2019 01-Biochem.indd 84 11/7/19 3:16 PM

#### Cystinuria



Hereditary defect of renal PCT and intestinal amino acid transporter that prevents reabsorption of Cystine, Ornithine, Lysine, and Arginine (COLA).

Excess cystine in the urine can lead to recurrent precipitation of hexagonal cystine stones A. Treatment: urinary alkalinization (eg, potassium citrate, acetazolamide) and chelating agents (eg, penicillamine) † solubility of cystine stones; good hydration.

Autosomal recessive. Common (1:7000). Urinary cyanide-nitroprusside test is diagnostic.

Cystine is made of 2 cysteines connected by a disulfide bond.

#### **Organic acidemias**

Most commonly present in infancy with poor feeding, vomiting, hypotonia, high anion gap metabolic acidosis, hepatomegaly, seizures. Organic acid accumulation:

- Inhibits gluconeogenesis → ↓ fasting blood glucose levels, ↑ ketoacidosis → high anion gap metabolic acidosis
- Inhibits urea cycle → hyperammonemia

#### Propionic acidemia

Deficiency of propionyl-CoA carboxylase

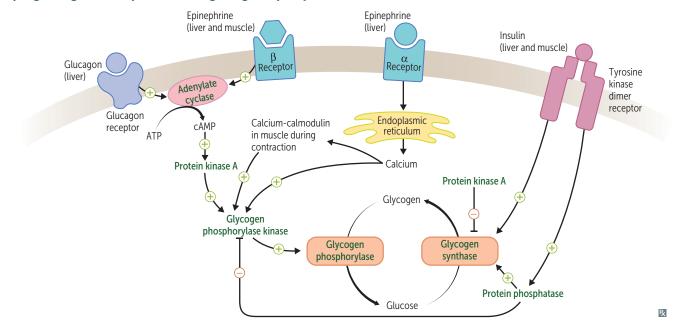
→ ↑ propionyl-CoA, ↓ methylmalonic acid.

### Methylmalonic acidemia

Deficiency of methylmalonyl-CoA mutase or vitamin  $B_{12}$ .

Treatment: low-protein diet limited in substances that metabolize into propionyl-CoA: Valine, Odd-chain fatty acids, Methionine, Isoleucine, Threonine (VOMIT).

#### Glycogen regulation by insulin and glucagon/epinephrine



FAS1\_2019\_01-Biochem.indd 85

Glycogen	Branches have $\alpha$ -(1,6) bonds; linkages have $\alpha$ -(1,4) bonds.		
Skeletal muscle	Glycogen undergoes glycogenolysis → glucose-l-phosphate → glucose-6-phosphate, which is rapidly metabolized during exercise.		
Hepatocytes	Glycogen phosphory glucose units remain 3 of the 4 glucose un enzyme (6) cleaves (6)	undergoes glycogenolysis to maintain blase  (1) liberates glucose-l-phosphate resion a branch. Then 4-α-D-glucanotransfeits from the branch to the linkage. Then off the last residue, liberating glucose. To the two to four residues remaining on a lit.	dues off branched glycogen until 4 erase (debranching enzyme <b>⑤</b> ) moves α-1,6-glucosidase (debranching
			Glycogen storage
			disease type
			Von Gierke disease
			II Pompe disease
Change			III Cori disease
Glucose			V McArdle disease
<b>#1</b>	Lysosome only	· · · · · · · · · · · · · · · · · · ·	Glycogen enzymes
Glucose-6-P	•	<b>6</b>	■ UDP-glucose pyrophosphorylase
11			② Glycogen synthase
Glucose-1-P	<ul><li>Branching enzyme</li><li>Glycogen phosphorylase</li></ul>		
o.l			
UDP-glucose		6	<b>5</b> Debranching enzyme (4-α- <sub>D</sub> -glucanotransferase)
<b>2</b>	0	0	<b>6</b> Debranching enzyme (α-1,6-glucosidase)
Glycogen		Limit dextrin	$\alpha$ -1,4-glucosidase

Note: A small amount of glycogen is degraded in lysosomes by  ${\bf 20}$   $\alpha$ -1,4-glucosidase (acid maltase).

FAS1\_2019\_01-Biochem.indd 86 11/7/19 3:16 PM

### Glycogen storage diseases

At least 15 types have been identified, all resulting in abnormal glycogen metabolism and an accumulation of glycogen within cells. Periodic acid–Schiff stain identifies glycogen and is useful in identifying these diseases.

Very Poor Carbohydrate Metabolism.

Types I, II, III, and V are autosomal recessive.

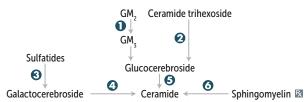
DISEASE	FINDINGS	DEFICIENT ENZYME	COMMENTS
Von Gierke disease (type I)	Severe fasting hypoglycemia,  †† Glycogen in liver and kidneys, † blood lactate, † triglycerides, † uric acid (Gout), and hepatomegaly, renomegaly. Liver does not regulate blood glucose.	Glucose-6-phosphatase	Treatment: frequent oral glucose/cornstarch; avoidance of fructose and galactose Impaired gluconeogenesis and glycogenolysis
Pompe disease (type II)	Cardiomegaly, hypertrophic cardiomyopathy, hypotonia, exercise intolerance, and systemic findings lead to early death.	Lysosomal acid $\alpha$ -1,4-glucosidase (acid maltase) with $\alpha$ -1,6-glucosidase activity	PomPe trashes the PumP (1st and 4th letter; heart, liver, and muscle)
Cori disease (type III)	Similar to von Gierke disease, but milder symptoms and normal blood lactate levels. Can lead to cardiomyopathy. Limit dextrin–like structures accumulate in cytosol.	Debranching enzymes $(\alpha\text{-}1,6\text{-}glucosidase and }4\text{-}\alpha\text{-}D\text{-}glucanotransferase})$	Gluconeogenesis is intact
McArdle disease (type V)	↑ glycogen in muscle, but muscle cannot break it down → painful Muscle cramps, Myoglobinuria (red urine) with strenuous exercise, and arrhythmia from electrolyte abnormalities. Second-wind phenomenon noted during exercise due to ↑ muscular blood flow.	Skeletal muscle glycogen phosphorylase (Myophosphorylase) Characterized by a flat venous lactate curve with normal rise in ammonia levels during exercise	Blood glucose levels typically unaffected  McArdle = Muscle

FAS1\_2019\_01-Biochem.indd 87 11/7/19 3:16 PM

### Lysosomal storage diseases

Each is caused by a deficiency in one of the many lysosomal enzymes. Results in an accumulation of abnormal metabolic products.

DISEASE	FINDINGS	DEFICIENT ENZYME	ACCUMULATED SUBSTRATE	INHERITANCE
Sphingolipidoses				
Tay-Sachs disease	Progressive neurodegeneration, developmental delay, hyperreflexia, hyperacusis, "cherry-red" spot on macula A, lysosomes with onion skin, no hepatosplenomegaly (vs Niemann-Pick).	• HeXosaminidase A ("TAy-SaX")	$\mathrm{GM}_2$ ganglioside	AR
Fabry disease	Early: triad of episodic peripheral neuropathy, angiokeratomas B, hypohidrosis.  Late: progressive renal failure, cardiovascular disease.	<b>2</b> α-galactosidase A	Ceramide trihexoside (globotriaosylce- ramide)	XR
Metachromatic leukodystrophy	Central and peripheral demyelination with ataxia, dementia.	3 Arylsulfatase A	Cerebroside sulfate	AR
Krabbe disease	Peripheral neuropathy, destruction of oligodendrocytes, developmental delay, optic atrophy, globoid cells.	<b>4</b> Galactocerebrosidase (galactosylceramidase)	Galactocerebroside, psychosine	AR
Saucher disease	Most common. Hepatosplenomegaly, pancytopenia, osteoporosis, avascular necrosis of femur, bone crises, Gaucher cells (lipid-laden macrophages resembling crumpled tissue paper).	<b>5</b> Glucocerebrosidase (β-glucosidase); treat with recombinant glucocerebrosidase	Glucocerebroside	AR
liemann-Pick disease	Progressive neurodegeneration, hepatosplenomegaly, foam cells (lipid-laden macrophages) D, "cherry-red" spot on macula A.	6 Sphingomyelinase	Sphingomyelin	AR
Aucopolysaccharidoses				
lurler syndrome	Developmental delay, gargoylism, airway obstruction, corneal clouding, hepatosplenomegaly.	α-L-iduronidase	Heparan sulfate, dermatan sulfate	AR
lunter syndrome	Mild Hurler + aggressive behavior, no corneal clouding.	Iduronate-2-sulfatase	Heparan sulfate, dermatan sulfate	XR



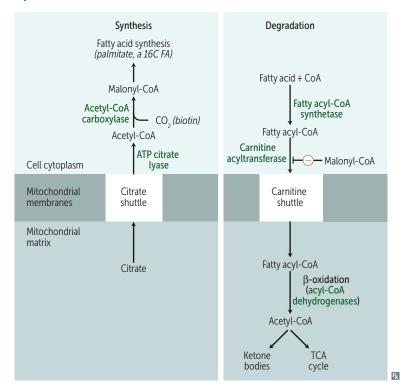
No man picks (Niemann-Pick) his nose with his sphinger (sphingomyelinase).

**Hunters** see clearly (no corneal clouding) and aggressively aim for the **X** (**X**-linked recessive).

† incidence of Tay-Sachs, Niemann-Pick, some forms of Gaucher disease in Ashkenazi Jews.

FAS1\_2019\_01-Biochem.indd 88 11/7/19 3:16 PM

#### **Fatty acid metabolism**



Fatty acid synthesis requires transport of citrate from mitochondria to cytosol. Predominantly occurs in liver, lactating mammary glands, and adipose tissue.

Long-chain fatty acid (LCFA) degradation requires carnitine-dependent transport into the mitochondrial matrix.

"SYtrate" = SYnthesis.
CARnitine = CARnage of fatty acids.

Systemic 1° carnitine deficiency—no cellular uptake of carnitine → no transport of LCFAs into mitochondria → toxic accumulation of LCFAs in the cytosol. Causes weakness, hypotonia, hypoketotic hypoglycemia, dilated cardiomyopathy.

Medium-chain acyl-CoA dehydrogenase deficiency—↓ ability to break down fatty acids into acetyl-CoA → accumulation of fatty acyl carnitines in the blood with hypoketotic hypoglycemia. Causes vomiting, lethargy, seizures, coma, liver dysfunction, hyperammonemia. Can lead to sudden death in infants or children. Treat by avoiding fasting.

FAS1\_2019\_01-Biochem.indd 89 11/7/19 3:16 PM

#### **Ketone bodies**

In the liver, fatty acids and amino acids are metabolized to acetoacetate and β-hydroxybutyrate (to be used in muscle and brain).

In prolonged starvation and diabetic ketoacidosis, oxaloacetate is depleted for gluconeogenesis. In alcoholism, excess NADH shunts oxaloacetate to malate. All of these processes lead to a buildup of acetyl-CoA, which is shunted into ketone body synthesis.

Ketone bodies: acetone, acetoacetate, β-hydroxybutyrate.

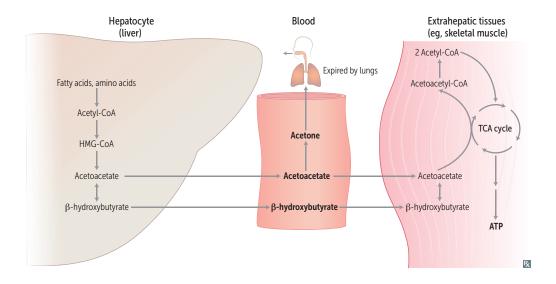
Breath smells like acetone (fruity odor).

Urine test for ketones can detect acetoacetate, but not  $\beta$ -hydroxybutyrate.

RBCs cannot utilize ketones; they strictly use glucose.

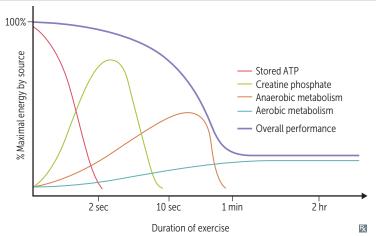
HMG-CoA lyase for ketone production.

HMG-CoA reductase for cholesterol synthesis.



FAS1\_2019\_01-Biochem.indd 90 11/7/19 3:16 PM

#### **Metabolic fuel use**



 $lg \frac{carb}{protein} = 4 kcal$  $\lg$  alcohol = 7 kcal lg fatty acid = 9 kcal (# letters = # kcal)

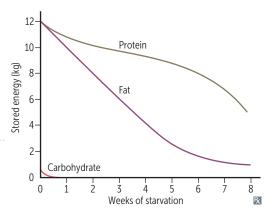
	Duration of exercise	
Fasting and starvation	Priorities are to supply sufficient glucose to the	e brain and RBCs and to preserve protein.
Fed state (after a meal)	Glycolysis and aerobic respiration.	Insulin stimulates storage of lipids, proglycogen.
Fasting (between meals)	Hepatic glycogenolysis (major); hepatic gluconeogenesis, adipose release of FFA (minor).	Glucagon and epinephrine stimulate reserves.
Starvation days 1–3	<ul> <li>Blood glucose levels maintained by:</li> <li>Hepatic glycogenolysis</li> <li>Adipose release of FFA</li> <li>Muscle and liver, which shift fuel use from glucose to FFA</li> <li>Hepatic gluconeogenesis from peripheral tissue lactate and alanine, and from adipose tissue glycerol and propionyl-CoA (from odd-chain FFA—the only triacylglycerol components that contribute to gluconeogenesis)</li> </ul>	12- 10- Protein (b) 8- A60- Fat
Starvation after day 3	Adipose stores (ketone bodies become the massource of energy for the brain). After these and depleted, vital protein degradation accelerate leading to organ failure and death.  Amount of excess stores determines survival time.	ce Carbohydrate

glycogen. Glucagon and epinephrine stimulate use of fuel

Insulin stimulates storage of lipids, proteins, and

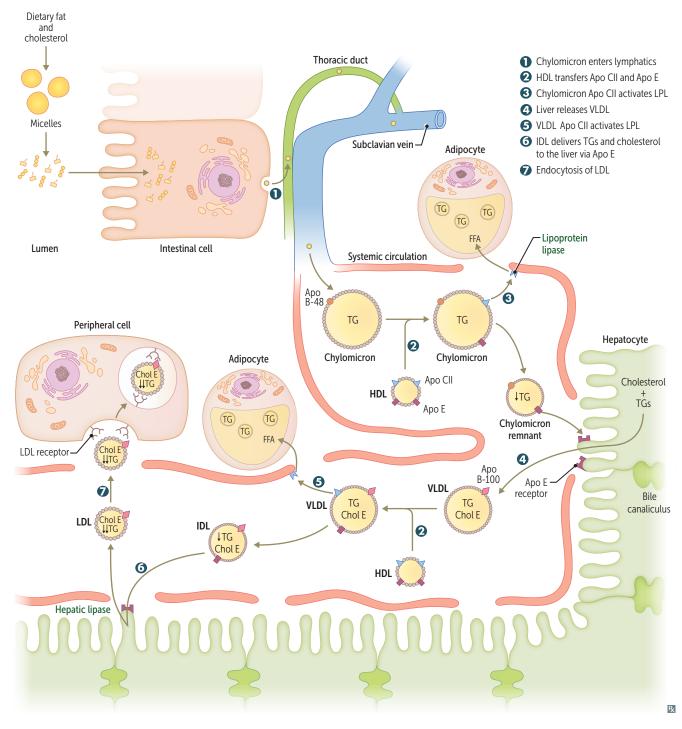
reserves.

Glycogen reserves depleted after day 1. RBCs lack mitochondria and therefore cannot use ketones.



FAS1\_2019\_01-Biochem.indd 91 11/7/19 3:16 PM

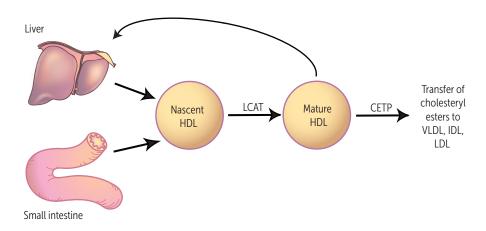
#### **Lipid transport**



FAS1\_2019\_01-Biochem.indd 92 11/7/19 3:16 PM

# Key enzymes in lipid transport

Cholesteryl ester transfer protein	Mediates transfer of cholesteryl esters to other lipoprotein particles.
Hepatic lipase	Degrades TGs remaining in IDL.
Hormone-sensitive lipase	Degrades TGs stored in adipocytes.
Lecithin-cholesterol acyltransferase	Catalyzes esterification of ¾ of plasma cholesterol.
Lipoprotein lipase	Degrades TGs in circulating chylomicrons.
Pancreatic lipase	Degrades dietary TGs in small intestine.
PCSK9	Degrades LDL receptor → ↑ serum LDL. Inhibition → ↑ LDL receptor recycling → ↓ serum LDL.



#### **Major apolipoproteins**

			Chylomicron				
Apolipoprotein	Function	Chylomicron	remnant	VLDL	IDL	LDL	HDL
Е	Mediates remnant uptake (everything except LDL)	✓	✓	✓	✓		✓
A-I	Found only on alphalipoproteins (HDL), activates LCAT						✓
C-II	Lipoprotein lipase cofactor that catalyzes cleavage.	✓		✓	✓		✓
B-48	Mediates chylomicron secretion into lymphatics Only on particles originating from the intestines	<b>/</b>	✓				
B-100	Binds LDL receptor Only on particles originating from the liver			✓	<b>√</b>	<b>√</b>	

FAS1\_2019\_01-Biochem.indd 93 11/7/19 3:16 PM

Lipoprotein functions	Lipoproteins are composed of varying proportions of cholesterol, TGs, and phospholipids. LDL and HDL carry the most cholesterol.  Cholesterol is needed to maintain cell membrane integrity and synthesize bile acids, steroids, and vitamin D.
Chylomicron	Delivers dietary TGs to peripheral tissues. Delivers cholesterol to liver in the form of chylomicron remnants, which are mostly depleted of their TGs. Secreted by intestinal epithelial cells.
VLDL	Delivers hepatic TGs to peripheral tissue. Secreted by liver.
IDL	Delivers TGs and cholesterol to liver. Formed from degradation of VLDL.
LDL	Delivers hepatic cholesterol to peripheral tissues. Formed by hepatic lipase modification of IDL in the liver and peripheral tissue. Taken up by target cells via receptor-mediated endocytosis. LDL is Lethal.
HDL	Mediates reverse cholesterol transport from peripheral tissues to liver. Acts as a repository for apolipoproteins C and E (which are needed for chylomicron and VLDL metabolism). Secreted from both liver and intestine. Alcohol † synthesis. HDL is Healthy.

#### Abetalipoproteinemia

Autosomal recessive. Mutation in gene that encodes microsomal transfer protein (*MTP*). Chylomicrons, VLDL, LDL absent. Deficiency in ApoB-48, ApoB-100. Affected infants present with severe fat malabsorption, steatorrhea, failure to thrive. Later manifestations include retinitis pigmentosa, spinocerebellar degeneration due to vitamin E deficiency, progressive ataxia, acanthocytosis. Intestinal biopsy shows lipid-laden enterocytes.

Treatment: restriction of long-chain fatty acids, large doses of oral vitamin E.

#### **Familial dyslipidemias**

ТҮРЕ	INHERITANCE	PATHOGENESIS	† BLOOD LEVEL	CLINICAL
I—Hyper- chylomicronemia	AR	Lipoprotein lipase or apolipoprotein C-II deficiency	Chylomicrons, TG, cholesterol	Pancreatitis, hepatosplenomegaly, and eruptive/pruritic xanthomas (no † risk for atherosclerosis). Creamy layer in supernatant.
II—Familial hyper- cholesterolemia	AD	Absent or defective LDL receptors, or defective ApoB-100	IIa: LDL, cholesterol IIb: LDL, cholesterol, VLDL	Heterozygotes (1:500) have cholesterol ≈ 300 mg/dL; homozygotes (very rare) have cholesterol ≥ 700 mg/dL.  Accelerated atherosclerosis (may have MI before age 20), tendon (Achilles) xanthomas, and corneal arcus.
III—Dysbeta- lipoproteinemia	AR	Defective ApoE	Chylomicrons, VLDL	Premature atherosclerosis, tuberoeruptive and palmar xanthomas.
IV—Hyper- triglyceridemia	AD	Hepatic overproduction of VLDL	VLDL, TG	Hypertriglyceridemia (> 1000 mg/dL) can cause acute pancreatitis. Related to insulin resistance.

FAS1\_2019\_01-Biochem.indd 94 11/7/19 3:16 PM

### HIGH-YIELD PRINCIPLES IN

# **Immunology**

"I hate to disappoint you, but my rubber lips are immune to your charms."

—Batman & Robin

"The fully engaged heart is the antibody for the infection of violence."

-Mark Nepo

Learning the components of the immune system and their roles in host defense at the cellular level is essential for both the understanding of disease pathophysiology and clinical practice. Know the immune mechanisms of responses to vaccines. Both congenital and acquired immunodeficiencies are very testable. Cell surface markers are high yield for understanding immune cell interactions and for laboratory diagnosis. Know the roles and functions of major cytokines and chemokines.

- ▶ Lymphoid Structures 96
- ▶ Cellular Components 99
- ▶ Immune Responses 104
- ▶ Immunosuppressants 120

FAS1\_2019\_02-Immunology.indd 95 11/7/19 3:24 PM

#### ► IMMUNOLOGY—LYMPHOID STRUCTURES

### Immune system organs

l° organs:

- Bone marrow—immune cell production, B cell maturation
- Thymus—T cell maturation

2° organs:

- Spleen, lymph nodes, tonsils, Peyer patches
- Allow immune cells to interact with antigen

#### Lymph node

A 2° lymphoid organ that has many afferents, 1 or more efferents. Encapsulated, with trabeculae A B. Functions are nonspecific filtration by macrophages, circulation of B and T cells, and immune response activation.

#### **Follicle**

Site of B-cell localization and proliferation. In outer cortex. 1° follicles are dense and quiescent. 2° follicles have pale central germinal centers and are active.

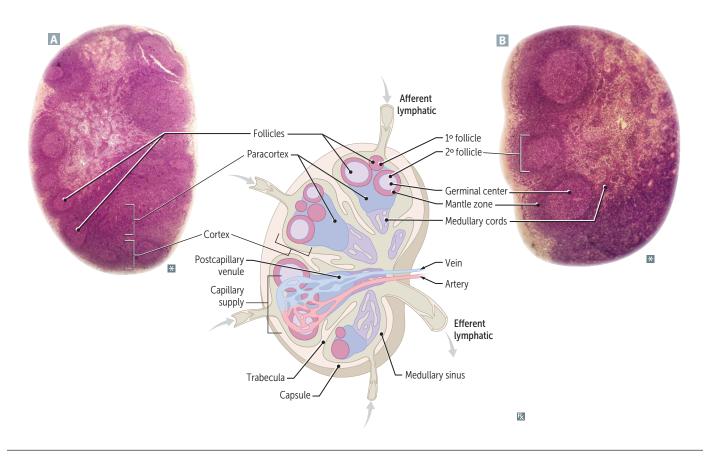
#### Medulla

Consists of medullary cords (closely packed lymphocytes and plasma cells) and medullary sinuses. Medullary sinuses communicate with efferent lymphatics and contain reticular cells and macrophages.

#### **Paracortex**

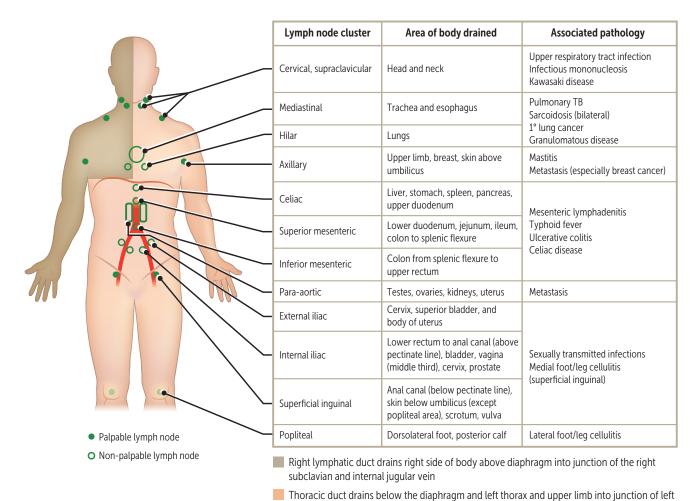
Contains T cells. Region of cortex between follicles and medulla. Contains high endothelial venules through which T and B cells enter from blood. Not well developed in patients with DiGeorge syndrome.

Paracortex enlarges in an extreme cellular immune response (eg, EBV and other viral infections → paracortical hyperplasia → lymphadenopathy).



FAS1\_2019\_02-Immunology.indd 96 11/7/19 3:24 PM

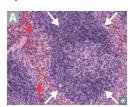
#### Lymphatic drainage associations



subclavian and internal jugular veins (rupture of thoracic duct can cause chylothorax)

FAS1\_2019\_02-Immunology.indd 97 11/7/19 3:24 PM

#### **Spleen**



Located in LUQ of abdomen, anterolateral to left kidney, protected by 9th-11th ribs. Sinusoids are long, vascular channels in red pulp (red arrows in A) with fenestrated "barrel hoop" basement membrane.

- T cells are found in the periarteriolar lymphatic sheath (PALS) within the white pulp (white arrows in A).
- B cells are found in follicles within the white pulp.
- The marginal zone, in between the red pulp and white pulp, contains macrophages and specialized B cells, and is where antigenpresenting cells (APCs) capture blood-borne antigens for recognition by lymphocytes.

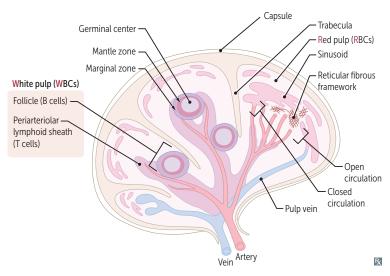
Splenic macrophages remove encapsulated bacteria.

Splenic dysfunction (eg, postsplenectomy state, sickle cell disease autosplenectomy):

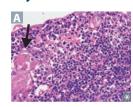
↓ IgM → ↓ complement activation → ↓ C3b opsonization → ↑ susceptibility to encapsulated organisms.

Postsplenectomy blood findings:

- Howell-Jolly bodies (nuclear remnants)
- Target cells
- Thrombocytosis (loss of sequestration and removal)
- Lymphocytosis (loss of sequestration)
   Vaccinate patients undergoing splenectomy or with splenic dysfunction against encapsulated organisms (pneumococci, Hib, meningococci).



#### **Thymus**





Located in the anterosuperior mediastinum. Site of T-cell differentiation and maturation. Encapsulated. Thymus epithelium is derived from Third pharyngeal pouch (endoderm), whereas thymic lymphocytes are of mesodermal origin. Cortex is dense with immature T cells; Medulla is pale with Mature T cells and Hassall corpuscles A containing epithelial reticular cells. Normal neonatal thymus "sail-shaped" on CXR B, involutes by age 3 years.

T cells = Thymus

 $\mathbf{B}$  cells =  $\mathbf{B}$ one marrow

Absent thymic shadow or hypoplastic thymus seen in some immunodeficiencies (eg, SCID, DiGeorge syndrome).

**Thymoma**—neoplasm of thymus. Associated with myasthenia gravis, superior vena cava syndrome, pure red cell aplasia, Good syndrome.

FAS1\_2019\_02-Immunology.indd 98 11/7/19 3:24 PM

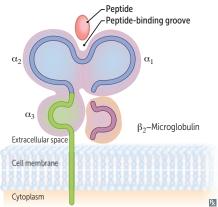
### ► IMMUNOLOGY—CELLULAR COMPONENTS

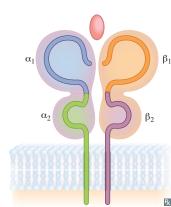
#### Innate vs adaptive immunity

	Innate immunity	Adaptive immunity
COMPONENTS	Neutrophils, macrophages, monocytes, dendritic cells, natural killer (NK) cells (lymphoid origin), complement, physical epithelial barriers, secreted enzymes	T cells, B cells, circulating antibodies
MECHANISM	Germline encoded	Variation through V(D)J recombination during lymphocyte development
RESISTANCE	Resistance persists through generations; does not change within an organism's lifetime	Microbial resistance not heritable
RESPONSE TO PATHOGENS	Nonspecific Occurs rapidly (minutes to hours) No memory response	Highly specific, refined over time Develops over long periods; memory response is faster and more robust
SECRETED PROTEINS	Lysozyme, complement, C-reactive protein (CRP), defensins, cytokines	Immunoglobulins
KEY FEATURES IN PATHOGEN RECOGNITION	Toll-like receptors (TLRs): pattern recognition receptors that recognize pathogen-associated molecular patterns (PAMPs) and lead to activation of NF-κB. Examples of PAMPs include LPS (gram ⊖ bacteria), flagellin (bacteria), nucleic acids (viruses)	Memory cells: activated B and T cells; subsequent exposure to a previously encountered antigen → stronger, quicker immune response

FAS1\_2019\_02-Immunology.indd 99 11/7/19 3:24 PM

Major histocompatibility complex I and II	MHC encoded by HLA genes. Present antigen fra (TCRs).	agments to T cells and bind T-cell receptors
	MHCI	MHCII
LOCI	HLA-A, HLA-B, HLA-C MHC I loci have 1 letter	HLA- <b>DP</b> , HLA- <b>DQ</b> , HLA- <b>DR</b> MHC <b>II</b> loci have <b>2</b> letters
BINDING	TCR and CD8	TCR and CD4
STRUCTURE	1 long chain, 1 short chain	2 equal-length chains (2 $\alpha$ , 2 $\beta$ )
EXPRESSION	All nucleated cells, APCs, platelets (except RBCs)	APCs
FUNCTION	Present endogenous antigens (eg, viral or cytosolic proteins) to CD8+ cytotoxic T cells	Present exogenous antigens (eg, bacterial proteins) to CD4+ helper T cells
ANTIGEN LOADING	Antigen peptides loaded onto MHC I in RER after delivery via TAP (transporter associated with antigen processing)	Antigen loaded following release of invariant chain in an acidified endosome
ASSOCIATED PROTEINS	$eta_2$ -microglobulin	Invariant chain
STRUCTURE	Peptide - Peptid	





#### **HLA subtypes associated with diseases**

HLA SUBTYPE	DISEASE	MNEMONIC
A3	Hemochromatosis	HA3mochromatosis
B8	Addison disease, myasthenia gravis, Graves disease	Don't <b>B</b> e late(8), Dr. <b>Addison</b> , or else you'll send <b>my</b> patient to the <b>grave</b>
B27	Psoriatic arthritis, Ankylosing spondylitis, IBD-associated arthritis, Reactive arthritis	PAIR. Also called seronegative arthropathies
С	Psoriasis	
DQ2/DQ8	Celiac disease	I ate (8) too (2) much gluten at Dairy Queen
DR2	Multiple sclerosis, hay fever, SLE, Good <mark>pasture</mark> syndrome	DRive 2 multiple hay pastures
DR3	DM type 1, <b>SLE</b> , Graves disease, Hashimoto thyroiditis, Addison disease	2-3, S-L-E
DR4	Rheumatoid arthritis, DM type 1, Addison disease	There are 4 walls in 1 "rheum" (room)
DR5	Hashimoto thyroiditis	Hashimoto is an odd Dr (DR3, DR5)

FAS1\_2019\_02-Immunology.indd 100 11/7/19 3:24 PM

## Functions of natural killer cells

Lymphocyte member of innate immune system.

Use perforin and granzymes to induce apoptosis of virally infected cells and tumor cells.

Activity enhanced by IL-2, IL-12, IFN- $\alpha$ , and IFN- $\beta$ .

Induced to kill when exposed to a nonspecific activation signal on target cell and/or to an absence

of MHC I on target cell surface.

Also kills via antibody-dependent cell-mediated cytotoxicity (CD16 binds Fc region of bound IgG,

activating the NK cell).

### Major functions of B and T cells

B cells Humoral immunity.

Recognize and present antigen—undergo somatic hypermutation to optimize antigen specificity.

Produce antibody—differentiate into plasma cells to secrete specific immunoglobulins.

Maintain immunologic memory—memory B cells persist and accelerate future response to antigen.

T cells Cell-mediated immunity.

CD4+ T cells help B cells make antibodies and produce cytokines to recruit phagocytes and

activate other leukocytes.

CD8+ T cells directly kill virus-infected and tumor cells via perforin and granzymes (similar to NK

cells).

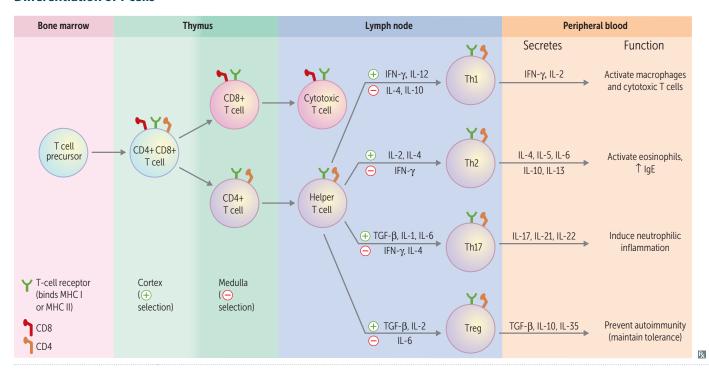
Delayed cell-mediated hypersensitivity (type IV).

Acute and chronic cellular organ rejection.

Rule of 8: MHC II  $\times$  CD4 = 8; MHC I  $\times$  CD8 = 8.

FAS1\_2019\_02-Immunology.indd 101 11/7/19 3:24 PM

#### **Differentiation of T cells**



#### Positive selection

Thymic cortex. T cells expressing TCRs capable of binding self-MHC on cortical epithelial cells survive.

#### **Negative selection**

Thymic medulla. T cells expressing TCRs with high affinity for self antigens undergo apoptosis or become regulatory T cells. Tissue-restricted self-antigens are expressed in the thymus due to the action of autoimmune regulator (AIRE); deficiency leads to autoimmune polyendocrine syndrome-l (Chronic mucocutaneous candidiasis, Hypoparathyroidism, Adrenal insufficiency, Recurrent Candida infections). "Without AIRE, your body will CHAR".

### Macrophagelymphocyte interaction

Th1 cells secrete IFN- $\gamma$ , which enhances the ability of monocytes and macrophages to kill microbes they ingest. This function is also enhanced by interaction of T cell CD40L with CD40 on macrophages. Macrophages also activate lymphocytes via antigen presentation.

## **Cytotoxic T cells**

Kill virus-infected, neoplastic, and donor graft cells by inducing apoptosis. Release cytotoxic granules containing preformed proteins (eg, perforin, granzyme B). Cytotoxic T cells have CD8, which binds to MHC I on virus-infected cells.

#### **Regulatory T cells**

Help maintain specific immune tolerance by suppressing CD4<sup>+</sup> and CD8<sup>+</sup> T-cell effector functions. Identified by expression of CD3, CD4, CD25, and FOXP3. Activated regulatory T cells (Tregs) produce anti-inflammatory cytokines (eg, IL-10, TGF-β).

**IPEX** (Immune dysregulation, Polyendocrinopathy, Enteropathy, X-linked) syndrome—genetic deficiency of FOXP3 → autoimmunity. Characterized by enteropathy, endocrinopathy, nail dystrophy, dermatitis, and/or other autoimmune dermatologic conditions. Associated with diabetes in male infants.

FAS1\_2019\_02-Immunology.indd 102 11/7/19 3:24 PM

#### T- and B-cell activation

APCs: B cells, dendritic cells, Langerhans cells, macrophages.

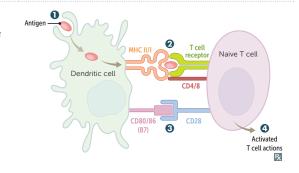
Two signals are required for T-cell activation, B-cell activation, and class switching.

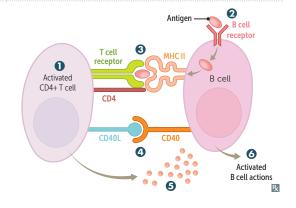
#### **T-cell activation**

- Dendritic cell (specialized APC) samples and processes antigen, then migrates to the draining lymph node.
- 2 T-cell activation (signal 1): exogenous antigen is presented on MHC II and recognized by TCR on Th (CD4+) cell. Endogenous or cross-presented antigen is presented on MHC I to Tc (CD8+) cell.
- 3 Proliferation and survival (signal 2): costimulatory signal via interaction of B7 protein (CD80/86) on dendritic cell and CD28 on naïve T cell.
- Activated Th cell produces cytokines. To cell able to recognize and kill virus-infected cell.

## B-cell activation and class switching

- Th-cell activation as above.
- **2** B-cell receptor–mediated endocytosis.
- **3** Exogenous antigen is presented on MHC II and recognized by TCR on Th cell.
- 4 CD40 receptor on B cell binds CD40 ligand (CD40L) on Th cell.
- **5** Th cells secrete cytokines that determine Ig class switching of B cells.
- **6** B cells are activated, undergo class switching and affinity maturation, and begin producing antibodies.



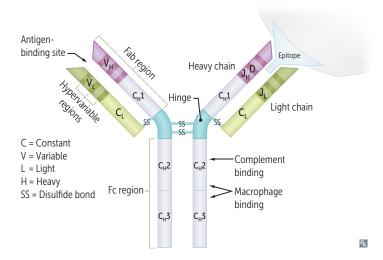


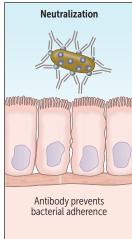
FAS1\_2019\_02-Immunology.indd 103 11/7/19 3:24 PM

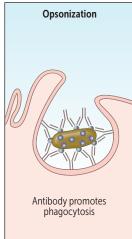
## ► IMMUNOLOGY—IMMUNE RESPONSES

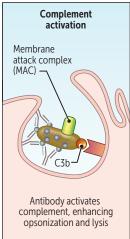
## Antibody structure and function

Fab (containing the variable/hypervariable regions) consisting of light (L) and heavy (H) chains recognizes antigens. Fc region of IgM and IgG fixes complement. Heavy chain contributes to Fc and Fab regions. Light chain contributes only to Fab region.









#### Fab:

- Fragment, antigen binding
- Determines idiotype: unique antigen-binding pocket; only 1 antigenic specificity expressed per B cell

### Fc (5 C's):

- Constant
- Carboxy terminal
- Complement binding
- Carbohydrate side chains
- Confers (determines) isotype (IgM, IgD, etc)

## Generation of antibody diversity (antigen independent)

- 1. Random recombination of VJ (light-chain) or V(D)J (heavy-chain) genes
- 2. Random addition of nucleotides to DNA during recombination by terminal deoxynucleotidyl transferase (TdT)
- 3. Random combination of heavy chains with light chains

## Generation of antibody specificity (antigen dependent)

- 4. Somatic hypermutation and affinity maturation (variable region)
- 5. Isotype switching (constant region)

FAS1\_2019\_02-Immunology.indd 104 11/7/19 3:24 PM

## Immunoglobulin isotypes

All isotypes can exist as monomers. Mature, naïve B cells prior to activation express IgM and IgD on their surfaces. They may differentiate in germinal centers of lymph nodes by isotype switching (gene rearrangement; induced by cytokines and CD40L) into plasma cells that secrete IgA, IgE, or IgG.

Affinity refers to the individual antibody-antigen interaction, while avidity describes the cumulative binding strength of all antibody-antigen interactions in a multivalent molecule.

#### **IgG**



Main antibody in 2° response to an antigen. Most abundant isotype in serum. Fixes complement, opsonizes bacteria, neutralizes bacterial toxins and viruses. Only isotype that crosses the placenta (provides infants with passive immunity that starts to wane after birth). "IgG Greets the Growing fetus."

#### **IgA**



Prevents attachment of bacteria and viruses to mucous membranes; does not fix complement. Monomer (in circulation) or dimer (with J chain when secreted). Crosses epithelial cells by transcytosis. Produced in GI tract (eg, by Peyer patches) and protects against gut infections (eg, *Giardia*). Most produced antibody overall, but has lower serum concentrations. Released into secretions (tears, saliva, mucus) and breast milk. Picks up secretory component from epithelial cells, which protects the Fc portion from luminal proteases.

### **IgM**



Produced in the 1° (immediate) response to an antigen. Fixes complement. Antigen receptor on the surface of B cells. Monomer on B cell, pentamer with J chain when secreted. Pentamer enables avid binding to antigen while humoral response evolves.

#### **IgD**

Unclear function. Found on surface of many B cells and in serum.



#### **IgE**



Binds mast cells and basophils; cross-links when exposed to allergen, mediating immediate (type I) hypersensitivity through release of inflammatory mediators such as histamine. Contributes to immunity to parasites by activating eosinophils.

### **Antigen type and memory**

Thymus-independen	t
antigens	

Antigens lacking a peptide component (eg, lipopolysaccharides from gram ⊖ bacteria); cannot be presented by MHC to T cells. Weakly immunogenic; vaccines often require boosters and adjuvants (eg, capsular polysaccharide subunit of *Streptococcus pneumoniae* PPSV23 vaccine).

## Thymus-dependent antigens

Antigens containing a protein component (eg, *Streptococcus pneumoniae* PCV13 vaccine, polysaccharides conjugated to diphtheria toxin-like protein). Class switching and immunologic memory occur as a result of direct contact of B cells with Th cells.

FAS1\_2019\_02-Immunology.indd 105 11/7/19 3:24 PM

FAS1\_2019\_02-Immunology.indd 106 11/7/19 3:24 PM

**SECTION II** 

### **Complement disorders**

### Complement protein deficiencies

**Early complement** deficiencies (C1-C4) Increased risk of severe, recurrent pyogenic sinus and respiratory tract infections. Increased risk of

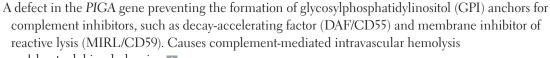
**Terminal complement** Increased susceptibility to recurrent Neisseria bacteremia. deficiencies (C5-C9)

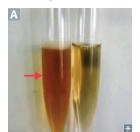
#### Complement regulatory protein deficiencies

C1 esterase inhibitor deficiency

Causes hereditary angioedema due to unregulated activation of kallikrein → ↑ bradykinin. Characterized by \$\ddot C4\$ levels. ACE inhibitors are contraindicated (also \$\ddot\$ bradykinin).

Paroxysmal nocturnal hemoglobinuria





→ \ haptoglobin, dark urine A.

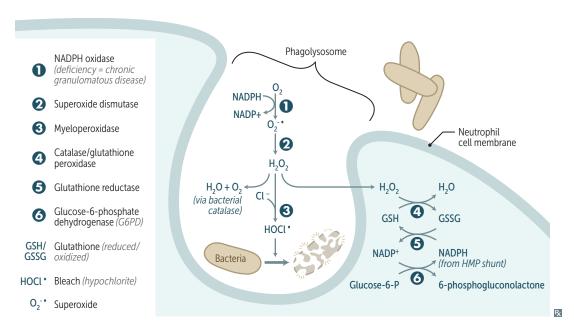
FAS1\_2019\_02-Immunology.indd 107 11/7/19 3:24 PM

Important cytokines	Acute (IL-1, IL-6, TNF-α), then recruit (IL-8, IL-	-12).
SECRETED BY MACROPHAGES		
Interleukin-1	Causes fever, acute inflammation. Activates endothelium to express adhesion molecules. Induces chemokine secretion to recruit WBCs. Also called osteoclast-activating factor.	"Hot T-bone stEAK":  IL-1: fever (hot).  IL-2: stimulates T cells.  IL-3: stimulates bone marrow.  IL-4: stimulates IgE production.  IL-5: stimulates IgA production.  IL-6: stimulates aKute-phase protein production.
Interleukin-6	Causes fever and stimulates production of acute- phase proteins.	
Tumor necrosis factor- $\alpha$	Activates endothelium. Causes WBC recruitment, vascular leak.	Causes cachexia in malignancy. Maintains granulomas in TB. IL-1, IL-6, TNF-α can mediate fever and sepsis.
Interleukin-8	Major chemotactic factor for neutrophils.	"Clean up on aisle 8." Neutrophils are recruited by IL-8 to clear infections.
Interleukin-12	Induces differentiation of T cells into Th1 cells. Activates NK cells.	
SECRETED BY ALL T CELLS		
Interleukin-2	Stimulates growth of helper, cytotoxic, and regulatory T cells, and NK cells.	
Interleukin-3	Supports growth and differentiation of bone marrow stem cells. Functions like GM-CSF.	
FROM Th1 CELLS		
Interferon-γ	Secreted by NK cells and T cells in response to antigen or IL-12 from macrophages; stimulates macrophages to kill phagocytosed pathogens. Inhibits differentiation of Th2 cells.	Also activates NK cells to kill virus-infected cells. Increases MHC expression and antigen presentation by all cells. Activates macrophages to induce granuloma formation.
FROM Th2 CELLS		
Interleukin-4	Induces differentiation of T cells into Th (helper) 2 cells. Promotes growth of B cells. Enhances class switching to IgE and IgG.	Ain't too proud 2 BEG 4 help.
Interleukin-5	Promotes growth and differentiation of B cells. Enhances class switching to IgA. Stimulates growth and differentiation of eosinophils.	
Interleukin-10	Attenuates inflammatory response. Decreases expression of MHC class II and Th1 cytokines. Inhibits activated macrophages and dendritic cells. Also secreted by regulatory T cells.	TGF- $\beta$ and IL-10 both attenuate the immune response.

FAS1\_2019\_02-Immunology.indd 108 11/7/19 3:24 PM

#### **Respiratory burst**

Also called oxidative burst. Involves the activation of the phagocyte NADPH oxidase complex (eg, in neutrophils, monocytes), which utilizes  $O_2$  as a substrate. Plays an important role in the immune response  $\rightarrow$  rapid release of reactive oxygen species (ROS). NADPH plays a role in both the creation and neutralization of ROS. Myeloperoxidase contains a blue-green, heme-containing pigment that gives sputum its color.



Phagocytes of patients with CGD can utilize  $H_2O_2$  generated by invading organisms and convert it to ROS. Patients are at † risk for infection by catalase  $\oplus$  species (eg, *S aureus*, *Aspergillus*) capable of neutralizing their own  $H_2O_2$ , leaving phagocytes without ROS for fighting infections. Pyocyanin of *P aeruginosa* generates ROS to kill competing pathogens. Oxidative burst also leads to  $K^+$  influx, which releases lysosomal enzymes. Lactoferrin is a protein found in secretory fluids and neutrophils that inhibits microbial growth via iron chelation.

Interferons	IFN- $\alpha$ , IFN- $\beta$ , IFN- $\gamma$
MECHANISM	A part of innate host defense, interferons interfere with both RNA and DNA viruses. Cells infected with a virus synthesize these glycoproteins, which act on local cells, priming them for viral defense by downregulating protein synthesis to resist potential viral replication and by upregulating MHC expression to facilitate recognition of infected cells. Also play a major role in activating antitumor immunity.
CLINICAL USE	Chronic HBV, Kaposi sarcoma, hairy cell leukemia, condyloma acuminatum, renal cell carcinoma, malignant melanoma, multiple sclerosis, chronic granulomatous disease.
ADVERSE EFFECTS	Flu-like symptoms, depression, neutropenia, myopathy, interferon-induced autoimmunity.

FAS1\_2019\_02-Immunology.indd 109 11/7/19 3:24 PM

110 SECTION II

**IMMUNOLOGY** ► IMMUNOLOGY—IMMUNE RESPONSES

## **Cell surface proteins**

T cells	TCR (binds antigen-MHC complex) CD3 (associated with TCR for signal	
	transduction) CD28 (binds B7 on APC)	
Helper T cells	CD4, CD40L, CXCR4/CCR5 (co-receptors for HIV)	
Cytotoxic T cells	CD8	
Regulatory T cells	CD4, CD25	
B cells	Ig (binds antigen) CD19, CD20, CD21 (receptor for Epstein-Barr virus), CD40 MHC II, B7	Must be <b>21</b> to drink <b>B</b> eer in a <b>Barr</b>
Macrophages	CD14 (receptor for PAMPs, eg, LPS), CD40 CCR5 MHC II, B7 (CD80/86) Fc and C3b receptors (enhanced phagocytosis)	
NK cells	CD16 (binds Fc of IgG), CD56 (suggestive marker for NK)	
Hematopoietic stem cells	CD34	
A	See 1 · 1·1 · 11 · 11 · 11 · 11	11

## **Anergy**

State during which a cell cannot become activated by exposure to its antigen. T and B cells become anergic when exposed to their antigen without costimulatory signal (signal 2). Another mechanism of self-tolerance.

## Passive vs active immunity

	Passive	Active
MEANS OF ACQUISITION	Receiving preformed antibodies	Exposure to exogenous antigens
ONSET	Rapid	Slow
DURATION	Short span of antibodies (half-life = 3 weeks)	Long-lasting protection (memory)
EXAMPLES	IgA in breast milk, maternal IgG crossing placenta, antitoxin, humanized monoclonal antibody	Natural infection, vaccines, toxoid
After exposure to Tetanus toxin, Botulinum toxin, HBV, Varicella, Rabies virus, or Diphtheria toxin, unvaccinated patients are given preformed antibodies (passive)—"To Be Healed Very Rapidly before Dying"		Combined passive and active immunizations can be given for hepatitis B or rabies exposure

FAS1\_2019\_02-Immunology.indd 110 11/7/19 3:24 PM

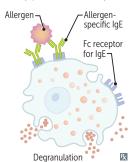
<b>Vaccination</b> Induces an active immune response (humoral and/or cellular) to specific pathogens.
---

VACCINE TYPE	DESCRIPTION	PROS/CONS	EXAMPLES
Live attenuated vaccine	Microorganism loses its pathogenicity but retains capacity for transient growth within inoculated host. Induces <b>cellular and humoral responses</b> . MMR and varicella vaccines can be given to HIV ⊕ patients without evidence of immunity if CD4 cell count ≥ 200 cells/mm <sup>3</sup> .	Pros: induces strong, often lifelong immunity.  Cons: may revert to virulent form. Often contraindicated in pregnancy and immunodeficiency.	Adenovirus (nonattenuated, given to military recruits), Typhoid (Ty2la, oral), Polio (Sabin), Varicella (chickenpox), Smallpox, BCG, Yellow fever, Influenza (intranasal), MMR, Rotavirus "Attention Teachers! Please Vaccinate Small, Beautiful Young Infants with MMR Regularly!"
Killed or inactivated vaccine	Pathogen is inactivated by heat or chemicals. Maintaining epitope structure on surface antigens is important for immune response. Mainly induces a humoral response.	Pros: safer than live vaccines. Cons: weaker immune response; booster shots usually required.	Hepatitis A, Typhoid (Vi polysaccharide, intramuscular), Rabies, Influenza, Polio (SalK) A TRIP could Kill you
Subunit	Includes only the antigens that best stimulate the immune system.	Pros: lower chance of adverse reactions. Cons: expensive, weaker immune response.	HBV (antigen = HBsAg), HPV (types 6, 11, 16, and 18), acellular pertussis (aP), Neisseria meningitidis (various strains), Streptococcus pneumoniae, Haemophilus influenzae type b.
Toxoid	Denatured bacterial toxin with an intact receptor binding site. Stimulates the immune system to make antibodies without potential for causing disease.	Pros: protects against the bacterial toxins.  Cons: antitoxin levels decrease with time, may require a booster.	Clostridium tetani, Corynebacterium diphtheriae

FAS1\_2019\_02-Immunology.indd 111 11/7/19 3:24 PM

**Hypersensitivity types** Four types (ABCD): Anaphylactic and Atopic (type I), AntiBody-mediated (type II), Immune Complex (type III), Delayed (cell-mediated, type IV). Types I, II, and III are all antibody-mediated.

## Type I hypersensitivity



Anaphylactic and atopic—two phases:

- Immediate (minutes): antigen crosslinks
  preformed IgE on presensitized mast cells
   → immediate degranulation → release of
  histamine (a vasoactive amine) and tryptase
   (a marker of mast cell activation).
- Late (hours): chemokines (attract inflammatory cells, eg, eosinophils) and other mediators (eg, leukotrienes) from mast cells → inflammation and tissue damage.

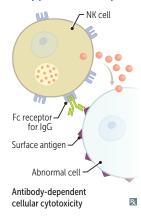
First (type) and Fast (anaphylaxis).

Test: skin test or blood test (ELISA) for allergenspecific IgE.

#### Example:

- Anaphylaxis (eg, food, drug, or bee sting allergies)
- Allergic asthma

## Type II hypersensitivity



Antibodies bind to cell-surface antigens

→ cellular destruction, inflammation, and cellular dysfunction.

Cellular destruction—cell is opsonized (coated) by antibodies, leading to either:

- Phagocytosis and/or activation of complement system.
- NK cell killing (antibody-dependent cellular cytotoxicity).

Inflammation—binding of antibodies to cell surfaces → activation of complement system and Fc receptor-mediated inflammation.

Cellular dysfunction—antibodies bind to cell surface receptors → abnormal blockade or activation of downstream process.

Direct Coombs test—detects antibodies attached directly to the RBC surface. Indirect Coombs test—detects presence of unbound antibodies in the serum

#### Examples:

- Autoimmune-hemolytic anemia
- Immune thrombocytopenia
- Transfusion reactions
- Hemolytic disease of the newborn

#### Examples:

- Goodpasture syndrome
- Rheumatic fever
- Hyperacute transplant rejection

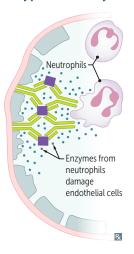
### Examples:

- Myasthenia gravis
- Graves disease
- Pemphigus vulgaris

FAS1\_2019\_02-Immunology.indd 112 11/7/19 3:24 PM

### Hypersensitivity types (continued)

## Type III hypersensitivity



Immune complex—antigen-antibody (mostly IgG) complexes activate complement, which attracts neutrophils; neutrophils release lysosomal enzymes.

Can be associated with vasculitis and systemic manifestations.

Serum sickness—the prototypic immune complex disease. Antibodies to foreign proteins are produced and 1–2 weeks later, antibodyantigen complexes form and deposit in tissues → complement activation → inflammation and tissue damage.

Arthus reaction—a local subacute immune complex-mediated hypersensitivity reaction. Intradermal injection of antigen into a presensitized (has circulating IgG) individual leads to immune complex formation in the skin (eg, enhanced local reaction to a booster vaccination). Characterized by edema, necrosis, and activation of complement.

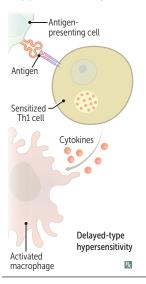
In type III reaction, imagine an immune complex as 3 things stuck together: antigenantibody-complement.

#### Examples:

- SLE
- Polyarteritis nodosa
- Poststreptococcal glomerulonephritis

Fever, urticaria, arthralgia, proteinuria, lymphadenopathy occur 1–2 weeks after antigen exposure. Serum sickness-like reactions are associated with some drugs (may act as haptens, eg, penicillin) and infections (eg, hepatitis B).

## Type IV hypersensitivity



Two mechanisms, each involving T cells:

- 1. Direct cell cytotoxicity: CD8+ cytotoxic T cells kill targeted cells.
- 2. Inflammatory reaction: effector CD4+ T cells recognize antigen and release inflammation-inducing cytokines (shown in illustration).

Response does not involve antibodies (vs types I, II, and III).

Examples: contact dermatitis (eg, poison ivy, nickel allergy) and graft-versus-host disease.

Tests: PPD for TB infection; patch test for contact dermatitis; *Candida* skin test for T cell immune function.

4T's: T cells, Transplant rejections, TB skin tests, Touching (contact dermatitis).

Fourth (type) and last (delayed).

FAS1\_2019\_02-Immunology.indd 113 117/19 3:24 PM

## **Blood transfusion reactions**

ТҮРЕ	PATHOGENESIS	TIMING	CLINICAL PRESENTATION	DONOR BLOOD	HOST BLOOD
Allergic/ anaphylactic reaction	Type I hypersensitivity reaction against plasma proteins in transfused blood IgA-deficient individuals should receive blood products without IgA	Within minutes to 2-3 hr (due to release of preformed inflammatory mediators in degranulating mast cells)	Allergies: urticaria, pruritus Anaphylaxis: wheezing, hypotension, respiratory arrest, shock	Donor plasma proteins, including IgA	IgE (anti-IgA) Host mast cell
Acute hemolytic transfusion reaction	Type II hypersensitivity reaction Typically causes intravascular hemolysis (ABO blood group incompatibility)	During transfusion or within 24 hr (due to preformed antibodies)	Fever, hypotension, tachypnea, tachycardia, flank pain, hemoglobinuria (intravascular), jaundice (extravascular)	Donor RBC with A and/ or B group antigens	Host anti-A, anti-B IgG, IgM
Febrile nonhemolytic transfusion reaction	Cytokines created by donor WBCs accumulate during storage of blood products Reactions prevented by leukoreduction of blood products	Within 1-6 hr (due to preformed cytokines)	Fever, headaches, chills, flushing More common in children	Donor WBC releases preformed cytokines ☑	
Transfusion- related acute lung injury	<ul> <li>Two-hit mechanism:</li> <li>Neutrophils are sequestered and primed in pulmonary vasculature due to recipient risk factors</li> <li>Neutrophils are activated by a product (eg, antileukocyte antibodies) in the transfused blood and release inflammatory mediators → † capillary permeability</li> <li>→ pulmonary edema</li> </ul>	Within minutes to 6 hr	Respiratory distress, noncardiogenic pulmonary edema	Host neutrophi  Donor antileukocyte IgG	ls ·
Delayed hemolytic transfusion reaction	Anamnestic response to a foreign antigen on donor RBCs (most commonly Rh or other minor blood group antigens) previously encountered by recipient Typically causes extravascular hemolysis	Onset over 24 hr Usually presents within 1-2 wk (due to slow destruction by reticuloendothelial system)	Generally self limited and clinically silent Mild fever, hyperbilirubinemia	Donor RBC with foreign antigens	Host IgG   ⋉

FAS1\_2019\_02-Immunology.indd 114 11/7/19 3:24 PM

Autoantibodies	AUTOANTIBODY	ASSOCIATED DISORDER
	Anti-postsynaptic ACh receptor	Myasthenia gravis
	Anti-presynaptic voltage-gated calcium channel	Lambert-Eaton myasthenic syndrome
	Anti-β <sub>2</sub> glycoprotein I	Antiphospholipid syndrome
	Antinuclear (ANA)	Nonspecific screening antibody, often associated with SLE
	Anticardiolipin, lupus anticoagulant	SLE, antiphospholipid syndrome
	Anti-dsDNA, anti-Smith	SLE
	Antihistone	Drug-induced lupus
	Anti-Ul RNP (ribonucleoprotein)	Mixed connective tissue disease
	Rheumatoid factor (IgM antibody against IgG Fc region), anti-CCP (more specific)	Rheumatoid arthritis
	Anti-Ro/SSA, anti-La/SSB	Sjögren syndrome
	Anti-Scl-70 (anti-DNA topoisomerase I)	Seleroderma (diffuse)
	Anticentromere	Limited scleroderma (CREST syndrome)
	Antisynthetase (eg, anti-Jo-l), anti-SRP, anti- helicase (anti-Mi-2)	Polymyositis, dermatomyositis
	Antimitochondrial	1° biliary cholangitis
	Anti-smooth muscle	Autoimmune hepatitis type 1
	MPO-ANCA/p-ANCA	Microscopic polyangiitis, eosinophilic granulomatosis with polyangiitis (Churg- Strauss syndrome), ulcerative colitis
	PR3-ANCA/c-ANCA	Granulomatosis with polyangiitis (Wegener)
	Anti-phospholipase A <sub>2</sub> receptor	1° membranous nephropathy
	Anti-hemidesmosome	Bullous pemphigoid
	Anti-desmoglein (anti-desmosome)	Pemphigus vulgaris
	Antithyroglobulin, antithyroid peroxidase (antimicrosomal)	Hashimoto thyroiditis
	Anti-TSH receptor	Graves disease
	IgA anti-endomysial, IgA anti-tissue transglutaminase, IgA and IgG deamidated gliadin peptide	Celiac disease
	Anti-glutamic acid decarboxylase, islet cell cytoplasmic antibodies	Type 1 diabetes mellitus
	Antiparietal cell, anti-intrinsic factor	Pernicious anemia
	Anti-glomerular basement membrane	Goodpasture syndrome

FAS1\_2019\_02-Immunology.indd 115 11/7/19 3:24 PM

## **Immunodeficiencies**

DISEASE	DEFECT	PRESENTATION	FINDINGS	
B-cell disorders				
X-linked (Bruton) agammaglobulinemia	Defect in <i>BTK</i> , a tyrosine kinase gene → no <b>B</b> -cell maturation; X-linked recessive († in <b>B</b> oys)	Recurrent bacterial and enteroviral infections after 6 months (\$\ddagger\$ maternal IgG)	Absent B cells in peripheral blood, ↓ Ig of all classes.  Absent/scanty lymph nodes and tonsils (1° follicles and germinal centers absent) → live vaccines contraindicated	
Selective IgA deficiency	Cause unknown Most common 1° immunodeficiency	Majority Asymptomatic Can see Airway and GI infections, Autoimmune disease, Atopy, Anaphylaxis to IgA-containing products	↓ IgA with normal IgG, IgM levels  ↑ susceptibility to giardiasis Can cause false-positive β-hCG test	
Common variable immunodeficiency	Defect in B-cell differentiation.  Cause unknown in most cases	May present in childhood but usually diagnosed after puberty  † risk of autoimmune disease, bronchiectasis, lymphoma, sinopulmonary infections	↓ plasma cells, ↓ immunoglobulins	
T-cell disorders				
Thymic aplasia	22qll microdeletion; failure to develop 3rd and 4th pharyngeal pouches → absent thymus and parathyroids DiGeorge syndrome—thymic, parathyroid, cardiac defects Velocardiofacial syndrome—palate, facial, cardiac defects	CATCH-22: Cardiac defects (conotruncal abnormalities [eg, tetralogy of Fallot, truncus arteriosus]), Abnormal facies, Thymic hypoplasia → T-cell deficiency (recurrent viral/ fungal infections), Cleft palate, Hypocalcemia 2° to parathyroid aplasia → tetany	↓ T cells, ↓ PTH, ↓ Ca <sup>2+</sup> Thymic shadow absent on CXR	
IL-12 receptor deficiency	↓ Th1 response; autosomal recessive	Disseminated mycobacterial and fungal infections; may present after administration of BCG vaccine	↓ IFN-γ Most common cause of Mendelian susceptibility to mycobacterial diseases (MSMD)	
Autosomal dominant hyper-IgE syndrome	Deficiency of Th17 cells due to STAT3 mutation → impaired	Cold (noninflamed) staphylococcal Abscesses,	↑ IgE ↑ eosinophils	
(Job syndrome)	recruitment of neutrophils to sites of infection	retained Baby teeth, Coarse facies, Dermatologic problems (eczema), † IgE, bone Fractures from minor trauma	Learn the ABCDEF's to get a Job!	
Chronic mucocutaneous candidiasis	T-cell dysfunction Impaired cell-mediated immunity against <i>Candida</i> sp Classic form caused by defects in <i>AIRE</i>	Persistent noninvasive <i>Candida</i> albicans infections of skin and mucous membranes	Absent in vitro T-cell proliferation in response to Candida antigens Absent cutaneous reaction to Candida antigens	

FAS1\_2019\_02-Immunology.indd 116 11/7/19 3:24 PM

## Immunodeficiencies (continued)

DISEASE	DEFECT	PRESENTATION	FINDINGS
B- and T-cell disorders			
Severe combined immunodeficiency	Several types including defective IL-2R gamma chain (most common, X-linked recessive); adenosine deaminase deficiency (autosomal recessive); RAG mutation → VDJ recombination defect	Failure to thrive, chronic diarrhea, thrush Recurrent viral, bacterial, fungal, and protozoal infections	↓ T-cell receptor excision circles (TRECs) Absence of thymic shadow (CXR), germinal centers (lymph node biopsy), and T cells (flow cytometry)
Ataxia-telangiectasia	Defects in ATM gene → failure to detect DNA damage → failure to halt progression of cell cycle → mutations accumulate; autosomal recessive	Triad: cerebellar defects (Ataxia), spider Angiomas (telangiectasia A), IgA deficiency  † sensitivity to radiation (limit x-ray exposure)	↑ AFP ↓ IgA, IgG, and IgE Lymphopenia, cerebellar atrophy ↑ risk of lymphoma and leukemia
Hyper-IgM syndrome	Most commonly due to defective CD40L on Th cells → class switching defect; X-linked recessive	Severe pyogenic infections early in life; opportunistic infection with <i>Pneumocystis</i> , <i>Cryptosporidium</i> , CMV	Normal or ↑ IgM ↓↓ IgG, IgA, IgE Failure to make germinal centers
Wiskott-Aldrich syndrome	Mutation in WAS gene; leukocytes and platelets unable to reorganize actin cytoskeleton → defective antigen presentation; X-linked recessive	WATER: Wiskott-Aldrich: Thrombocytopenia, Eczema, Recurrent (pyogenic) infections ↑ risk of autoimmune disease and malignancy	↓ to normal IgG, IgM † IgE, IgA Fewer and smaller platelets
Phagocyte dysfunction			
Leukocyte adhesion deficiency (type 1)	Defect in LFA-1 integrin (CD18) protein on phagocytes; impaired migration and chemotaxis; autosomal recessive	Late separation (>30 days) of umbilical cord, absent pus, dysfunctional neutrophils  → recurrent skin and mucosal bacterial infections	† neutrophils in blood Absence of neutrophils at infection sites → impaired wound healing
Chédiak-Higashi syndrome	Defect in lysosomal trafficking regulator gene (LYST) Microtubule dysfunction in phagosome-lysosome fusion; autosomal recessive	PLAIN: Progressive neurodegeneration, Lymphohistiocytosis, Albinism (partial), recurrent pyogenic Infections, peripheral Neuropathy	Giant granules (B, arrows) in granulocytes and platelets. Pancytopenia Mild coagulation defects
Chronic granulomatous disease	Defect of NADPH oxidase  → ↓ reactive oxygen species (eg, superoxide) and ↓ respiratory burst in neutrophils; X-linked form most common	↑ susceptibility to catalase ⊕ organisms	Abnormal dihydrorhodamine (flow cytometry) test († green fluorescence) Nitroblue tetrazolium dye reduction test (obsolete) fails to turn blue

FAS1\_2019\_02-Immunology.indd 117 11/7/19 3:24 PM

118 SECTION II

**IMMUNOLOGY** ► IMMUNOLOGY—IMMUNE RESPONSES

## Infections in immunodeficiency

PATHOGEN	↓ T CELLS	↓ B CELLS	↓ GRANULOCYTES	↓ COMPLEMENT
Bacteria	Sepsis	Encapsulated (Please SHINE my SKiS): Pseudomonas aeruginosa, Streptococcus pneumoniae, Haemophilus Influenzae type b, Neisseria meningitidis, Escherichia coli, Salmonella, Klebsiella pneumoniae, Group B Streptococcus	Some Bacteria Produce No Serious granules: Staphylococcus, Burkholderia cepacia, Pseudomonas aeruginosa, Nocardia, Serratia	Encapsulated species with early complement deficiencies Neisseria with late complement (C5–C9) deficiencies
Viruses	CMV, EBV, JC virus, VZV, chronic infection with respiratory/GI viruses	Enteroviral encephalitis, poliovirus (live vaccine contraindicated)	N/A	N/A
Fungi/parasites	Candida (local), PCP, Cryptococcus	GI giardiasis (no IgA)	Candida (systemic), Aspergillus, Mucor	N/A

Note: **B**-cell deficiencies tend to produce recurrent bacterial infections, whereas T-cell deficiencies produce more fungal and viral infections.

FAS1\_2019\_02-Immunology.indd 118 11/7/19 3:24 PM

## **Transplant rejection**

TYPE OF REJECTION	ONSET	PATHOGENESIS	FEATURES
Hyperacute A	Within minutes	Pre-existing recipient antibodies react to donor antigen (type II hypersensitivity reaction), activate complement	Widespread thrombosis of graft vessels (arrows within glomerulus ♠) → ischemia/necrosis Graft must be removed
Acute B	Weeks to months	Cellular: CD8+ T cells and/ or CD4+ T cells activated against donor MHCs (type IV hypersensitivity reaction) Humoral: similar to hyperacute, except antibodies develop after transplant	Vasculitis of graft vessels with dense interstitial lymphocytic infiltrate B Prevent/reverse with immunosuppressants
Chronic	Months to years	CD4+ T cells respond to recipient APCs presenting donor peptides, including allogeneic MHC Both cellular and humoral components (type II and IV hypersensitivity reactions)	Recipient T cells react and secrete cytokines → proliferation of vascular smooth muscle, parenchymal atrophy, interstitial fibrosis  Dominated by arteriosclerosis C  Organ-specific examples: Chronic allograft nephropathy Bronchiolitis obliterans Accelerated atherosclerosis (heart) Vanishing bile duct syndrome
Graft-versus-host disease	Varies	Grafted immunocompetent T cells proliferate in the immunocompromised host and reject host cells with "foreign" proteins → severe organ dysfunction Type IV hypersensitivity reaction	Maculopapular rash, jaundice, diarrhea, hepatosplenomegaly Usually in bone marrow and liver transplants (rich in lymphocytes) Potentially beneficial in bone marrow transplant for leukemia (graft-versus-tumor effect) For immunocompromised patients, irradiate blood products prior to transfusion to prevent GVHD

11/7/19 3:24 PM FAS1\_2019\_02-Immunology.indd 119

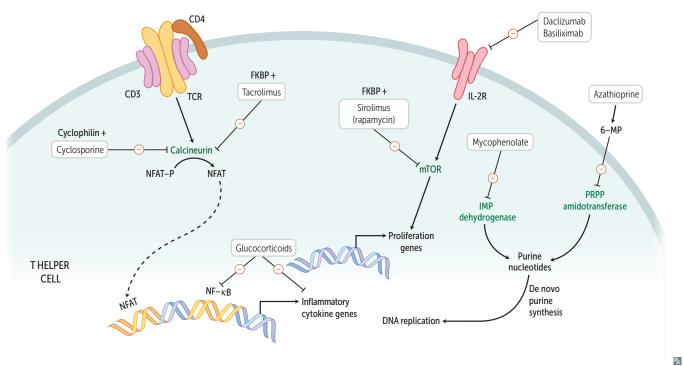
## ► IMMUNOLOGY—IMMUNOSUPPRESSANTS

Immunosuppressants	Agents that block lymphocyte activation and proliferation. Reduce acute transplant rejection by
	suppressing cellular immunity (used as prophylaxis). Frequently combined to achieve greater
	efficacy with \(\frac{1}{2}\) toxicity. Chronic suppression \(\frac{1}{2}\) risk of infection and malignancy

DRUG	MECHANISM	INDICATIONS	TOXICITY	NOTES
Cyclosporine	Calcineurin inhibitor; binds cyclophilin Blocks T-cell activation by preventing IL-2 transcription	Psoriasis, rheumatoid arthritis	Nephrotoxicity, hypertension, hyperlipidemia, neurotoxicity, gingival hyperplasia, hirsutism	Both calcineurin inhibitors are highly nephrotoxic,
Tacrolimus (FK506)	Calcineurin inhibitor; binds FK506 binding protein (FKBP) Blocks T-cell activation by preventing IL-2 transcription		Similar to cyclosporine, † risk of diabetes and neurotoxicity; no gingival hyperplasia or hirsutism	especially in higher doses or in patients with decreased renal function
Sirolimus (Rapamycin)	mTOR inhibitor; binds FKBP Blocks T-cell activation and B-cell differentiation by preventing response to IL-2	Kidney transplant rejection prophylaxis specifically Sir Basil's kidney transplant	"PanSirtopenia" (pancytopenia), insulin resistance, hyperlipidemia; not nephrotoxic	Kidney "sir-vives." Synergistic with cyclosporine Also used in drug- eluting stents
Basiliximab	Monoclonal antibody; blocks IL-2R		Edema, hypertension, tremor	
Azathioprine	Antimetabolite precursor of 6-mercaptopurine Inhibits lymphocyte proliferation by blocking nucleotide synthesis	Rheumatoid arthritis, Crohn disease, glomerulonephritis, other autoimmune conditions	Pancytopenia	6-MP degraded by xanthine oxidase; toxicity † by allopurinol Pronounce "azathiopurine"
Mycophenolate Mofetil	Reversibly inhibits  IMP dehydrogenase, preventing purine synthesis of B and T cells	Lupus nephritis	GI upset, pancytopenia, hypertension, hyperglycemia Less nephrotoxic and neurotoxic	Associated with invasive CMV infection
Glucocorticoids	Inhibit NF-κB Suppress both B- and T-cell function by ↓ transcription of many cytokines Induce T cell apoptosis	Many autoimmune and inflammatory disorders, adrenal insufficiency, asthma, CLL, non-Hodgkin lymphoma	Cushing syndrome, osteoporosis, hyperglycemia, diabetes, amenorrhea, adrenocortical atrophy, peptic ulcers, psychosis, cataracts, avascular necrosis (femoral head)	Demargination of WBCs causes artificial leukocytosis Adrenal insufficiency may develop if drug is stopped abruptly after chronic use

FAS1\_2019\_02-Immunology.indd 120 11/7/19 3:24 PM

### **Immunosuppression targets**



**Recombinant cytokines and clinical uses** 

CYTOKINE	AGENT	CLINICAL USES
Bone marrow stimulati	ion	
Erythropoietin	Epoetin alfa (EPO analog)	Anemias (especially in renal failure)
Colony stimulating factors	Filgrastim (G-CSF), Sargramostim (GM-CSF)	Leukopenia; recovery of granulocyte and monocyte counts
Thrombopoietin	Romi <b>pl</b> os <b>tim</b> (TPO analog), eltrombopag (TPO receptor agonist)	Autoimmune thrombocytopenia  Platelet stimulator
Immunotherapy		
Interleukin-2	Aldesleukin	Renal cell carcinoma, metastatic melanoma
Interferons	IFN-α	Chronic hepatitis C (not preferred) and B, renal cell carcinoma
	IFN-β	Multiple sclerosis
	IFN-γ	Chronic granulomatous disease

FAS1\_2019\_02-Immunology.indd 121 11/7/19 3:24 PM

## Therapeutic antibodies

AGENT AGENT	TARGET	CLINICAL USE	NOTES
Cancer therapy			
Alemtuzumab	CD52	CLL, multiple sclerosis	"A <mark>lym</mark> tuzumab"—chronic lymphocytic leukemia
Bevacizumab	VEGF	Colorectal cancer, renal cell carcinoma, non-small cell lung cancer	Also used for neovascular agerelated macular degeneration, proliferative diabetic retinopathy, and macular edema
Rituximab	CD20	B-cell non-Hodgkin lymphoma, CLL, rheumatoid arthritis, ITP, multiple sclerosis	Risk of PML in patients with JC virus CD20—"ri2ximab"
Trastuzumab	HER2	Breast cancer, gastric cancer	HER <mark>2</mark> —"tras <mark>2</mark> zumab"
Autoimmune disease the	erapy		
Adalimumab, infliximab	Soluble TNF-α	IBD, rheumatoid arthritis, ankylosing spondylitis, psoriasis	Etanercept is a decoy TNF-α receptor and not a monoclonal antibody
Eculizumab	Complement protein C5	Paroxysmal nocturnal hemoglobinuria	
Ixekizumab, secukinumab	IL-17A	Psoriasis, psoriatic arthritis	
Natalizumab	α4-integrin	Multiple sclerosis, Crohn disease	α4-integrin: WBC adhesion Risk of PML in patients with JC virus
Ustekinumab	IL-12/IL-23	Psoriasis, psoriatic arthritis	
Other applications			
Abciximab	Platelet glycoproteins IIb/IIIa	Antiplatelet agent for prevention of ischemic complications in patients undergoing percutaneous coronary intervention	ABC is as easy as 123
Denosumab	RANKL	Osteoporosis; inhibits osteoclast maturation (mimics osteoprotegerin)	Denosumab helps make dense bones
Omalizumab	IgE	Refractory allergic asthma; prevents IgE binding to FcεRI	
Palivizumab	RSV F protein	RSV prophylaxis for high-risk infants	Pali <b>VI</b> zumab— <b>VI</b> rus

FAS1\_2019\_02-Immunology.indd 122 11/7/19 3:24 PM

## HIGH-YIELD PRINCIPLES IN

## Microbiology

"Support bacteria. They're the only culture some people have."

-Steven Wright

"What lies behind us and what lies ahead of us are tiny matters compared to what lies within us."

-Henry S. Haskins

"Infectious disease is merely a disagreeable instance of a widely prevalent tendency of all living creatures to save themselves the bother of building, by their own efforts, the things they require."

-Hans Zinsser

Microbiology questions on the Step 1 exam often require two (or more) steps: Given a certain clinical presentation, you will first need to identify the most likely causative organism, and you will then need to provide an answer regarding some features of that organism or relevant antimicrobial agents. For example, a description of a child with fever and a petechial rash will be followed by a question that reads, "From what site does the responsible organism usually enter the blood?"

This section therefore presents organisms in two major ways: in individual microbial "profiles" and in the context of the systems they infect and the clinical presentations they produce. You should become familiar with both formats. When reviewing the systems approach, remind yourself of the features of each microbe by returning to the individual profiles. Also be sure to memorize the laboratory characteristics that allow you to identify microbes.

▶ Basic Bacteriology	124
Clinical Bacteriology	134
▶ Mycology	151
▶ Parasitology	155
▶Virology	162
Systems	178
▶ Antimicrobials	187

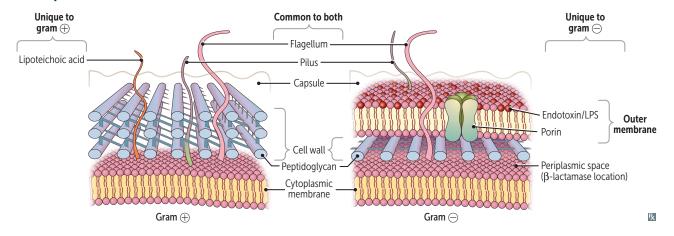
FAS1\_2019\_03-Microbiology.indd 123 11/14/19 12:19 PM

## ► MICROBIOLOGY—BASIC BACTERIOLOGY

#### **Bacterial structures**

STRUCTURE	CHEMICAL COMPOSITION	FUNCTION
Appendages		
Flagellum	Proteins	Motility
Pilus/fimbria	Glycoprotein	Mediate adherence of bacteria to cell surface; sex pilus forms during conjugation
Specialized structures	5	
Spore	Keratin-like coat; dipicolinic acid; peptidoglycan, DNA	Gram ⊕ only Survival: resist dehydration, heat, chemicals
Cell envelope		
Capsule	Discrete layer usually made of polysaccharides (and rarely proteins)	Protects against phagocytosis
Slime (S) layer	Loose network of polysaccharides	Mediates adherence to surfaces, especially foreign surfaces (eg, indwelling catheters)
Outer membrane	Outer leaflet: contains endotoxin (LPS/LOS) Embedded proteins: porins and other outer membrane proteins (OMPs) Inner leaflet: phospholipids	Gram ⊝ only Endotoxin: lipid A induces TNF and IL-1; antigenic O polysaccharide component Most OMPs are antigenic Porins: transport across outer membrane
Periplasm	Space between cytoplasmic membrane and outer membrane in gram ⊖ bacterial (peptidoglycan in middle)	Accumulates components exiting gram  Θ cells, including hydrolytic enzymes (eg, β-lactamases)
Cell wall	Peptidoglycan is a sugar backbone with peptide side chains cross-linked by transpeptidase	Net-like structure gives rigid support, protects against osmotic pressure damage
Cytoplasmic membrane	Phospholipid bilayer sac with embedded proteins (eg, penicillin-binding proteins [PBPs]) and other enzymes  Lipoteichoic acids (gram positive) only extend from membrane to exterior	Site of oxidative and transport enzymes; PBPs involved in cell wall synthesis Lipoteichoic acids induce TNF-α and IL-1

### **Cell envelope**



FAS1\_2019\_03-Microbiology.indd 124 11/14/19 12:19 PM

Gram stain	First-line lab test in bacterial identification. Bacteria with thick peptidoglycan layer retain crystal violet dye (gram ⊕); bacteria with thin peptidoglycan layer turn red or pink (gram ⊕) with counterstain.  These bugs do not Gram stain well (These Little Microbes May Unfortunately Lack Real Color But Are Everywhere):		
	Treponema, Leptospira	Too thin to be visualized	
	Mycobacteria	Cell wall has high lipid content	
	Mycoplasma, Ureaplasma	No cell wall	
	Legionella, Rickettsia, Chlamydia, Bartonella, Anaplasma, Ehrlichia	Primarily intracellular; also, <i>Chlamydia</i> lack classic peptidoglycan because of ‡ muramic acid	
Giemsa stain	Rickettsia, Chlamydia, Trypanosomes A, Plasmodium, Borrelia, Helicobacter pylori	Ricky got <i>Chlamydia</i> as he Tried to Please the Bored Hot "Geisha"	
Periodic acid–Schiff stain	Stains <b>glycogen</b> , mucopolysaccharides; used to diagnose Whipple disease ( <i>Tropheryma whipplei</i> <b>B</b> )	PaSs the sugar	
Ziehl-Neelsen stain (carbol fuchsin)	Acid-fast bacteria (eg, <i>Mycobacteria</i> C, <i>Nocardia</i> ; stains mycolic acid in cell wall); protozoa (eg, <i>Cryptosporidium</i> oocysts)	Auramine-rhodamine stain is more often used for screening (inexpensive, more sensitive)	
India ink stain	Cryptococcus neoformans D; mucicarmine can also be used to stain thick polysaccharide capsule red		
Silver stain	Fungi (eg, Coccidioides E, Pneumocystis jirovecii), Legionella, Helicobacter pylori		
Fluorescent antibody stain	Used to identify many bacteria, viruses, Pneumocystis jirovecii, Giardia, and Cryptosporidium	Example is FTA-ABS for syphilis	
A	B C		

11/14/19 12:19 PM FAS1\_2019\_03-Microbiology.indd 125

Properties of growth media	The same type of media can possess both (or neither) of these properties.	
Selective media	Favors the growth of particular organism while preventing growth of other organisms. Example: Thayer-Martin agar contains antibiotics that allow the selective growth of <i>Neisseria</i> by inhibiting the growth of other sensitive organisms.	
Indicator (differential) media	Yields a color change in response to the metabolism of certain organisms. Example: MacConkey agar contains a pH indicator; a lactose fermenter like <i>E coli</i> will convert lactose to acidic metabolites → color change to pink.	
Special culture requirer	nents	
BUG	MEDIA USED FOR ISOLATION	MEDIA CONTENTS/OTHER
H influenzae	Chocolate agar	Factors V (NAD+) and X (hematin)
N gonorrhoeae,	Thayer-Martin agar	Selectively favors growth of Neisseria by

BUG	MEDIA USED FOR ISOLATION	MEDIA CONTENTS/OTHER
H influenzae	Chocolate agar	Factors V (NAD+) and X (hematin)
N gonorrhoeae, N meningitidis	Thayer-Martin agar	Selectively favors growth of <i>Neisseria</i> by inhibiting growth of gram ⊕ organisms with Vancomycin, gram ⊖ organisms except <i>Neisseria</i> with Trimethoprim and Colistin, and fungi with Nystatin Very Typically Cultures Neisseria
B pertussis	Bordet-Gengou agar ( <b>Bordet</b> for <b>Bordet</b> ella) Regan-Lowe medium	Potato extract Charcoal, blood, and antibiotic
C diphtheriae	Tellurite agar, Löffler medium	
M tuberculosis	Löwenstein-Jensen medium, Middlebrook medium, rapid automated broth cultures	
M pneumoniae	Eaton agar	Requires cholesterol
Lactose-fermenting enterics	MacConkey agar	Fermentation produces acid, causing colonies to turn pink
E coli	Eosin-methylene blue (EMB) agar	Colonies with green metallic sheen
Brucella, Francisella, Legionella, Pasteurella	Charcoal yeast extract agar buffered with cysteine and iron	The Ella siblings, Bruce, Francis, a legionnaire, and a pasteur (pastor), built the Sistine (cysteine) chapel out of charcoal and iron.
Fungi	Sabouraud agar	"Sab's a fun guy!"
Aerobes	Use an O <sub>2</sub> -dependent system to generate ATP. Examples include <i>Nocardia</i> , <i>Pseudomonas aeru pertussis</i> .  Reactivation of <i>M tuberculosis</i> (eg, after immur predilection for the apices of the lung.	ginosa, Mycobacterium tuberculosis, and Bordetella nocompromise or TNF- $lpha$ inhibitor use) has a

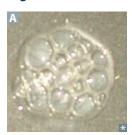
11/14/19 12:19 PM FAS1\_2019\_03-Microbiology.indd 126

Anaerobes	Examples include <i>Clostridium</i> , <i>Bacteroides</i> , <i>Fusobacterium</i> , and <i>Actinomyces israelii</i> . They lack catalase and/or superoxide dismutase and are thus susceptible to oxidative damage. Generally foul smelling (short-chain fatty acids), are difficult to culture, and produce gas in tissue (CO <sub>2</sub> and H <sub>2</sub> ).	Anaerobes Can't Breathe Fresh Air.  Anaerobes are normal flora in GI tract, typically pathogenic elsewhere. AminO2glycosides are ineffective against anaerobes because these antibiotics require O2 to enter into bacterial cell.
Facultative anaerobes	May use O <sub>2</sub> as a terminal electron acceptor to generate ATP, but can also use fermentation and other O <sub>2</sub> -independent pathways.	Streptococci, staphylococci, and enteric gram ⊖ bacteria.
Intracellular bacteria		
Obligate intracellular	Rickettsia, Chlamydia, Coxiella Rely on host ATP	Stay inside (cells) when it is <b>Really Chilly</b> and <b>Col</b> d
Facultative intracellular	Salmonella, Neisseria, Brucella, Mycobacterium, Listeria, Francisella, Legionella, Yersinia pestis	Some Nasty Bugs May Live FacultativeLY
Encapsulated bacteria  A  ***  ***  ***  ***	Examples are Pseudomonas aeruginosa, Streptococcus pneumoniae A, Haemophilus influenzae type b, Neisseria meningitidis, Escherichia coli, Salmonella, Klebsiella pneumoniae, and group B Strep. Their capsules serve as an antiphagocytic virulence factor. Capsular polysaccharide + protein conjugate serves as an antigen in vaccines.	Please SHiNE my SKiS.  Are opsonized, and then cleared by spleen.  Asplenics (No Spleen Here) have ↓ opsonizing ability and thus ↑ risk for severe infections; need vaccines to protect against:  N meningitidis  S pneumoniae H influenzae
Encapsulated bacteria vaccines	Some vaccines containing polysaccharide capsule antigens are conjugated to a carrier protein, enhancing immunogenicity by promoting T-cell activation and subsequent class switching. A polysaccharide antigen alone cannot be presented to T cells.	Pneumococcal vaccines: PCV13 (pneumococcal conjugate vaccine), PPSV23 (pneumococcal polysaccharide vaccine with no conjugated protein).  H influenzae type b (conjugate vaccine).  Meningococcal vaccine (conjugate vaccine).
Urease-positive organisms	Proteus, Cryptococcus, H pylori, Ureaplasma, Nocardia, Klebsiella, S epidermidis, S saprophyticus. Urease hydrolyzes urea to release ammonia and CO <sub>2</sub> → ↑ pH. Predisposes to struvite (ammonium magnesium phosphate) stones, particularly Proteus.	Pee CHUNKSS.

11/14/19 12:19 PM FAS1\_2019\_03-Microbiology.indd 127

## MICROBIOLOGY → MICROBIOLOGY—BASIC BACTERIOLOGY

## Catalase-positive organisms



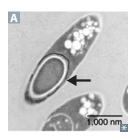
Catalase degrades  $H_2O_2$  into  $H_2O$  and bubbles of  $O_2$   $\blacksquare$  before it can be converted to microbicidal products by the enzyme myeloperoxidase. People with chronic granulomatous disease (NADPH oxidase deficiency) have recurrent infections with certain catalase  $\oplus$  organisms.

Examples: Nocardia, Staphylococci, Serratia, Candida, Listeria, E coli, Burkholderia cepacia, Pseudomonas, Aspergillus, Helicobacter pylori, Bordetella pertussis.

Pigment-producing bacteria	Actinomyces israelii—yellow "sulfur" granules, which are composed of filaments of bacteria	Israel has yellow sand
	S aureus—yellow pigment	Aureus (Latin) = gold
	P aeruginosa—blue-green pigment (pyocyanin and pyoverdin)	Aerugula is green
	Serratia marcescens—red pigment	Think red Sriracha hot sauce
In vivo biofilm-	S epidermidis	Catheter and prosthetic device infections
producing bacteria	Viridans streptococci (S mutans, S sanguinis)	Dental plaques, infective endocarditis
	P aeruginosa	Respiratory tree colonization in patients with cystic fibrosis, ventilator-associated pneumonia Contact lens–associated keratitis
	Nontypeable (unencapsulated) H influenzae	Otitis media

FAS1\_2019\_03-Microbiology.indd 128 11/14/19 12:20 PM

## Spore-forming bacteria



Some gram  $\oplus$  bacteria can form spores  $\blacksquare$  when nutrients are limited. Spores lack metabolic activity and are highly resistant to heat and chemicals. Core contains dipicolinic acid. Must autoclave to kill spores (as is done to surgical equipment) by steaming at 121°C for 15 minutes.

Examples: *B anthracis* (anthrax), *B cereus* (food poisoning), *C botulinum* (botulism), *C difficile* (pseudomembranous colitis), *C perfringens* (gas gangrene), *C tetani* (tetanus).

Bacterial virulence factors	These promote evasion of host immune response.
Protein A	Binds Fc region of IgG. Prevents opsonization and phagocytosis. Expressed by S aureus.
lgA protease	Enzyme that cleaves IgA, allowing bacteria to adhere to and colonize mucous membranes. Secreted by <i>S pneumoniae</i> , <i>H influenzae</i> type b, and <i>Neisseria</i> (SHiN).
M protein	Helps prevent phagocytosis. Expressed by group A streptococci. Shares similar epitopes to human cellular proteins (molecular mimicry); possibly underlies the autoimmune response seen in acute rheumatic fever.

FAS1\_2019\_03-Microbiology.indd 129 11/14/19 12:20 PM

## **Bacterial genetics**

#### **Transformation** Competent bacteria can bind and import short Degraded uncombined Recipient DNA pieces of environmental naked bacterial DNA Donor DNA chromosomal DNA (from bacterial cell lysis). The transfer and expression of newly Naked DNA Recipient cell Transformed cell transferred genes is called transformation. A feature of many bacteria, especially S pneumoniae, H influenzae type b, and Neisseria (SHiN). Adding deoxyribonuclease degrades naked DNA, preventing transformation. Conjugation $F^+ \times F^-$ F<sup>+</sup> plasmid contains genes required for sex pilus Single strand Sex pilus transferred and conjugation. Bacteria without this plasmid are termed F<sup>-</sup>. Sex pilus on F<sup>+</sup> bacterium contacts F bacterium. A single strand of plasmid DNA is transferred across the F+ cell F-cell F+ cell F-cell conjugal bridge ("mating bridge"). No transfer of chromosomal DNA. Transfer and replication F<sup>+</sup> plasmid can become incorporated into Plasmid incorporates $Hfr \times F$ bacterial chromosomal DNA, termed highfrequency recombination (Hfr) cell. Transfer of leading part of plasmid and a few flanking Hfr cell Hfr cell F-cel chromosomal genes. High-frequency Ŗ recombination may integrate some of those bacterial genes. Recipient cell remains F- but now may have new bacterial genes. **Transduction** Generalized A packaging "error." Lytic phage infects Bacterial DNA packaged Cleavage of Bacteria bacterial DNA in phage capsids bacterium, leading to cleavage of bacterial DNA. Parts of bacterial chromosomal DNA may become packaged in phage capsid. Phage infects another bacterium, transferring these genes. Release of new phage Infects other Genes transferred from lysed cell bacteria to new bacteria Viral DNA Specialized An "excision" event. Lysogenic phage infects iral DNA incorporates in Phage particles Lysogenic bacterium; viral DNA incorporates into bacterial DNA bacterial chromosome. When phage DNA is excised, flanking bacterial genes may be excised with it. DNA is packaged into phage capsid and can infect another bacterium. Genes for the following 5 bacterial toxins are encoded in a lysogenic phage (ABCD'S): Group A strep erythrogenic toxin, Botulinum toxin, Release of new phage Infects other Genes different from Cholera toxin, Diphtheria toxin, Shiga toxin.

FAS1\_2019\_03-Microbiology.indd 130 11/14/19 12:20 PM

from lysed cell

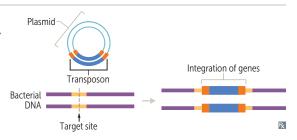
bacteria

donor and recipient

### **Bacterial genetics (continued)**

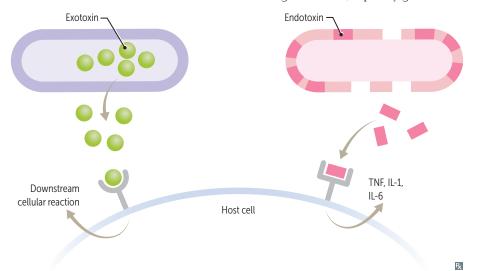
### **Transposition**

A "jumping" process involving a transposon (specialized segment of DNA), which can copy and excise itself and then insert into the same DNA molecule or an unrelated DNA (eg, plasmid or chromosome). Critical in creating plasmids with multiple drug resistance and transfer across species lines (eg, Tn1546 with vanA from Enterococcus to S aureus).



#### Main features of exotoxins and endotoxins

	Exotoxins	Endotoxins	
SOURCE	Certain species of gram $\oplus$ and gram $\ominus$ bacteria	Outer cell membrane of most gram ⊖ bacteria	
SECRETED FROM CELL	Yes	No	
CHEMISTRY	Polypeptide	Lipid A component of LPS (structural part of bacteria; released when lysed)	
LOCATION OF GENES	Plasmid or bacteriophage	Bacterial chromosome	
ADVERSE EFFECTS	High (fatal dose on the order of 1 $\mu g$ )	Low (fatal dose on the order of hundreds of micrograms)	
CLINICAL EFFECTS	Various effects (see following pages)	Fever, shock (hypotension), DIC	
MODE OF ACTION	Various modes (see following pages)	Induces TNF, IL-1, and IL-6	
ANTIGENICITY	Induces high-titer antibodies called antitoxins	Poorly antigenic	
VACCINES	Toxoids used as vaccines	No toxoids formed and no vaccine available	
HEAT STABILITY	Destroyed rapidly at 60°C (except staphylococcal enterotoxin and <i>E coli</i> heatstable toxin)	Stable at 100°C for 1 hr	
TYPICAL DISEASES	Tetanus, botulism, diphtheria, cholera	Meningococcemia; sepsis by gram ⊖ rods	



FAS1\_2019\_03-Microbiology.indd 131 11/14/19 12:20 PM

### **Bacteria with exotoxins**

Dacteria With Exotoxins			
BACTERIA	TOXIN	MECHANISM	MANIFESTATION
Inhibit protein synthesis			
Corynebacterium diphtheriae	Diphtheria toxin <sup>a</sup>	Inactivate elongation factor (EF-2)	Pharyngitis with pseudomembranes in throat and severe lymphadenopathy (bull neck), myocarditis
Pseudomonas aeruginosa	Exotoxin A <sup>a</sup>		Host cell death
Shigella spp	Shiga toxin (ST) <sup>a</sup>	Inactivate 60S ribosome by removing adenine from rRNA	GI mucosal damage → dysentery; ST also enhances cytokine release, causing hemolytic- uremic syndrome (HUS)
Enterohemorrhagic <i>E coli</i>	Shiga-like toxin (SLT) <sup>a</sup>		SLT enhances cytokine release, causing HUS (prototypically in EHEC serotype O157:H7) Unlike <i>Shigella</i> , EHEC does not invade host cells
Increase fluid secretion			
Enterotoxigenic <i>E coli</i>	Heat-labile toxin (LT) <sup>a</sup>	Overactivates adenylate cyclase († cAMP) → † Cl <sup>-</sup> secretion in gut and H <sub>2</sub> O efflux	Watery diarrhea: "labile in the Air (Adenylate cyclase), stable on the Ground (Guanylate cyclase)"
	Heat-stable toxin (ST)	Overactivates guanylate cyclase († cGMP) → ↓ resorption of NaCl and H <sub>2</sub> O in gut	
Bacillus anthracis	Anthrax toxin <sup>a</sup>	Mimics adenylate cyclase († cAMP)	Likely responsible for characteristic edematous borders of black eschar in cutaneous anthrax
Vibrio cholerae	Cholera toxin <sup>a</sup>	Overactivates adenylate cyclase († cAMP) by permanently activating $G_s$ $\rightarrow$ † $Cl^-$ secretion in gut and $H_2O$ efflux	Voluminous "rice-water" diarrhea
Inhibit phagocytic ability	y		
Bordetella pertussis	Pertussis toxin <sup>a</sup>	Inactivates inhibitory G subunit (G <sub>i</sub> ) → activation of adenylate cyclase → ↑ cAMP	Whooping cough—child coughs on expiration and "whoops" on inspiration (toxin may not actually be a cause of cough; can cause "100-day cough" in adults)
Inhibit release of neuroti	ransmitter		
Clostridium tetani	Tetanospasmin <sup>a</sup>	Both are proteases that cleave SNARE (soluble NSF attachment protein receptor), a set of proteins required for neurotransmitter release via vesicular fusion	Toxin prevents release of <b>inhibitory</b> (GABA and glycine) neurotransmitters from Renshaw cells in spinal cord → spastic paralysis, risus sardonicus, trismus (lockjaw)
Clostridium botulinum	Botulinum toxin <sup>a</sup>		Toxin prevents release of <b>stimulatory</b> (ACh) signals at neuromuscular junction → flaccid paralysis (floppy baby)

<sup>&</sup>lt;sup>a</sup>An AB toxin (aka, two-component toxin [or three for anthrax]) with **B** enabling **b**inding and triggering uptake (endocytosis) of the **a**ctive **A** component. The A components are usually ADP ribosyltransferases; others have enzymatic activities as listed in chart.

FAS1\_2019\_03-Microbiology.indd 132 11/14/19 12:20 PM

#### **Bacteria with exotoxins (continued)**

BACTERIA	TOXIN	MECHANISM	MANIFESTATION	
Lyse cell membranes				
Clostridium perfringens	Alpha toxin	Phospholipase (lecithinase) that degrades tissue and cell membranes	Degradation of phospholipids → myonecrosis ("gas gangrene") and hemolysis ("double zone" of hemolysis on blood agar)	
Streptococcus pyogenes	Streptolysin O	Protein that degrades cell membrane	Lyses RBCs; contributes to β-hemolysis; host antibodies against toxin (ASO) used to diagnose rheumatic fever (do not confuse with immune complexes of poststreptococcal glomerulonephritis)	
Superantigens causing shock				
Staphylococcus aureus	Toxic shock syndrome toxin (TSST-1)	Cross-links β region of TCR to MHC class II on APCs outside of the antigen binding site  → overwhelming release of IL-1, IL-2, IFN-γ, and TNF-α → shock	Toxic shock syndrome: fever, rash, shock; other toxins cause scalded skin syndrome (exfoliative toxin) and food poisoning (heat-stable enterotoxin)	
Streptococcus pyogenes	Erythrogenic exotoxin A		Toxic shock–like syndrome: fever, rash, shock; scarlet fever	

#### **Endotoxin**

LPS found in outer membrane of gram ⊖ bacteria (both cocci and rods). Composed of O antigen + core polysaccharide + lipid A (the toxic component).

Released upon cell lysis or by living cells by blebs detaching from outer surface membrane (vs exotoxin, which is actively secreted).

Three main effects: macrophage activation (TLR4/CDl4), complement activation, and tissue factor activation.

### **ENDOTOXINS:**

Edema

Nitric oxide

DIC/Death

Outer membrane

TNF-α

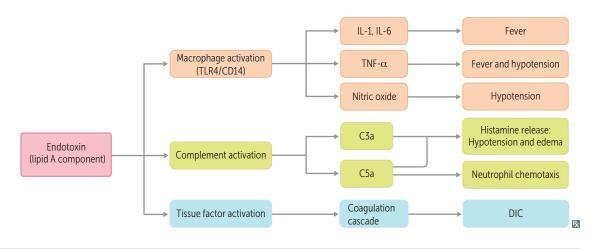
O-antigen + core polysaccharide + lipid A

eXtremely heat stable

IL-1 and IL-6

Neutrophil chemotaxis

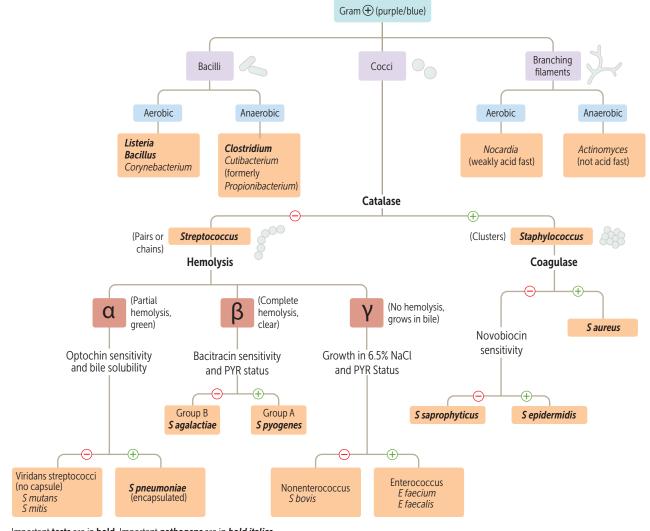
Shock



FAS1\_2019\_03-Microbiology.indd 133 11/14/19 12:20 PM

## ► MICROBIOLOGY — CLINICAL BACTERIOLOGY

#### **Gram-positive lab algorithm**



Important tests are in **bold**. Important *pathogens* are in *bold italics*.

Note: Enterococcus is either  $\alpha$ - or  $\gamma$ -hemolytic.

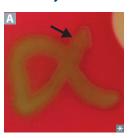
#### **Gram-positive cocci antibiotic tests**

Staphylococci	Novobiocin—Saprophyticus is Resistant; Epidermidis is Sensitive	On the office's "staph" retreat, there was no stress
Streptococci	Optochin—Viridans is Resistant; Pneumoniae is Sensitive	OVRPS (overpass)
	Bacitracin—group B strep are Resistant; group A strep are Sensitive	B-BRAS

Ŗ

FAS1\_2019\_03-Microbiology.indd 134 11/14/19 12:20 PM

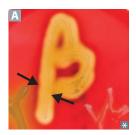
#### α-hemolytic bacteria



Gram ⊕ cocci. Partial oxidation of hemoglobin causes greenish or brownish color without clearing around growth on blood agar ⚠. Include the following organisms:

- *Streptococcus pneumoniae* (catalase ⊖ and optochin sensitive)
- Viridans streptococci (catalase 
   ⊖ and optochin resistant)

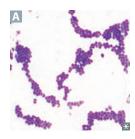
#### β-hemolytic bacteria



Gram ⊕ cocci. Complete lysis of RBCs → pale/clear area surrounding colony on blood agar A. Include the following organisms:

- Staphylococcus aureus (catalase and coagulase ⊕)
- *Streptococcus pyogenes*—group A strep (catalase ⊝ and bacitracin sensitive)
- *Streptococcus agalactiae*—group *B* strep (catalase  $\ominus$  and bacitracin resistant)

### Staphylococcus aureus



Gram ⊕, β-hemolytic, catalase ⊕, coagulase ⊕ cocci in clusters A. Protein A (virulence factor) binds Fc-IgG, inhibiting complement activation and phagocytosis. Commonly colonizes the nares, ears, axilla, and groin. Causes:

- Inflammatory disease—skin infections, organ abscesses, pneumonia (often after influenza virus infection), endocarditis, septic arthritis, and osteomyelitis.
- Toxin-mediated disease—toxic shock syndrome (TSST-1), scalded skin syndrome (exfoliative toxin), rapid-onset food poisoning (enterotoxins).

#### MRSA (methicillin-resistant Saureus)—

important cause of serious nosocomial and community-acquired infections; resistance due to altered penicillin-binding protein. *mecA* gene from staphylococcal chromosomal cassette involved in penicillin resistance.

TSST-1 is a superantigen that binds to MHC II and T-cell receptor, resulting in polyclonal T-cell activation and cytokine release.

## Staphylococcal toxic shock syndrome (TSS)—

fever, vomiting, rash, desquamation, shock, end-organ failure. TSS results in † AST, † ALT, † bilirubin. Associated with prolonged use of vaginal tampons or nasal packing.

- Compare with *Streptococcus pyogenes* TSS (a toxic shock–like syndrome associated with painful skin infection).
- S aureus food poisoning due to ingestion of preformed toxin → short incubation period (2–6 hr) followed by nonbloody diarrhea and emesis. Enterotoxin is heat stable → not destroyed by cooking.
- S aureus makes coagulase and toxins. Forms fibrin clot around itself → abscess.

## Staphylococcus epidermidis

Gram  $\oplus$ , catalase  $\oplus$ , coagulase  $\ominus$ , urease  $\oplus$  cocci in clusters. Novobiocin sensitive. Does not ferment mannitol (vs *S aureus*).

Normal flora of skin; contaminates blood cultures.

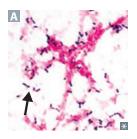
Infects prosthetic devices (eg, hip implant, heart valve) and IV catheters by producing adherent biofilms.

FAS1\_2019\_03-Microbiology.indd 135 11/14/19 12:20 PM

## Staphylococcus saprophyticus

Gram  $\oplus$ , catalase  $\oplus$ , coagulase  $\ominus$ , urease  $\oplus$  cocci in clusters. Novobiocin resistant. Normal flora of female genital tract and perineum. Second most common cause of uncomplicated UTI in young women (most common is E coli).

## Streptococcus pneumoniae



Gram ⊕, α-hemolytic, lancet-shaped diplococci A.

Encapsulated. IgA protease. Optochin sensitive and bile soluble. Most commonly causes:

- Meningitis
- Otitis media (in children)
- Pneumonia
- Sinusitis

Pneumococcus is associated with "rusty" sputum, sepsis in patients with sickle cell disease, and asplenic patients.

No virulence without capsule.

## Viridans group streptococci

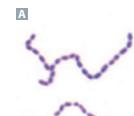
Gram  $\oplus$ ,  $\alpha$ -hemolytic cocci. Optochin resistant and bile insoluble. Normal flora of the oropharynx.

Streptococcus mutans and S mitis cause dental caries.

S sanguinis makes dextrans that bind to fibrinplatelet aggregates on damaged **heart** valves, causing subacute bacterial endocarditis. Viridans group strep live in the mouth, because they are not afraid of-the-chin (op-to-chin resistant).

Sanguinis = blood. Think, "there is lots of blood in the heart" (endocarditis).

# Streptococcus pyogenes (group A streptococci)



Gram ⊕ cocci in chains A. Group A strep cause:

- Pyogenic—pharyngitis, cellulitis, impetigo ("honey-crusted" lesions), erysipelas
- Toxigenic—scarlet fever, toxic shock—like syndrome, necrotizing fasciitis
- Immunologic—rheumatic fever, glomerulonephritis

Bacitracin sensitive,  $\beta$ -hemolytic, pyrrolidonyl arylamidase (PYR)  $\oplus$ . Hyaluronic acid capsule and M protein inhibit phagocytosis. Antibodies to M protein enhance host defenses against S pyogenes but can give rise to rheumatic fever.

ASO titer or anti-DNase B antibodies indicate recent *S pyogenes* infection.

"Ph"yogenes pharyngitis can result in rheumatic "phever" and glomerulonephritis. Strains causing impetigo can induce glomerulonephritis.

Scarlet fever—blanching, sandpaper-like body rash, strawberry tongue, and circumoral pallor in the setting of group A streptococcal pharyngitis (erythrogenic toxin ⊕).

FAS1\_2019\_03-Microbiology.indd 136 11/14/19 12:20 PM

# Streptococcus agalactiae (group B streptococci)

Gram ⊕ cocci, bacitracin resistant, β-hemolytic, colonizes vagina; causes pneumonia, meningitis, and sepsis, mainly in babies.

Produces CAMP factor, which enlarges the area of hemolysis formed by *S aureus*. (Note: CAMP stands for the authors of the test, not cyclic AMP.) Hippurate test ⊕. PYR ⊝.

Screen pregnant women at 35–37 weeks of gestation with rectal and vaginal swabs.

Patients with ⊕ culture receive intrapartum penicillin/ampicillin prophylaxis.

### Streptococcus bovis

Gram ⊕ cocci, colonizes the gut. *S gallolyticus* (*S bovis* biotype 1) can cause bacteremia and subacute endocarditis and is associated with colon cancer.

Bovis in the blood = cancer in the colon.

#### **Enterococci**

Gram  $\oplus$  cocci. Enterococci (E faecalis and E faecium) are normal colonic flora that are penicillin G resistant and cause UTI, biliary tract infections, and subacute endocarditis (following GI/GU procedures). Catalase  $\ominus$ , PYR  $\oplus$ , variable hemolysis.

VRE (vancomycin-resistant enterococci) are an important cause of nosocomial infection.

Enterococci are more resilient than streptococci, can grow in 6.5% NaCl and bile (lab test).

Entero = intestine, faecalis = feces, strepto = twisted (chains), coccus = berry.

### **Bacillus anthracis**

Gram  $\oplus$ , spore-forming rod that produces anthrax toxin (an exotoxin consisting of protective antigen, lethal factor, and edema factor). Has a polypeptide capsule (poly D-glutamate). Colonies show a halo of projections, sometimes referred to as "medusa head" appearance.

#### **Cutaneous anthrax**

Painless papule surrounded by vesicles → ulcer with black eschar 🖪 (painless, necrotic) → uncommonly progresses to bacteremia and death.



#### **Pulmonary anthrax**

Inhalation of spores, most commonly from contaminated animals or animal products, although also a potential bioweapon → flu-like symptoms that rapidly progress to fever, pulmonary hemorrhage, mediastinitis (CXR may show widened mediastinum), and shock. Also called woolsorter's disease.

FAS1\_2019\_03-Microbiology.indd 137 11/14/19 12:20 PM

#### **Bacillus cereus**

Gram ⊕ rod. Causes food poisoning. Spores survive cooking rice (reheated rice syndrome). Keeping rice warm results in germination of spores and enterotoxin formation. Emetic type causes nausea and vomiting within 1–5 hours. Caused by cereulide, a preformed toxin. Diarrheal type causes watery, nonbloody diarrhea and GI pain within 8–18 hours. Management: supportive care (antibiotics are ineffective against toxins).

#### Clostridia

Gram ⊕, spore-forming, obligate anaerobic rods. Tetanus toxin and botulinum toxin are proteases that cleave SNARE proteins involved in neurotransmission.

### Clostridium tetani

Produces tetanospasmin, an exotoxin causing tetanus. Tetanospasmin blocks release of GABA and glycine from Renshaw cells in spinal cord.

Causes spastic paralysis, trismus (lockjaw), risus sardonicus (raised eyebrows and open grin), opisthotonos (spasms of spinal extensors).

Prevent with tetanus vaccine. Treat with antitoxin +/- vaccine booster, antibiotics, diazepam (for muscle spasms), and wound

Tetanus is tetanic paralysis.

#### Clostridium botulinum

Produces a heat-labile toxin that inhibits ACh release at the neuromuscular junction, causing botulism. In adults, disease is caused by ingestion of preformed toxin. In babies, ingestion of spores (eg, in honey) leads to disease (floppy baby syndrome). Treat with human botulinum immunoglobulin.

debridement.

Symptoms of botulism (the 4 D's): Diplopia, Dysarthria, Dysphagia, Dyspnea.

Botulinum is from bad bottles of food, juice, and honey (causes a descending flaccid paralysis).

Local botulinum toxin A (Botox) injections used to treat focal dystonia, hyperhidrosis, muscle spasms, and cosmetic reduction of facial wrinkles.

## Clostridium perfringens



Produces α-toxin (lecithinase, a phospholipase) that can cause myonecrosis (gas gangrene A; presents as soft tissue crepitus) and hemolysis. If heavily spore-contaminated food is cooked but left standing too long at < 60°C, spores germinate → vegetative bacteria → heat-labile enterotoxin → food poisoning symptoms in 10-12 hours, resolution in 24 hours.

Perfringens perforates a gangrenous leg.

### Clostridioides difficile



Produces toxins A and B, which damage enterocytes. Both toxins lead to watery diarrhea → pseudomembranous colitis B. Often 2° to antibiotic use, especially clindamycin or ampicillin; associated with PPIs.

Diagnosed by PCR or antigen detection of one or both toxins in stool.

Complications: toxic megacolon.

Difficile causes diarrhea.

Treatment: oral vancomycin, metronidazole, or fidaxomicin. For recurrent cases, consider repeating prior regimen or fecal microbiota transplant.

FAS1\_2019\_03-Microbiology.indd 138 11/14/19 12:20 PM

## Corynebacterium diphtheriae



Gram ⊕ rods occurring in angular arrangements; transmitted via respiratory droplets. Causes diphtheria via exotoxin encoded by β-prophage. Potent exotoxin inhibits protein synthesis via ADP-ribosylation of EF-2, leading to possible necrosis in pharynx, cardiac, and CNS tissue.

Symptoms include pseudomembranous pharyngitis (grayish-white membrane A) with lymphadenopathy. Toxin dissemination may cause myocarditis, arrhythmias, neuropathies.

Lab diagnosis based on gram ⊕ rods with metachromatic (blue and red) granules and ⊕ Elek test for toxin.

Toxoid vaccine prevents diphtheria.

Coryne = club shaped (metachromatic granules on Löffler media).

Black colonies on cystine-tellurite agar.

### ABCDEFG:

**A**DP-ribosylation

**β**-prophage

**C**orynebacterium

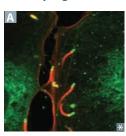
**D**iphtheriae

Elongation Factor 2

Granules

Treatment: antibiotic therapy +/- diphtheria antitoxin.

### Listeria monocytogenes



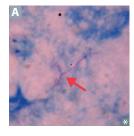
Gram  $\oplus$ , facultative intracellular rod; acquired by ingestion of unpasteurized dairy products and cold deli meats, transplacental transmission, by vaginal transmission during birth. Grows well at refrigeration temperatures ("cold enrichment").

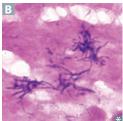
Forms "rocket tails" (red in A) via actin polymerization that allow intracellular movement and cell-to-cell spread across cell membranes, thereby avoiding antibody. Characteristic tumbling motility in broth.

Can cause amnionitis, septicemia, and spontaneous abortion in pregnant women; granulomatosis infantiseptica; meningitis in immunocompromised patients, neonates, and older adults; mild, self-limited gastroenteritis in healthy individuals.

Treatment: ampicillin.

### Nocardia vs Actinomyces





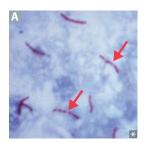
Both are gram ⊕ and form long, branching filaments resembling fungi.

Nocardia	Actinomyces
Aerobe	Anaerobe
Acid fast (weak) A	Not acid fast B
Found in soil	Normal oral, reproductive, and GI flora
Causes pulmonary infections in immunocompromised (can mimic TB but with ⊖ PPD); cutaneous infections after trauma in immunocompetent; can spread to CNS	Causes oral/facial abscesses that drain through sinus tracts; often associated with dental caries, extraction and other maxillofacial trauma; forms yellow "sulfur granules"; can also cause PID with IUDs
Treat with sulfonamides (TMP-SMX)	Treat with penicillin

Treatment is a **SNAP**: **S**ulfonamides—**N**ocardia; **A**ctinomyces—**P**enicillin

FAS1\_2019\_03-Microbiology.indd 139 11/14/19 12:20 PM

### Mycobacteria



Gram ⊕ acid fast rods (pink rods, arrows in A). Mycobacterium tuberculosis (TB, often resistant to multiple drugs).

M avium—intracellulare (causes disseminated, non-TB disease in AIDS; often resistant to multiple drugs). Prophylaxis with azithromycin when CD4+ count < 50 cells/mm<sup>3</sup>.

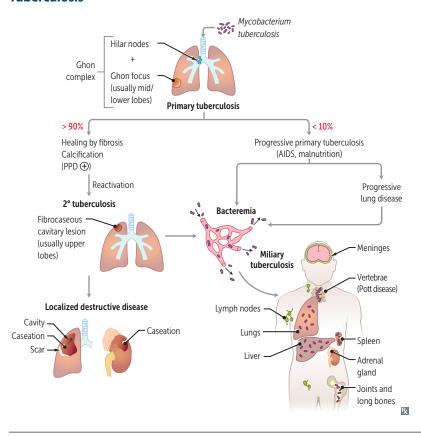
M scrofulaceum (cervical lymphadenitis in children).

*M marinum* (hand infection in aquarium handlers).

TB symptoms include fever, night sweats, weight loss, cough (nonproductive or productive), hemoptysis.

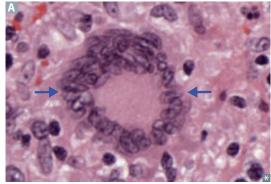
Cord factor creates a "serpentine cord" appearance in virulent M tuberculosis strains; activates macrophages (promoting granuloma formation) and induces release of TNF- $\alpha$ . Sulfatides (surface glycolipids) inhibit phagolysosomal fusion.

### **Tuberculosis**



Interferon-γ release assay (IGRA) has fewer false positives from BCG vaccination.
PPD ⊕ if current infection or past exposure.
PPD ⊝ if no infection and in sarcoidosis or
HIV infection (especially with low CD4+ cell count).

Caseating granulomas with central necrosis and Langhans giant cell (single example in A) are characteristic of 2° tuberculosis.



FAS1\_2019\_03-Microbiology.indd 140 11/14/19 12:20 PM

### Leprosy





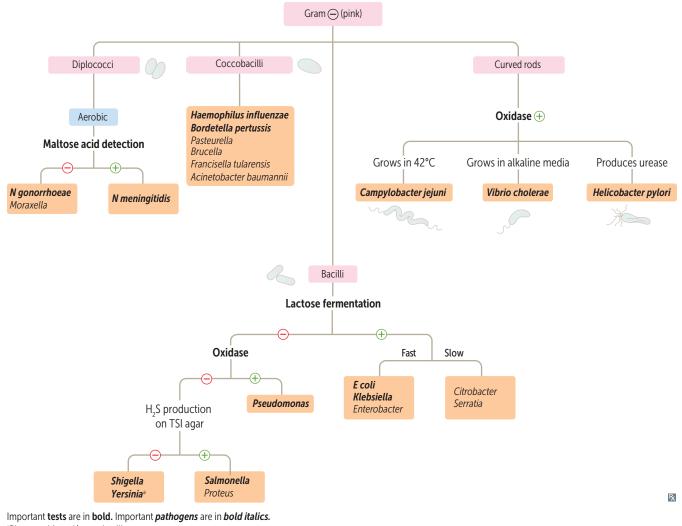
Also called Hansen disease. Caused by Mycobacterium leprae, an acid-fast bacillus that likes cool temperatures (infects skin and superficial nerves—"glove and stocking" loss of sensation A) and cannot be grown in vitro. Diagnosed via skin biopsy or tissue PCR. Reservoir in United States: armadillos.

Leprosy has 2 forms (many cases fall temporarily between two extremes):

- Lepromatous—presents diffusely over the skin, with Leonine (Lion-like) facies B, and is communicable (high bacterial load); characterized by low cell-mediated immunity with a largely Th2 response. Lepromatous form can be Lethal.
- Tuberculoid—limited to a few hypoesthetic, hairless skin plaques; characterized by high cellmediated immunity with a largely Th1-type response and low bacterial load.

Treatment: dapsone and rifampin for tuberculoid form; clofazimine is added for lepromatous form.

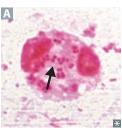
### **Gram-negative lab algorithm**



<sup>a</sup>Pleomorphic rod/coccobacillus

FAS1\_2019\_03-Microbiology.indd 141 11/14/19 12:20 PM

#### Neisseria





Gram ⊜ diplococci. Metabolize glucose and produce IgA proteases. Contain lipooligosaccharides (LOS) with strong endotoxin activity. *N gonorrhoeae* is often intracellular (within neutrophils) A.

Acid production: MeninGococci—Maltose and Glucose; Gonococci—Glucose.

Gonococci	Meningococci
No polysaccharide capsule	Polysaccharide capsule
No maltose acid detection	Maltose acid detection
<b>No</b> vaccine due to antigenic variation of pilus proteins	Vaccine (type B vaccine available for at-risk individuals)
Sexually or perinatally transmitted	Transmitted via respiratory and oral secretions
Causes gonorrhea, septic arthritis, neonatal conjunctivitis (2–5 days after birth), pelvic inflammatory disease (PID), and Fitz-Hugh–Curtis syndrome	Causes meningococcemia with petechial hemorrhages and gangrene of toes B, meningitis, Waterhouse-Friderichsen syndrome (adrenal insufficiency, fever, DIC, shock)
Diagnosed with NAT	Diagnosed via culture-based tests or PCR
Condoms I sexual transmission, erythromycin eye ointment prevents neonatal blindness	Rifampin, ciprofloxacin, or ceftriaxone prophylaxis in close contacts
Treatment: ceftriaxone (+ azithromycin or doxycycline, for possible chlamydial coinfection)	Treatment: ceftriaxone or penicillin G

## Haemophilus influenzae





Small gram ⊖ (coccobacillary) rod. Aerosol transmission. Nontypeable (unencapsulated) strains are the most common cause of mucosal infections (otitis media, conjunctivitis, bronchitis) as well as invasive infections since the vaccine for capsular type b was introduced. Produces IgA protease.

Culture on chocolate agar, which contains factors V (NAD+) and X (hematin) for growth; can also be grown with S aureus, which provides factor V via RBC hemolysis.

HaEMOPhilus causes Epiglottitis (endoscopic appearance in A, can be "cherry red" in children; "thumb sign" on lateral neck x-ray B), Meningitis, Otitis media, and Pneumonia.

Vaccine contains type b capsular polysaccharide (polyribosylribitol phosphate) conjugated to diphtheria toxoid or other protein. Given between 2 and 18 months of age.

Does not cause the flu (influenza virus does). Treatment: amoxicillin +/- clavulanate for mucosal infections; ceftriaxone for meningitis; rifampin prophylaxis for close contacts.

### Acinetobacter baumannii

Gram  $\ominus$ , strictly aerobic, oxidase  $\ominus$  coccobacillus. Commensal opportunist but increasingly associated with resistant hospital-acquired infections, especially in ICU. Can cause ventilator-associated pneumonia and septicemia in immunocompromised patients.

FAS1\_2019\_03-Microbiology.indd 142 11/14/19 12:20 PM

#### **Bordetella** pertussis

Gram ⊝, aerobic coccobacillus. Virulence factors include pertussis toxin (disables G<sub>i</sub>), adenylate cyclase toxin († cAMP), and tracheal cytotoxin. Three clinical stages:

- Catarrhal—low-grade fevers, Coryza.
- Paroxysmal—paroxysms of intense cough followed by inspiratory "whooP" ("whooping cough"),
  posttussive vomiting.
- Convalescent—gradual recovery of chronic cough.

Prevented by Tdap, DTaP vaccines. May be mistaken as viral infection due to lymphocytic infiltrate resulting from immune response.

Treatment: macrolides; if allergic use TMP-SMX.

#### Brucella

Gram ⊝, aerobic coccobacillus. Transmitted via ingestion of contaminated animal products (eg, unpasteurized milk). Survives in macrophages in the reticuloendothelial system. Can form non-caseating granulomas. Typically presents with undulant fever, night sweats, and arthralgia. Treatment: doxycycline + rifampin or streptomycin.

## Legionella pneumophila



Gram ⊖ rod. Gram stains poorly—use silver stain. Grow on charcoal yeast extract medium with iron and cysteine. Detected by presence of antigen in urine. Labs may show hyponatremia.

Aerosol transmission from environmental water source habitat (eg, air conditioning systems, hot water tanks). No person-to-person transmission.

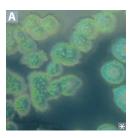
Treatment: macrolide or quinolone.

Think of a French legionnaire (soldier) with his silver helmet, sitting around a campfire (charcoal) with his iron dagger—he is no sissy (cysteine).

Legionnaires' disease—severe pneumonia (often unilateral and lobar A), fever, GI and CNS symptoms. Common in smokers and in chronic lung disease.

Pontiac fever—mild flu-like syndrome.

## Pseudomonas aeruginosa





Aeruginosa—aerobic; motile, catalase ⊕, gram ⊝ rod. Non-lactose fermenting.
Oxidase ⊕. Frequently found in water. Has a grape-like odor.

PSEUDOMONAS is associated with:
Pneumonia, Sepsis, Ecthyma gangrenosum,
UTIs, Diabetes, Osteomyelitis, Mucoid
polysaccharide capsule, Otitis externa
(swimmer's ear), Nosocomial infections (eg,
catheters, equipment), Addicts (drug abusers),
Skin infections (eg, hot tub folliculitis, wound
infection in burn victims).

Mucoid polysaccharide capsule may contribute to chronic pneumonia in cystic fibrosis patients due to biofilm formation.

Produces PEEP: Phospholipase C (degrades cell membranes); Endotoxin (fever, shock); Exotoxin A (inactivates EF-2); Pigments: pyoverdine and pyocyanin (blue-green pigment A; also generates reactive oxygen species).

Corneal ulcers/keratitis in contact lens wearers/ minor eye trauma.

Ecthyma gangrenosum—rapidly progressive, necrotic cutaneous lesion **B** caused by *Pseudomonas* bacteremia. Typically seen in immunocompromised patients.

Treatments include "CAMPFIRE" drugs:

- Carbapenems
- Aminoglycosides
- Monobactams
- Polymyxins (eg, polymyxin B, colistin)
- Fluoroquinolones (eg, ciprofloxacin, levofloxacin)
- ThIRd- and fourth-generation cephalosporins (eg, ceftazidime, cefepime)
- Extended-spectrum penicillins (eg, piperacillin, ticarcillin)

FAS1\_2019\_03-Microbiology.indd 143 11/14/19 12:20 PM

**Salmonella vs Shigella** Both Salmonella and Shigella are gram ⊖ rods, non-lactose fermenters, oxidase ⊖, and can invade the GI tract via M cells of Peyer patches.

	Salmonella typhi (ty-Vi)	Salmonella spp. (except S typhi)	Shigella
RESERVOIRS	Humans only	Humans and animals	Humans only
SPREAD	Can disseminate hematogenously	Can disseminate hematogenously	Cell to cell; no hematogenous spread
H <sub>2</sub> S PRODUCTION	Yes	Yes	No
FLAGELLA	Yes (salmon swim)	Yes (salmon swim)	No
VIRULENCE FACTORS	Endotoxin; Vi capsule	Endotoxin	Endotoxin; Shiga toxin (enterotoxin)
INFECTIOUS DOSE (ID <sub>50</sub> )	High—large inoculum required; acid-labile (inactivated by gastric acids)	High	Low—very small inoculum required; acid stable (resistant to gastric acids)
EFFECT OF ANTIBIOTICS ON FECAL EXCRETION	Prolongs duration	Prolongs duration	Shortens duration
IMMUNE RESPONSE	Primarily monocytes	PMNs in disseminated disease	Primarily PMN infiltration
GIMANIFESTATIONS	Constipation, followed by diarrhea	Diarrhea (possibly bloody)	Crampy abdominal pain → tenesmus, bloody mucoid stools (bacillary dysentery)
VACCINE	Oral vaccine contains live attenuated S typhi IM vaccine contains Vi capsular polysaccharide	No vaccine	No vaccine
UNIQUE PROPERTIES	<ul> <li>Causes typhoid         fever (rose spots on         abdomen, constipation,         abdominal pain, fever;         later GI ulceration         and hemorrhage); treat         with ceftriaxone or         fluoroquinolone</li> <li>Carrier state with         gallbladder colonization</li> </ul>	<ul> <li>Poultry, eggs, pets, and turtles are common sources</li> <li>Antibiotics not indicated</li> <li>Gastroenteritis is usually caused by non-typhoidal Salmonella</li> </ul>	<ul> <li>4 F's: Fingers, Flies, Food, Feces</li> <li>In order of decreasing severity (less toxin produced): S dysenteriae, S flexneri, S boydii, S sonnei</li> <li>Invasion of M cells is key to pathogenicity: organisms that produce little toxin can cause disease</li> </ul>

### Yersinia enterocolitica

Gram ⊝ pleomorphic rod/coccobacillus. Usually transmitted from pet feces (eg, puppies), contaminated milk, or pork. Can cause acute bloody diarrhea, pseudoappendicitis (right lower abdominal pain due to mesenteric adenitis and/or terminal ileitis), reactive arthritis in adults.

### **Lactose-fermenting** enteric bacteria

Fermentation of **lactose** → pink colonies on MacConkey agar. Examples include E coli, Enterobacter, Klebsiella. E coli produces β-galactosidase, which breaks down lactose into glucose and galactose.

### Lactose is key.

EMB agar—lactose fermenters grow as purple/ black colonies. E coli grows colonies with a green sheen.

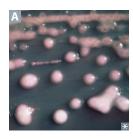
FAS1\_2019\_03-Microbiology.indd 144 11/14/19 12:20 PM

### Escherichia coli

Gram  $\odot$ , indole  $\oplus$  rod. *E coli* virulence factors: fimbriae—cystitis and pyelonephritis (P pili); K capsule—pneumonia, neonatal meningitis; LPS endotoxin—septic shock.

STRAIN	TOXIN AND MECHANISM	PRESENTATION
Enteroinvasive <i>E coli</i>	Microbe invades intestinal mucosa and causes necrosis and inflammation.	EIEC is Invasive; dysentery. Clinical manifestations similar to Shigella.
Enterotoxigenic <i>E coli</i>	Produces heat-labile and heat-stable enteroToxins. No inflammation or invasion.	ETEC; Traveler's diarrhea (watery).
Enteropathogenic <i>E coli</i>	No toxin produced. Adheres to apical surface, flattens villi, prevents absorption.	Diarrhea, usually in children (think EPEC and Pediatrics).
Enterohemorrhagic <i>E coli</i>	O157:H7 is most common serotype in US. Often transmitted via undercooked meat, raw leafy vegetables.  Shiga-like toxin causes hemolytic-uremic syndrome: triad of anemia, thrombocytopenia, and acute kidney injury due to microthrombi forming on damaged endothelium  → mechanical hemolysis (with schistocytes on peripheral blood smear), platelet consumption, and ↓ renal blood flow.	Dysentery (toxin alone causes necrosis and inflammation).  Does not ferment sorbitol (vs other <i>E coli</i> ).  Hemorrhagic, Hamburgers, Hemolytic-uremic syndrome.

### Klebsiella



Gram ⊖ rod; intestinal flora that causes lobar pneumonia in alcoholics and diabetics when aspirated. Very mucoid colonies A caused by abundant polysaccharide capsules. Dark red "currant jelly" sputum (blood/mucus).

Also cause of nosocomial UTIs. Associated with evolution of multidrug resistance (MDR).

**ABCDE**'s of Klebsiella:

Aspiration pneumonia

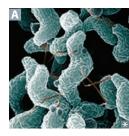
aBscess in lungs and liver

"Currant jelly" sputum

Diabetes

EtOH abuse

### Campylobacter jejuni



Gram ⊖, comma or S shaped (with polar flagella) ♠, oxidase ⊕, grows at 42°C ("Campylobacter likes the hot campfire").

Major cause of bloody diarrhea, especially in children. Fecal-oral transmission through person-to-person contact or via ingestion of undercooked contaminated poultry or meat, unpasteurized milk. Contact with infected animals (dogs, cats, pigs) is also a risk factor.

Common antecedent to Guillain-Barré syndrome and reactive arthritis.

FAS1\_2019\_03-Microbiology.indd 145 11/14/19 12:20 PM

### Vibrio cholerae



Gram  $\ominus$ , flagellated, comma shaped A, oxidase  $\oplus$ , grows in alkaline media. Endemic to developing countries. Produces profuse rice-water diarrhea via enterotoxin that permanently activates  $G_s$ ,  $\uparrow$  cAMP. Sensitive to stomach acid (acid labile); requires large inoculum (high ID<sub>50</sub>) unless host has  $\downarrow$  gastric acidity. Transmitted via ingestion of contaminated water or uncooked food (eg, raw shellfish). Treat promptly with oral rehydration solution.

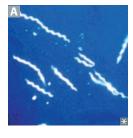
### Helicobacter pylori



Curved, flagellated (motile), gram ⊖ rod A that is **triple** ⊕: catalase ⊕, oxidase ⊕, and urease ⊕ (can use urea breath test or fecal antigen test for diagnosis). Urease produces ammonia, creating an alkaline environment, which helps *H pylori* survive in acidic mucosa. Colonizes mainly antrum of stomach; causes gastritis and peptic ulcers (especially duodenal). Risk factor for peptic ulcer disease, gastric adenocarcinoma, and MALT lymphoma.

Most common initial treatment is **triple** therapy: Amoxicillin (metronidazole if penicillin allergy) + Clarithromycin + Proton pump inhibitor; Antibiotics Cure Pylori. Bismuth-based quadruple therapy if concerned about macrolide resistance.

### **Spirochetes**



Spiral-shaped bacteria A with axial filaments. Includes Borrelia (big size), Leptospira, and Treponema. Only Borrelia can be visualized using aniline dyes (Wright or Giemsa stain) in light microscopy due to size. Treponema is visualized by dark-field microscopy or direct fluorescent antibody (DFA) microscopy.

### BLT.

Borrelia is Big.

### Lyme disease





Caused by *Borrelia burgdorferi*, which is transmitted by the *Ixodes* deer tick (also vector for *Anaplasma* spp. and protozoa *Babesia*). Natural reservoir is the mouse; deer are essential to tick life cycle but do not harbor *Borrelia*.

Common in northeastern United States. Stage 1—early localized: erythema migrans (typical "bulls-eye" configuration **B** is pathognomonic but not always present), flu-like symptoms.

Stage 2—early disseminated: secondary lesions, carditis, AV block, facial nerve (Bell) palsy, migratory myalgias/transient arthritis.

Stage 3—late disseminated: encephalopathy,

chronic arthritis.

A Key Lyme pie to the FACE:

Facial nerve palsy (typically bilateral)

**A**rthritis

Cardiac block

Erythema migrans

Treatment: doxycycline (1st line); amoxicillin and, if severe illness, CNS signs, or heart block, ceftriaxone

FAS1\_2019\_03-Microbiology.indd 146 11/14/19 12:20 PM

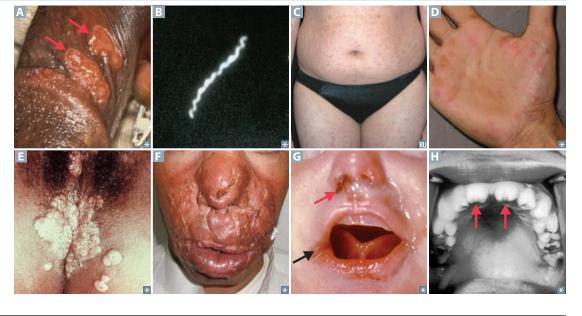
### Leptospira interrogans

Spirochete with hook-shaped ends found in water contaminated with animal urine.

**Leptospirosis**—flu-like symptoms, myalgias (classically of calves), jaundice, photophobia with conjunctival suffusion (erythema without exudate). Prevalent among surfers and in tropics (eg, Hawaii).

**Weil disease** (icterohemorrhagic leptospirosis)—severe form with jaundice and azotemia from liver and kidney dysfunction, fever, hemorrhage, and anemia.

Syphilis	Caused by spirochete <i>Treponema pallidum</i> . Treatment: penicillin G.
Primary syphilis	Localized disease presenting with <b>painless</b> chancre $\blacksquare$ . Use fluorescent or dark-field microscopy to visualize treponemes in fluid from chancre $\blacksquare$ . VDRL $\oplus$ in $\sim$ 80%.
Secondary syphilis	Disseminated disease with constitutional symptoms, maculopapular rash (including palms and soles), condylomata lata (smooth, painless, wart-like white lesions on genitals), lymphadenopathy, patchy hair loss; also confirmable with dark-field microscopy.  Serologic testing: VDRL/RPR (nonspecific), confirm diagnosis with specific test (eg, FTA-ABS).  Secondary syphilis = Systemic. Latent syphilis (⊕ serology without symptoms) may follow.
Tertiary syphilis	Gummas F (chronic granulomas), aortitis (vasa vasorum destruction), neurosyphilis (tabes dorsalis, "general paresis"), Argyll Robertson pupil (constricts with accommodation but is not reactive to light; also called "prostitute's pupil" since it accommodates but does not react).  Signs: broad-based ataxia, ⊕ Romberg, Charcot joint, stroke without hypertension.  For neurosyphilis: test spinal fluid with VDRL, FTA-ABS, and PCR.
Congenital syphilis	Presents with facial abnormalities such as rhagades (linear scars at angle of mouth, black arrow in <b>G</b> ), snuffles (nasal discharge, red arrow in <b>G</b> ), saddle nose, notched (Hutchinson) teeth <b>H</b> , mulberry molars, and short maxilla; saber shins; CN VIII deafness.  To prevent, treat mother early in pregnancy, as placental transmission typically occurs after first trimester.



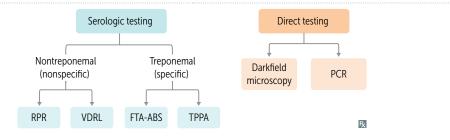
FAS1\_2019\_03-Microbiology.indd 147 11/14/19 12:20 PM

### **VDRL** false positives

VDRL detects nonspecific antibody that reacts with beef cardiolipin. Quantitative, inexpensive, and widely available test for syphilis (sensitive but not specific).

False-Positive results on VDRL with:

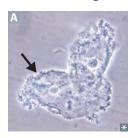
- Pregnancy
- Viral infection (eg, EBV, hepatitis)
- Drugs (eg, chlorpromazine, procainamide)
- Rheumatic fever (rare)
- Lupus and leprosy



## Jarisch-Herxheimer reaction

Flu-like syndrome (fever, chills, headache, myalgia) after antibiotics are started; due to killed bacteria (usually spirochetes) releasing toxins.

### Gardnerella vaginalis



A pleomorphic, gram-variable rod involved in bacterial vaginosis. Presents as a gray vaginal discharge with a **fishy** smell; nonpainful (vs vaginitis). Associated with sexual activity, but not sexually transmitted. Bacterial **vaginosis** is also characterized by overgrowth of certain anaerobic bacteria in vagina (due to ↓ lactobacilli). **Clue** cells (vaginal epithelial cells covered with **Gardnerella**) have stippled appearance along outer margin (arrow in ▲).

I don't have a **clue** why I smell **fish** in the **vagina** garden!

Amine whiff test—mixing discharge with 10% KOH enhances fishy odor.

Treatment: metronidazole or clindamycin.

### Chlamydiae



Chlamydiae cannot make their own ATP. They are obligate intracellular organisms that cause mucosal infections. 2 forms:

- Elementary body (small, dense)
   is "Enfectious" and Enters cell via
   Endocytosis; transforms into reticulate body.
- Reticulate body Replicates in cell by fission;
   Reorganizes into elementary bodies.

Chlamydia trachomatis causes neonatal and follicular adult conjunctivitis A, nongonococcal urethritis, PID, and reactive arthritis.

Chlamydophila pneumoniae and Chlamydophila psittaci cause atypical pneumonia; transmitted by aerosol.

Chlamydial cell wall lacks classic peptidoglycan (due to reduced muramic acid), rendering  $\beta$ -lactam antibiotics ineffective.

Chlamys = cloak (intracellular).

C psittaci—has an avian reservoir (parrots), causes atypical pneumonia.

Lab diagnosis: PCR, nucleic acid amplification test. Cytoplasmic inclusions (reticulate bodies) seen on Giemsa or fluorescent antibody—stained smear.

Treatment: azithromycin (favored because one-time treatment) or doxycycline. Add ceftriaxone for possible concomitant gonorrhea.

FAS1\_2019\_03-Microbiology.indd 148 11/14/19 12:20 PM

### Chlamydia trachomatis serotypes

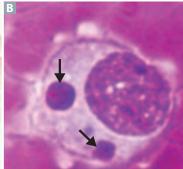
Types A, B, and C	Chronic infection, cause blindness due to follicular conjunctivitis in Africa.	<b>ABC</b> = <b>A</b> frica, <b>B</b> lindness, <b>C</b> hronic infection.
Types D-K	Urethritis/PID, ectopic pregnancy, neonatal pneumonia (staccato cough) with eosinophilia, neonatal conjunctivitis (1–2 weeks after birth).	D–K = everything else.  Neonatal disease can be acquired during passage through infected birth canal.
Types L1, L2, and L3	Lymphogranuloma venereum—small, painless ulcers on genitals → swollen, painful inguinal lymph nodes that ulcerate (buboes). Treat with doxycycline.	
Zoonotic bacteria	Zoonosis—infectious disease transmitted between	n animals and humans.
SPECIES	DISEASE	TRANSMISSION AND SOURCE
Anaplasma spp	Anaplasmosis	Ixodes ticks (live on deer and mice)
Bartonella spp	Cat scratch disease, bacillary angiomatosis	Cat scratch
Borrelia burgdorferi	Lyme disease	Ixodes ticks (live on deer and mice)
Borrelia recurrentis	Relapsing fever	Louse (recurrent due to variable surface antigens)
Brucella spp	Brucellosis/undulant fever	Unpasteurized dairy
Campylobacter	Bloody diarrhea	Feces from infected pets/animals; contaminated meats/foods/hands
Chlamydophila psittaci	Psittacosis	Parrots, other birds
Coxiella burnetii	Q fever	Aerosols of cattle/sheep amniotic fluid
Ehrlichia chaffeensis	Ehrlichiosis	Amblyomma (Lone Star tick)
Francisella tularensis	Tularemia	Ticks, rabbits, deer flies
Leptospira spp	Leptospirosis	Animal urine in water; recreational water use
Mycobacterium leprae	Leprosy	Humans with lepromatous leprosy; armadillo (rare)
Pasteurella multocida	Cellulitis, osteomyelitis	Animal bite, cats, dogs
Rickettsia prowazekii	Epidemic typhus	Human to human via human body louse
Rickettsia rickettsii	Rocky Mountain spotted fever	Dermacentor (dog tick)
Rickettsia typhi	Endemic typhus	Fleas
Salmonella spp (except S typhi)	Diarrhea (which may be bloody), vomiting, fever, abdominal cramps	Reptiles and poultry
Yersinia pestis	Plague	Fleas (rats and prairie dogs are reservoirs)

FAS1\_2019\_03-Microbiology.indd 149 11/14/19 12:20 PM

## Rickettsial diseases and vector-borne

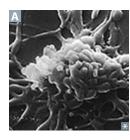
illnesses	Treatment: doxycycline.	
RASH COMMON		
Rocky Mountain spotted fever	Rickettsia rickettsii, vector is tick. Despite its name, disease occurs primarily in the South Atlantic states, especially North Carolina. Rash typically starts at wrists A and ankles and then spreads to trunk, palms, and soles.	Classic triad—headache, fever, rash (vasculitis).  Palms and soles rash is seen in Coxsackievirus  A infection (hand, foot, and mouth disease),  Rocky Mountain spotted fever, and 2° Syphilis (you drive CARS using your palms and soles).
Typhus	Endemic (fleas)— <i>R typhi</i> . Epidemic (human body louse)— <i>R prowazekii</i> . Rash starts centrally and spreads out, sparing palms and soles.	Rickettsii on the wRists, Typhus on the Trunk.
RASH RARE		
Ehrlichiosis	Ehrlichia, vector is tick. Monocytes with morulae B (mulberry-like inclusions) in cytoplasm.	MEGA berry— Monocytes = Ehrlichiosis Granulocytes = Anaplasmosis
Anaplasmosis	Anaplasma, vector is tick. Granulocytes with morulae c in cytoplasm.	
Q fever	Coxiella burnetii, no arthropod vector. Spores inhaled as aerosols from cattle/sheep amniotic fluid. Presents with headache, cough, influenza-like symptoms, pneumonia, possibly in combination with hepatitis. Common cause of culture ⊖ endocarditis.	Q fever is caused by a Quite Complicated Bug because it has no rash or vector and its causative organism can survive outside in its endospore form. Not in the <i>Rickettsia</i> genus, but closely related.
	A	







## Mycoplasma pneumoniae



Classic cause of atypical "walking pneumonia" (insidious onset, headache, nonproductive cough, patchy or diffuse interstitial infiltrate). Occurs frequently in those <30 years old; outbreaks in military recruits, prisons, colleges. X-ray looks worse than patient. High titer of cold agglutinins (IgM), which can agglutinate RBCs.

Treatment: macrolides, doxycycline, or fluoroquinolone (penicillin ineffective since *Mycoplasma* has no cell wall).

Not seen on Gram stain. Pleomorphic A. Bacterial membrane contains sterols for stability. Grown on Eaton agar.

Mycoplasma gets cold without a coat (no cell wall). Can cause atypical variant of Stevens-Johnson syndrome, typically in children and adolescents.

FAS1\_2019\_03-Microbiology.indd 150 11/14/19 12:21 PM

### ► MICROBIOLOGY — MYCOLOGY

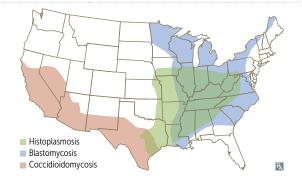
### **Systemic mycoses**

All of the following can cause pneumonia and can disseminate.

All are caused by dimorphic fungi: **cold** (20°C) = **mold**; **heat** (37°C) = **yeast**. Only exception is *Coccidioides*, which is a spherule (not yeast) in tissue.

Systemic mycoses can form granulomas (like TB); cannot be transmitted person-to-person (unlike TB). Treatment: fluconazole or itraconazole for **local** infection; amphotericin B for **systemic** infection.

			, 1	,
DISEASE	ENDEMIC LOCATION	PATHOLOGIC FEATURES	UNIQUE SIGNS/SYMPTOMS	NOTES
Histoplasmosis A	Mississippi and Ohio River Valleys	Macrophage filled with <i>Histoplasma</i> (smaller than RBC)	Palatal/tongue ulcers, splenomegaly, pancytopenia	Histo hides (within macrophages) Associated with bird or bat droppings (eg, spelunking) Diagnosis via urine/serum antigen
Blastomycosis	Eastern and Central US, Great Lakes	<b>Broad</b> -based budding of <i>Blastomyces</i> (same size as RBC)	Inflammatory lung disease Disseminates to bone/ skin (may mimic SCC) Forms granulomatous nodules	Blasto buds broadly
Coccidioidomycosis	Southwestern US, California	Spherule (much larger than RBC) filled with endospores of Coccidioides	Disseminates to skin/ bone Erythema nodosum (desert bumps) or multiforme Arthralgias (desert rheumatism) Can cause meningitis	Associated with dust exposure in endemic areas (eg, archeological excavations, earthquakes)
Para-coccidioidomycosis	Latin America	Budding yeast of Paracoccidioides with "captain's wheel" formation (much larger than RBC) D	Similar to blastomycosis, males > females	Paracoccidio parasails with the captain's wheel all the way to Latin America



FAS1\_2019\_03-Microbiology.indd 151 11/14/19 12:21 PM

### **Cutaneous mycoses**

Tinea (dermatophytes)	Clinical name for dermatophyte (cutaneous fungal) infections. Dermatophytes include <i>Microsporum</i> , <i>Trichophyton</i> , and <i>Epidermophyton</i> . Branching septate hyphae visible on KOH preparation with blue fungal stain A. Associated with pruritus.
Tinea capitis	Occurs on head, scalp. Associated with lymphadenopathy, alopecia, scaling B.
Tinea corporis	Occurs on body (usually torso). Characterized by enlarging erythematous, scaly rings ("ringworm" with central clearing . Can be acquired from contact with infected pets or farm animals.
Tinea cruris	Occurs in inguinal area D. Often does not show the central clearing seen in tinea corporis.
Tinea pedis	Three varieties: Interdigital E; most common Moccasin distribution E Vesicular type
Tinea unguium	Onychomycosis; occurs on nails.
Tinea (pityriasis) versicolor	Caused by <i>Malassezia</i> spp. ( <i>Pityrosporum</i> spp.), a yeast-like fungus (not a dermatophyte despite being called tinea). Degradation of lipids produces acids that inhibit tyrosinase (involved in melanin synthesis) → hypopigmentation ⑤; hyperpigmentation and/or pink patches can also occur due to inflammatory response. Less pruritic than dermatophytes.  Can occur any time of year, but more common in summer (hot, humid weather). "Spaghetti and meatballs" appearance on microscopy ℍ.  Treatment: selenium sulfide, topical and/or oral antifungal medications.



FAS1\_2019\_03-Microbiology.indd 152 11/14/19 12:21 PM

### **Opportunistic fungal infections**

### Candida albicans

alba = white. Dimorphic; forms pseudohyphae and budding yeasts at 20°C A, germ tubes at 37°C ■.

Systemic or superficial fungal infection. Causes oral [ and esophageal thrush in immunocompromised (neonates, steroids, diabetes, AIDS), vulvovaginitis (diabetes, use of antibiotics), diaper rash, endocarditis (IV drug users), disseminated candidiasis (especially in neutropenic patients), chronic mucocutaneous candidiasis.

Treatment: oral fluconazole/topical azoles for vaginal; nystatin, azoles, or, rarely, echinocandins for oral; fluconazole, echinocandins, or amphotericin B for esophageal or systemic disease.

### **Aspergillus** *fumigatus*

Septate hyphae that branch at 45° Acute Angle D E.

Causes invasive aspergillosis in immunocompromised patients, neutrophil dysfunction (eg, chronic granulomatous disease).

Can cause aspergillomas **F** in pre-existing lung cavities, especially after TB infection. Some species of Aspergillus produce Aflatoxins (associated with hepatocellular carcinoma). Treatment: voriconazole or echinocandins (2nd-line).

Allergic bronchopulmonary aspergillosis (ABPA)—hypersensitivity response to Aspergillus growing in lung mucus. Associated with asthma and cystic fibrosis; may cause bronchiectasis and eosinophilia.

### Cryptococcus neoformans

5–10 µm with narrow budding. Heavily encapsulated yeast. Not dimorphic.

Found in soil, pigeon droppings. Acquired through inhalation with hematogenous dissemination to meninges. Highlighted with India ink (clear halo G) and mucicarmine (red inner capsule H). Latex agglutination test detects polysaccharide capsular antigen and is more sensitive and specific. Causes cryptococcosis, cryptococcal meningitis, cryptococcal encephalitis ("soap bubble" lesions

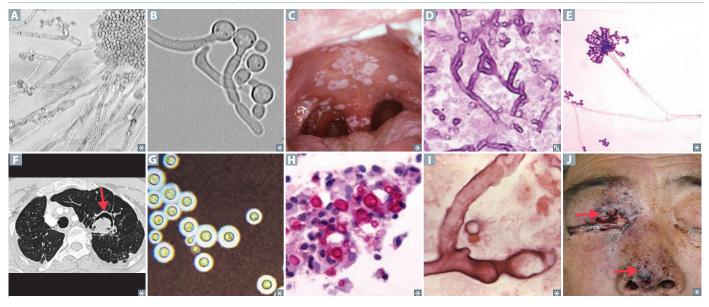
in brain), primarily in immunocompromised. Treatment: amphotericin B + flucytosine followed by fluconazole for cryptococcal meningitis.

### Mucor and Rhizopus spp

Irregular, broad, nonseptate hyphae branching at wide angles 1.

Causes mucormycosis, mostly in ketoacidotic diabetic and/or neutropenic patients (eg, leukemia). Inhalation of spores → fungi proliferate in blood vessel walls, penetrate cribriform plate, and enter brain. Rhinocerebral, frontal lobe abscess; cavernous sinus thrombosis. Headache, facial pain, black necrotic eschar on face **J**; may have cranial nerve involvement.

Treatment: surgical debridement, amphotericin B or isavuconazole.

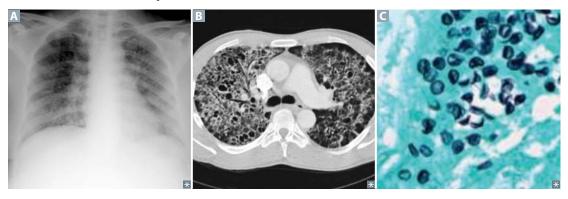


FAS1\_2019\_03-Microbiology.indd 153 11/14/19 12:21 PM

### Pneumocystis jirovecii

Causes *Pneumocystis* pneumonia (PCP), a diffuse interstitial pneumonia A. Yeast-like fungus (originally classified as protozoan). Most infections are asymptomatic. Immunosuppression (eg, AIDS) predisposes to disease. Diffuse, bilateral ground-glass opacities on chest imaging, with pneumatoceles B. Diagnosed by bronchoalveolar lavage or lung biopsy. Disc-shaped yeast seen on methenamine silver stain of lung tissue C or with fluorescent antibody.

Treatment/prophylaxis: TMP-SMX, pentamidine, dapsone (prophylaxis as single agent, or treatment in combination with TMP), atovaquone. Start prophylaxis when CD4+ count drops to < 200 cells/mm<sup>3</sup> in HIV patients.



### Sporothrix schenckii



Causes sporotrichosis. Dimorphic fungus. Exists as a **cigar**-shaped yeast at 37 °C in the human body and as hyphae with spores in soil (conidia). Lives on vegetation. When spores are traumatically introduced into the skin, typically by a thorn ("**rose gardener**'s disease"), causes local pustule or ulcer with nodules along draining lymphatics (ascending lymphangitis A). Disseminated disease possible in immunocompromised host.

Treatment: itraconazole or potassium iodide (only for cutaneous/lymphocutaneous).

Think of a rose gardener who smokes a cigar and pot.

FAS1\_2019\_03-Microbiology.indd 154 11/14/19 12:21 PM

## ► MICROBIOLOGY—PARASITOLOGY

### **Protozoa**—gastrointestinal infections

ORGANISM	DISEASE	TRANSMISSION	DIAGNOSIS	TREATMENT
Giardia lamblia	Giardiasis—bloating, flatulence, foul-smelling, fatty diarrhea (often seen in campers/hikers)—think fat-rich Ghirardelli chocolates for fatty stools of Giardia	Cysts in water	Multinucleated trophozoites A or cysts B in stool, antigen detection	Metronidazole
Entamoeba histolytica	Amebiasis—bloody diarrhea (dysentery), liver abscess ("anchovy paste" exudate), RUQ pain; histology of colon biopsy shows flask-shaped ulcers	Cysts in water	Serology, antigen testing, and/or trophozoites (with engulfed RBCs c in the cytoplasm) or cysts with up to 4 nuclei in stool p; Entamoeba Eats Erythrocytes	Metronidazole; paromomycin or iodoquinol for asymptomatic cyst passers
Cryptosporidium	Severe diarrhea in AIDS Mild disease (watery diarrhea) in immunocompetent hosts	Oocysts in water	Oocysts on acid-fast stain <b>E</b> , antigen detection	Prevention (by filtering city water supplies); nitazoxanide in immunocompetent hosts
A	B			<b>8</b>

11/14/19 12:21 PM FAS1\_2019\_03-Microbiology.indd 155

### **Protozoa—CNS infections**

ORGANISM	DISEASE	TRANSMISSION	DIAGNOSIS	TREATMENT
Toxoplasma gondii	Immunocompetent: mononucleosis-like symptoms, ⊝ heterophile antibody test Reactivation in AIDS → brain abscesses usually seen as multiple ring-enhancing lesions on MRI A Congenital toxoplasmosis: classic triad of chorioretinitis, hydrocephalus, and intracranial calcifications	Cysts in meat (most common); oocysts in cat feces; crosses placenta (pregnant women should avoid cats)	Serology, biopsy (tachyzoite) <b>B</b>	Sulfadiazine + pyrimethamine
Naegleria fowleri	Rapidly fatal meningoencephalitis	Swimming in warm freshwater; enters via cribriform plate	Amoebas in CSF C	Amphotericin B has been effective for a few survivors
Trypanosoma brucei	African sleeping sickness— enlarged lymph nodes, recurring fever (due to antigenic variation), somnolence, coma	Tsetse fly, a painful bite	Trypomastigote in blood smear D	Suramin for blood- borne disease or melarsoprol for CNS penetration ("I sure am mellow when I'm sleeping")
	A B	<b>∠</b>	*	*

FAS1\_2019\_03-Microbiology.indd 156 11/14/19 12:21 PM

### **Protozoa**—hematologic infections

ORGANISM	DISEASE	TRANSMISSION	DIAGNOSIS	TREATMENT
Plasmodium P vivax/ovale P falciparum P malariae	Malaria—fever, headache, anemia, splenomegaly P vivax/ovale—48-hr cycle (tertian; includes fever on first day and third day, thus fevers are actually 48 hr apart); dormant form (hypnozoite) in liver P falciparum—severe; irregular fever patterns; parasitized RBCs occlude capillaries in brain (cerebral malaria), kidneys, lungs P malariae—72-hr cycle (quartan)		Blood smear: trophozoite ring form within RBC A, schizont containing merozoites; red granules (Schüffner stippling) B throughout RBC cytoplasm seen with P vivax/ovale	Chloroquine (for sensitive species); if resistant, use mefloquine or atovaquone/ proguanil If life-threatening, use intravenous quinidine or artesunate (test for G6PD deficiency) For <i>P vivax/ovale</i> , add primaquine for hypnozoite (test for G6PD deficiency)
Babesia  C  2	Babesiosis — fever and hemolytic anemia; predominantly in northeastern United States; asplenia ↑ risk of severe disease	Ixodes tick (also vector for Borrelia burgdorferi and Anaplasma spp)	Blood smear: ring form C1, "Maltese cross" C2; PCR	Atovaquone + azithromycin

FAS1\_2019\_03-Microbiology.indd 157 11/14/19 12:21 PM

### Protozoa—others

ORGANISM	DISEASE	TRANSMISSION	DIAGNOSIS	TREATMENT
Visceral infections				
Trypanosoma cruzi	Chagas disease—dilated cardiomyopathy with apical atrophy, megacolon, megaesophagus; predominantly in South America Unilateral periorbital swelling (Romaña sign) characteristic of acute stage	Triatomine insect (kissing bug) bites and defecates around the mouth or eyes; fecal transmission into bite site or mucosa	Trypomastigote in blood smear A	Benznidazole or nifurtimox; cruzing in my Benz, with a fur coat on
Leishmania spp	Visceral leishmaniasis (kala-azar)—spiking fevers, hepatosplenomegaly, pancytopenia Cutaneous leishmaniasis—skin ulcers B	Sandfly	Macrophages containing amastigotes C	Amphotericin B, sodium stibogluconate
Sexually transmitted	d infections			
Trichomonas vaginalis	Vaginitis—foul-smelling, greenish discharge; itching and burning; do not confuse with <i>Gardnerella vaginalis</i> , a gram-variable bacterium associated with bacterial vaginosis	Sexual (cannot exist outside human because it cannot form cysts)	Trophozoites (motile)  on wet mount; punctate cervical hemorrhages ("strawberry cervix")	Metronidazole for patient and partner (prophylaxis; check for STI)
	A B	C	D *	×

# Nematode routes of infection

Ingested—Enterobius, Ascaris, Toxocara, Trichinella, Trichuris
Cutaneous—Strongyloides, Ancylostoma, Necator

Bites—Loa loa, Onchocerca volvulus, Wuchereria bancrofti You'll get sick if you **EATTT** these!

These get into your feet from the **SAN**d

Lay **LOW** to avoid getting bitten

FAS1\_2019\_03-Microbiology.indd 158 11/14/19 12:21 PM

### **Nematodes (roundworms)**

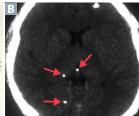
ORGANISM ORGANISM	DISEASE	TRANSMISSION	TREATMENT
Intestinal			
Enterobius vermicularis (pinworm)	Causes anal pruritus (diagnosed by seeing egg A via the tape test).	Fecal-oral.	Bendazoles (bendy worms), pyrantel pamoate.
Ascaris lumbricoides (giant roundworm)	May cause obstruction at ileocecal valve, biliary obstruction, intestinal perforation, migrates from nose/mouth.	Fecal-oral; knobby-coated, oval eggs seen in feces under microscope <b>B</b> .	Bendazoles.
Strongyloides stercoralis (threadworm)	GI (eg, duodenitis), pulmonary (eg, dry cough, hemoptysis), and cutaneous (eg, pruritus) symptoms. Hyperinfection syndrome caused by autoinfection (larvae enter bloodstream).	Larvae in soil penetrate skin; rhabditiform larvae seen in feces under microscope.	Ivermectin or bendazoles.
Ancylostoma spp, Necator americanus (hookworms)	Cause microcytic anemia by sucking blood from intestinal wall.  Cutaneous larva migrans—pruritic, serpiginous rash  from walking barefoot on contaminated beach.	Larvae penetrate skin.	Bendazoles or pyrantel pamoate.
Trichinella spiralis	Larvae enter bloodstream, encyst in striated muscle □ → myositis.  Trichinosis—fever, vomiting, nausea, periorbital edema, myalgia.	Undercooked meat (especially pork); fecal-oral (less likely).	Bendazoles.
Trichuris trichiura (whipworm)	Often asymptomatic; loose stools, anemia, rectal prolapse in children.	Fecal-oral.	Bendazoles.
Tissue			
Toxocara canis	Visceral larva migrans—nematodes migrate to blood through intestinal wall → inflammation affecting liver, eyes (visual impairment, blindness), CNS (seizures, coma), heart (myocarditis).	Fecal-oral.	Bendazoles.
Onchocerca volvulus	Skin changes, loss of elastic fibers, river blindness (black skin nodules, "black sight"); allergic reaction possible.	Female black fly.	Ivermectin (ivermectin for river blindness).
Loa loa	Swelling in skin, worm in conjunctiva.	Deer fly, horse fly, mango fly.	Diethylcarbamazine.
Wuchereria bancrofti	Lymphatic filariasis (elephantiasis)— worms invade lymph nodes.  → inflammation → lymphedema E; symptom onset after 9 mo−1 yr.	Female mosquito.	Diethylcarbamazine.
A **	B C	P n n	

FAS1\_2019\_03-Microbiology.indd 159 11/14/19 12:21 PM

### **Cestodes (tapeworms)**

ORGANISM	DISEASE	TRANSMISSION	TREATMENT
Taenia solium A	Intestinal tapeworm	Ingestion of larvae encysted in undercooked pork	Praziquantel
	Cysticercosis, neurocysticercosis (cystic CNS lesions, seizures)	Ingestion of eggs in food contaminated with human feces	Praziquantel; albendazole for neurocysticercosis
Diphyllobothrium latum	Vitamin B <sub>12</sub> deficiency (tapeworm competes for B <sub>12</sub> in intestine) → megaloblastic anemia	Ingestion of larvae in raw freshwater fish	Praziquantel
Echinococcus granulosus	Hydatid cysts <b>D</b> ("eggshell calcification") in liver <b>E</b> ; cyst rupture can cause anaphylaxis	Ingestion of eggs in food contaminated with dog feces Sheep are an intermediate host	Albendazole











### **Trematodes (flukes)**

ORGANISM	DISEASE	TRANSMISSION	TREATMENT
Schistosoma  A  B  **  **  **  **  **  **  **  **	Liver and spleen enlargement ( <i>S mansoni</i> , egg with lateral spine A), fibrosis, inflammation, portal hypertension Chronic infection with <i>S haematobium</i> (egg with terminal spine B) can lead to squamous cell carcinoma of the bladder (painless hematuria) and pulmonary hypertension	Snails are intermediate host; cercariae penetrate skin of humans in contact with contaminated fresh water (eg, swimming or bathing)	Praziquantel
Clonorchis sinensis	Biliary tract inflammation  → pigmented gallstones Associated with cholangiocarcinoma	Undercooked fish	Praziquantel

FAS1\_2019\_03-Microbiology.indd 160 11/14/19 12:21 PM

### **Ectoparasites**

### Sarcoptes scabiei

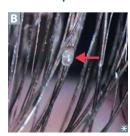


Mites burrow into stratum corneum and cause scabies-pruritus (worse at night) and serpiginous burrows (lines) often between fingers and toes A.

Common in children, crowded populations (jails, nursing homes); transmission through skin-to-skin contact (most common) or via fomites.

Treatment: permethrin cream, washing/drying all clothing/bedding, treat close contacts.

### Pediculus humanus/ Phthirus pubis



Blood-sucking lice that cause intense pruritus with associated excoriations, commonly on scalp and neck (head lice), waistband and axilla (body lice), or pubic and perianal regions (pubic lice).

Body lice can transmit Rickettsia prowazekii (epidemic typhus), Borrelia recurrentis (relapsing fever), Bartonella quintana (trench fever).

Treatment: pyrethroids, malathion, or ivermectin lotion, and nit B combing. Children with head lice can be treated at home without interrupting school attendance.

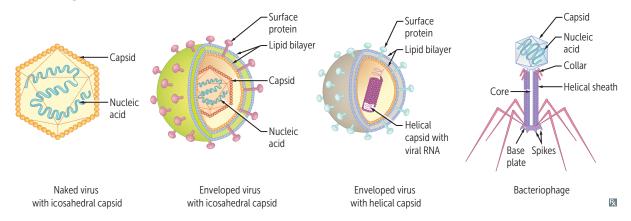
### **Parasite hints**

ASSOCIATIONS	ORGANISM
Biliary tract disease, cholangiocarcinoma	Clonorchis sinensis
Brain cysts, seizures	Taenia solium (neurocysticercosis)
Hematuria, squamous cell bladder cancer	Schistosoma haematobium
Liver (hydatid) cysts	Echinococcus granulosus
Microcytic anemia	Ancylostoma, Necator
Myalgias, periorbital edema	Trichinella spiralis
Perianal pruritus	Enterobius
Portal hypertension	Schistosoma mansoni, Schistosoma japonicum
Vitamin B <sub>12</sub> deficiency	Diphyllobothrium latum

FAS1\_2019\_03-Microbiology.indd 161 11/14/19 12:21 PM

### ► MICROBIOLOGY — VIROLOGY

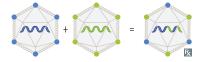
### Viral structure—general features



### **Viral genetics**

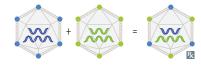
#### Recombination

Exchange of genes between 2 chromosomes by crossing over within regions of significant base sequence homology.



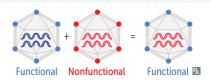
#### Reassortment

When viruses with segmented genomes (eg, influenza virus) exchange genetic material. For example, the 2009 novel H1N1 influenza A pandemic emerged via complex viral reassortment of genes from human, swine, and avian viruses. Has potential to cause antigenic shift.



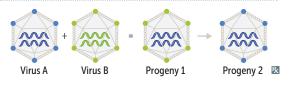
### Complementation

When 1 of 2 viruses that infect the cell has a mutation that results in a nonfunctional protein, the nonmutated virus "complements" the mutated one by making a functional protein that serves both viruses. For example, hepatitis D virus requires the presence of replicating hepatitis B virus to supply HBsAg, the envelope protein for HDV.



### Phenotypic mixing

Occurs with simultaneous infection of a cell with 2 viruses. For progeny 1, genome of virus A can be partially or completely coated (forming pseudovirion) with the surface proteins of virus B. Type B protein coat determines the tropism (infectivity) of the hybrid virus. Progeny from subsequent infection of a cell by progeny 1 will have a type A coat that is encoded by its type A genetic material.



FAS1\_2019\_03-Microbiology.indd 162 11/14/19 12:21 PM

### **DNA viral genomes**

All DNA viruses have dsDNA genomes except Parvoviridae (ssDNA).

All are linear except papilloma-, polyoma-, and hepadnaviruses (circular).

All are dsDNA (like our cells), except "part-of-a-virus" (parvovirus) is ssDNA.

Parvus = small.

### **RNA viral genomes**

All RNA viruses have ssRNA genomes except Reoviridae (dsRNA).

⊕ stranded RNA viruses: I went to a retro (retrovirus) toga (togavirus) party, where I drank flavored (flavivirus) Corona (coronavirus) and ate hippie (hepevirus) California (calicivirus) pickles (picornavirus).

All are ssRNA, except "repeato-virus" (reovirus) is dsRNA.

## Naked viral genome infectivity

Purified nucleic acids of most dsDNA viruses (except poxviruses and HBV) and ⊕ strand ssRNA (≈ mRNA) viruses are infectious. Naked nucleic acids of ⊝ strand ssRNA and dsRNA viruses are not infectious. They require polymerases contained in the complete virion.

### **Viral envelopes**

Generally, enveloped viruses acquire their envelopes from plasma membrane when they exit from cell. Exceptions include herpesviruses, which acquire envelopes from nuclear membrane.

Naked (nonenveloped) viruses include Papillomavirus, Adenovirus, Parvovirus, Polyomavirus, Calicivirus, Picornavirus, Reovirus, and Hepevirus. DNA = PAPP; RNA = CPR and hepevirus. Give PAPP smears and CPR to a naked hippie (hepevirus).

Enveloped DNA viruses Have Helpful Protection (Herpesvirus, Hepadnavirus, Poxvirus).

## DNA virus characteristics

Some general rules—all DNA viruses:

GENERAL RULE	COMMENTS	
Are <b>HHAPPPP</b> y viruses	Hepadna, Herpes, Adeno, Pox, Parvo, Papilloma, Polyoma.	
Are double stranded Except parvo (single stranded).		
Have linear genomes	Except papilloma and polyoma (circular, supercoiled) and hepadna (circular, incomplete).	
Are icosahedral	Except pox (complex).	
Replicate in the nucleus	Except pox (carries own DNA-dependent RNA polymerase).	

FAS1\_2019\_03-Microbiology.indd 163 11/14/19 12:21 PM

VIRAL FAMILY	ENVELOPE	DNA STRUCTURE	MEDICAL IMPORTANCE
Herpesviruses	Yes	DS and linear	See Herpesviruses entry
Poxvirus	Yes	DS and linear (largest DNA virus)	Smallpox eradicated world wide by use of the live- attenuated vaccine Cowpox ("milkmaid blisters") Molluscum contagiosum—flesh-colored papule with central umbilication
Hepadnavirus	Yes	Partially DS and circular	<ul><li>HBV:</li><li>Acute or chronic hepatitis</li><li>Not a retrovirus but has reverse transcriptase</li></ul>
Adenovirus	No	DS and linear	Febrile pharyngitis —sore throat Acute hemorrhagic cystitis Pneumonia Conjunctivitis—"pink eye" Gastroenteritis Myocarditis
Papillomavirus	No	DS and circular	HPV–warts (serotypes 1, 2, 6, 11), CIN, cervical cancer (most commonly 16, 18)
Polyomavirus	No	DS and circular	JC virus—progressive multifocal leukoencephalopathy (PML) in HIV BK virus—transplant patients, commonly targets kidney JC: Junky Cerebrum; BK: Bad Kidney
Parvovirus	No	SS and linear (smallest DNA virus)	B19 virus—aplastic crises in sickle cell disease, "slapped cheek" rash in children (erythema infectiosum, or fifth disease); infects RBC precursors and endothelial cells → RBC destruction → hydrops fetalis and death in fetus, pure RBC aplasia and rheumatoid arthritis—like symptoms in adults

Herpesviruses	Enveloped, DS, and	d linear viruses	
VIRUS	ROUTE OF TRANSMISSION	CLINICAL SIGNIFICANCE	NOTES
Herpes simplex virus-1	Respiratory secretions, saliva	Gingivostomatitis, keratoconjunctivitis A, herpes labialis (cold sores) B, herpetic whitlow on finger, temporal lobe encephalitis, esophagitis, erythema multiforme	Most commonly latent in trigeminal ganglia Most common cause of sporadic encephalitis, can present as altered mental status, seizures, and/or aphasia
Herpes simplex virus-2	Sexual contact, perinatal	Herpes genitalis <b>C</b> , neonatal herpes	Most commonly latent in sacral ganglia Viral meningitis more common with HSV-2 than with HSV-1

11/14/19 12:21 PM FAS1\_2019\_03-Microbiology.indd 164

### **Herpesviruses** (continued)

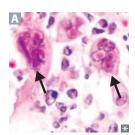
VIRUS	ROUTE OF TRANSMISSION	CLINICAL SIGNIFICANCE	NOTES
Varicella- Zoster virus (HHV-3)	Respiratory secretions, contact with fluid from vesicles	Varicella-zoster (chickenpox D, shingles E), encephalitis, pneumonia  Most common complication of shingles is post-herpetic neuralgia	Latent in dorsal root or trigeminal ganglia; CN V <sub>1</sub> branch involvement can cause herpes zoster ophthalmicus
Epstein-Barr virus (HHV-4)	Respiratory secretions, saliva; aka "kissing disease," (common in teens, young adults)	Mononucleosis — fever, hepatosplenomegaly F, pharyngitis, and lymphadenopathy (especially posterior cervical nodes); avoid contact sports until resolution due to risk of splenic rupture Associated with lymphomas (eg, endemic Burkitt lymphoma), nasopharyngeal carcinoma (especially Asian adults), lymphoproliferative disease in transplant patients	Infects B cells through CD21, "Must be 21 to drink Beer in a Barr" Atypical lymphocytes on peripheral blood smear  ☐—not infected B cells but reactive cytotoxic T cells  ⊕ Monospot test—heterophile antibodies detected by agglutination of sheep or horse RBCs Use of amoxicillin in mononucleosis can cause characteristic maculopapular rash
Cytomegalo- virus (HHV-5)	Congenital, transfusion, sexual contact, saliva, urine, transplant	Mononucleosis (⊖ Monospot) in immunocompetent patients; infection in immunocompromised, especially pneumonia in transplant patients; esophagitis; AIDS retinitis ("sightomegalovirus"): hemorrhage, cotton-wool exudates, vision loss Congenital CMV	Infected cells have characteristic "owl eye" intranuclear inclusions H Latent in mononuclear cells
Human herpes- viruses 6 and 7	Saliva	Roseola infantum (exanthem subitum): high fevers for several days that can cause seizures, followed by diffuse macular rash (starts on trunk then spreads to extremities)	Roseola: fever first, Rosy (rash) later. HHV-7—less common cause of roseola
Human herpesvirus 8	Sexual contact	Kaposi sarcoma (neoplasm of endothelial cells). Seen in HIV/AIDS and transplant patients. Dark/violaceous plaques or nodules representing vascular proliferations	Can also affect GI tract and lungs
E Liv	B Sp .	H RU	E ***

FAS1\_2019\_03-Microbiology.indd 165 11/14/19 12:22 PM

## 166 SECTION II

## MICROBIOLOGY → MICROBIOLOGY — VIROLOGY

### **HSV** identification



Viral culture for skin/genitalia.

CSF PCR for herpes encephalitis.

Tzanck test—a smear of an opened skin vesicle to detect multinucleated giant cells A commonly seen in HSV-1, HSV-2, and VZV infection. PCR of skin lesions is test of choice.

Tzanck heavens I do not have herpes.

Intranuclear eosinophilic Cowdry A inclusions also seen with HSV-1, HSV-2, VZV.

## Receptors used by viruses

VIRUS	RECEPTORS
CMV	Integrins (heparan sulfate)
EBV	CD21
HIV	CD4, CXCR4, CCR5
<b>P</b> arvovirus B19	P antigen on RBCs
Rabies	Nicotinic AChR
Rhinovirus	ICAM-1 (I came to see the rhino)

FAS1\_2019\_03-Microbiology.indd 166 11/14/19 12:22 PM

VIRAL FAMILY	ENVELOPE	RNA STRUCTURE	CAPSID SYMMETRY	MEDICAL IMPORTANCE	
Reoviruses	No	DS linear Multisegmented	Icosahedral (double)	Coltivirus <sup>a</sup> —Colorado tick fever Rotavirus—cause of fatal diarrhea in children	
Picornaviruses	No	SS ⊕ linear	Icosahedral	Poliovirus—polio-Salk/Sabin vaccines—IPV/OPV Echovirus—aseptic meningitis Rhinovirus—"common cold" Coxsackievirus—aseptic meningitis; herpangina (mouth blisters, fever); hand, foot, and mouth disease; myocarditis; pericarditis HAV—acute viral hepatitis PERCH	
Hepevirus	No	SS ⊕ linear	Icosahedral	HEV	
Caliciviruses	No	SS ⊕ linear	Icosahedral	Norovirus—viral gastroenteritis	
Flaviviruses	Yes	SS ⊕ linear	Icosahedral	HCV Yellow fever <sup>a</sup> Dengue <sup>a</sup> St. Louis encephalitis <sup>a</sup> West Nile virus <sup>a</sup> —meningoencephalitis, flaccid paralysis Zika virus <sup>a</sup>	
Togaviruses	Yes	SS ⊕ linear	Icosahedral	Toga CREW—Chikungunya virus <sup>a</sup> (co-infection with dengue virus can occur), Rubella, Eastern and Western equine encephalitis	
Retroviruses	Yes	SS ⊕ linear 2 copies	Icosahedral (HTLV), complex and conical (HIV)	HTLV—T-cell leukemia HIV—AIDS	
Coronaviruses	Yes	SS ⊕ linear	Helical	"Common cold," SARS, MERS	
Orthomyxoviruses	Yes	SS ⊝ linear 8 segments	Helical	Influenza virus	
Paramyxoviruses	Yes	SS ⊝ linear Nonsegmented	Helical	PaRaMyxovirus: Parainfluenza—croup RSV—bronchiolitis in babies Measles, Mumps	
Rhabdoviruses	Yes	$SS \ominus linear$	Helical	Rabies	
Filoviruses	Yes	$SS \ominus linear$	Helical	Ebola/Marburg hemorrhagic fever—often fatal.	
Arenaviruses	Yes	SS ⊕ and ⊖ circular 2 segments	Helical	LCMV—lymphocytic choriomeningitis virus Lassa fever encephalitis—spread by rodents	
Bunyaviruses	Yes	SS ⊖ circular 3 segments	Helical	California encephalitis <sup>a</sup> Sandfly/Rift Valley fevers <sup>a</sup> Crimean-Congo hemorrhagic fever <sup>a</sup> Hantavirus—hemorrhagic fever, pneumonia	
Delta virus	Yes	$SS \ominus$ circular	Uncertain	HDV is a "defective" virus that requires the presence of HBV to replicate	

SS, single-stranded; DS, double-stranded;  $\oplus$ , positive sense;  $\ominus$ , negative sense;  $^a$ = **arbov**irus, **arthropod borne** (mosquitoes, ticks).

FAS1\_2019\_03-Microbiology.indd 167 11/14/19 12:22 PM

168

**SECTION II** 

MICROBIOLOGY ► MICROBIOLOGY — VIROLOGY

## Negative-stranded viruses

Must transcribe ⊝ strand to ⊕. Virion brings its own RNA-dependent RNA polymerase. They include Arenaviruses, Bunyaviruses, Paramyxoviruses, Orthomyxoviruses, Filoviruses, and Rhabdoviruses.

Always Bring Polymerase Or Fail Replication.

### **Segmented viruses**

All are RNA viruses. They include

Bunyaviruses (3 segments), Orthomyxoviruses
(influenza viruses) (8 segments), Arenaviruses
(2 segments), and Reoviruses (10-12 segments).

BOARding flight 382 in 10-12 minutes.

#### **Picornavirus**

Includes Poliovirus, Echovirus, Rhinovirus, Coxsackievirus, and HAV. RNA is translated into 1 large polypeptide that is cleaved by virus-encoded proteases into functional viral proteins. Can cause aseptic (viral) meningitis (except rhinovirus and HAV). All are enteroviruses except rhinovirus and HAV.

PicoRNAvirus = small RNA virus. PERCH on a "peak" (pico).

### **Rhinovirus**

A picornavirus. Nonenveloped RNA virus. Cause of common cold; > 100 serologic types. Acid labile—destroyed by stomach acid; therefore, does not infect the GI tract (unlike the other picornaviruses).

Rhino has a runny nose.

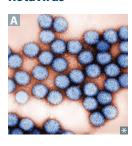
### **Yellow fever virus**

A flavivirus (also an arbovirus) transmitted by *Aedes* mosquitoes. Virus has a monkey or human reservoir.

Symptoms: high fever, black vomitus, and jaundice. May see Councilman bodies (eosinophilic apoptotic globules) on liver biopsy.

*Flavi* = yellow, jaundice.

### Rotavirus



Segmented dsRNA virus (a reovirus) A.

Most important global cause of infantile
gastroenteritis. Major cause of acute diarrhea
in the United States during winter, especially
in day care centers, kindergartens.

Villous destruction with atrophy leads to ↓ absorption of Na<sup>+</sup> and loss of K<sup>+</sup>. ROTAvirus = Right Out The Anus. CDC recommends routine vaccination of all infants except those with a history of intussusception or SCID.

FAS1\_2019\_03-Microbiology.indd 168 11/14/19 12:22 PM

#### Influenza viruses

Orthomyxoviruses. Enveloped, ⊜ ssRNA viruses with 8-segment genome. Contain hemagglutinin (binds sialic acid and promotes viral entry) and neuraminidase (promotes progeny virion release) antigens. Patients at risk for fatal bacterial superinfection, most commonly *S aureus*, *S pneumoniae*, and *H influenzae*.

Reformulated vaccine ("the flu shot") contains viral strains most likely to appear during the flu season, due to the virus' rapid genetic change. Killed viral vaccine is most frequently used. Live attenuated vaccine contains temperature-sensitive mutant that replicates in the nose but not in the lung; administered intranasally. Treatment: supportive +/- neuraminidase inhibitor (eg, oseltamivir, zanamivir).

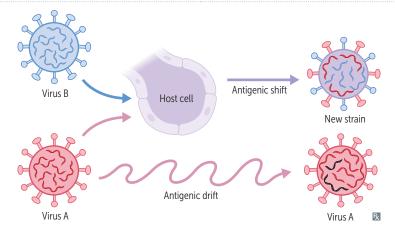
## Genetic/antigenic shift

Infection of 1 cell by 2 different segmented viruses (eg, swine influenza and human influenza viruses) → RNA segment reassortment → dramatically different virus (genetic shift)

Sudden shift is more deadly than gradual drift.

- → major global outbreaks (pandemics).
- Genetic/antigenic drift

Random mutation in hemagglutinin or neuraminidase genes → minor changes (antigenic drift) → local outbreaks (epidemics).



### **Rubella virus**



A togavirus. Causes rubella, once known as German (3-day) measles. Fever, postauricular and other lymphadenopathy, arthralgias, and fine, maculopapular rash that starts on face and spreads centrifugally to involve trunk and extremities A.

Causes mild disease in children but serious congenital disease (a TORCH infection). Congenital rubella findings include "blueberry muffin" appearance due to dermal extramedullary hematopoiesis.

#### **Paramyxoviruses**

Paramyxoviruses cause disease in children. They include those that cause parainfluenza (croup), mumps, measles, RSV, and human metapneumovirus, which causes respiratory tract infection (bronchiolitis, pneumonia) in infants. All contain surface F (fusion) protein, which causes respiratory epithelial cells to fuse and form multinucleated cells. Palivizumab (monoclonal antibody against F protein) prevents pneumonia caused by RSV infection in premature infants. Palivizumab for Paramyxovirus (RSV) Prophylaxis in Preemies.

FAS1\_2019\_03-Microbiology.indd 169 11/14/19 12:22 PM

### **Acute** laryngotracheobronchitis



Also called croup. Caused by parainfluenza viruses. Virus membrane contains hemagglutinin (binds sialic acid and promotes viral entry) and neuraminidase (promotes progeny virion release) antigens. Results in a "seal-like" barking cough and inspiratory stridor. Narrowing of upper trachea and subglottis leads to characteristic steeple sign on x-ray A. Severe croup can result in pulsus paradoxus 2° to upper airway obstruction.

### Measles (rubeola) virus





Usual presentation involves prodromal fever with cough, coryza, and conjunctivitis, then eventually Koplik spots (bright red spots with blue-white center on buccal mucosa A), followed 1-2 days later by a maculopapular rash B that starts at the head/neck and spreads downward.

Lymphadenitis with Warthin-Finkeldey giant cells (fused lymphocytes) in a background of paracortical hyperplasia. Possible sequelae:

- Subacute sclerosing panencephalitis (SSPE): personality changes, dementia, autonomic dysfunction, death (occurs years later)
- Encephalitis (1:1000): symptoms appear within few days of rash
- Giant cell pneumonia (rare except in immunosuppressed)

4 C's of measles:

Cough

Coryza

Conjunctivitis

"C"oplik spots

Vitamin A supplementation can reduce morbidity and mortality from measles, particularly in malnourished children.

Pneumonia is the most common cause of measles-associated death in children.

### **Mumps virus**



Uncommon due to effectiveness of MMR vaccine.

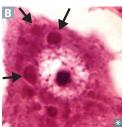
Symptoms: Parotitis A, Orchitis (inflammation of testes), aseptic Meningitis, and Pancreatitis. Can cause sterility (especially after puberty).

Mumps makes your parotid glands and testes as big as **POM-P**oms.

FAS1\_2019\_03-Microbiology.indd 170 11/14/19 12:22 PM

### **Rabies virus**





Bullet-shaped virus A. Negri bodies (cytoplasmic inclusions B) commonly found in Purkinje cells of cerebellum and in hippocampal neurons. Rabies has long incubation period (weeks to months) before symptom onset. Postexposure prophylaxis is wound cleaning plus immunization with killed vaccine and rabies immunoglobulin. Example of passive-active immunity.

Travels to the CNS by migrating in a retrograde fashion (via dynein motors) up nerve axons after binding to ACh receptors.

Progression of disease: fever, malaise

→ agitation, photophobia, hydrophobia,
hypersalivation → paralysis, coma → death.

Infection more commonly from bat, raccoon, and skunk bites than from dog bites in the United States; aerosol transmission (eg, bat caves) also possible.

#### **Ebola virus**



A filovirus A that targets endothelial cells, phagocytes, hepatocytes. Following an incubation period of up to 21 days, presents with abrupt onset of flu-like symptoms, diarrhea/vomiting, high fever, myalgia. Can progress to DIC, diffuse hemorrhage, shock. Diagnosed with RT-PCR within 48 hr of symptom onset. High mortality rate.

Transmission requires direct contact with bodily fluids, fomites (including dead bodies), infected bats or primates (apes/monkeys); high incidence of nosocomial infection.

Supportive care, no definitive treatment. Strict isolation of infected individuals and barrier practices for health care workers are key to preventing transmission.

### Zika virus

A flavivirus most commonly transmitted by *Aedes* mosquito bites.

Causes conjunctivitis, low-grade pyrexia, and itchy rash in 20% of cases. Can lead to congenital microcephaly or miscarriage if transmitted in utero.

Diagnose with RT-PCR or serology.

Sexual and vertical transmission possible. Outbreaks more common in tropical and subtropical climates. Supportive care, no definitive treatment.

FAS1\_2019\_03-Microbiology.indd 171 11/14/19 12:22 PM

## Hepatitis viruses

Signs and symptoms of all hepatitis viruses: episodes of fever, jaundice, † ALT and AST. Naked viruses (HAV and HEV) lack an envelope and are not destroyed by the gut: the vowels hit your bowels.

HBV DNA polymerase has DNA- and RNA-dependent activities. Upon entry into nucleus, the polymerase completes the partial dsDNA. Host RNA polymerase transcribes mRNA from viral DNA to make viral proteins. The DNA polymerase then reverse transcribes viral RNA to DNA, which is the genome of the progeny virus.

HCV lacks 3′-5′ exonuclease activity → no proofreading ability → antigenic variation of HCV envelope proteins. Host antibody production lags behind production of new mutant strains of HCV.

Virus	HAV	HBV	HCV	HDV	HEV
FAMILY	RNA picornavirus	DNA hepadnavirus	RNA flavivirus	RNA deltavirus	RNA hepevirus
TRANSMISSION	Fecal-oral (shellfish, travelers, day care)	Parenteral ( <b>B</b> lood), sexual ( <b>B</b> aby- making), perinatal ( <b>B</b> irthing)	Primarily blood (IVDU, post- transfusion)	Parenteral, sexual, perinatal	Fecal-oral, especially waterborne
INCUBATION	Short (weeks)	Long (months)	Long	Superinfection (HDV after HBV) = short Coinfection (HDV with HBV) = long	Short
CLINICAL COURSE	Acute and self limiting (adults), Asymptomatic (children)	Initially like serum sickness (fever, arthralgias, rash); may progress to carcinoma	May progress to Cirrhosis or Carcinoma	Similar to HBV	Fulminant hepatitis in Expectant (pregnant) women
PROGNOSIS	Good	Adults → mostly full resolution; neonates → worse prognosis	Majority develop stable, Chronic hepatitis C	Superinfection  → worse prognosis	High mortality in pregnant women
HCC RISK	No	Yes	Yes	Yes	No
LIVER BIOPSY	Hepatocyte swelling, monocyte infiltration, Councilman bodies	Granular eosinophilic "ground glass" appearance; cytotoxic T cells mediate damage	Lymphoid aggregates with focal areas of macrovesicular steatosis	Similar to HBV	Patchy necrosis
NOTES	No carrier state	Carrier state common	Carrier state very common	Defective virus, Depends on HBV HBsAg coat for entry into hepatocytes	Enteric, Epidemic (eg, in parts of Asia, Africa, Middle East), no carrier state

FAS1\_2019\_03-Microbiology.indd 172 11/14/19 12:22 PM

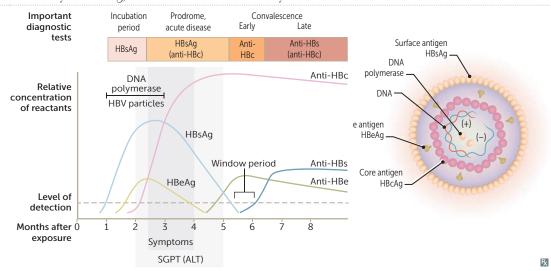
### Extrahepatic manifestations of hepatitis B and C

	Hepatitis B	Hepatitis C
HEMATOLOGIC	Aplastic anemia	Essential mixed cryoglobulinemia, † risk B-cell NHL, ITP, autoimmune hemolytic anemia
RENAL		Membranoproliferative GN > membranous GN
VASCULAR	Polyarteritis nodosa	Leukocytoclastic vasculitis
DERMATOLOGIC		Sporadic porphyria cutanea tarda, lichen planus
ENDOCRINE		† risk of diabetes mellitus, autoimmune hypothyroidism

FAS1\_2019\_03-Microbiology.indd 173 11/14/19 12:22 PM

### **Hepatitis serologic markers**

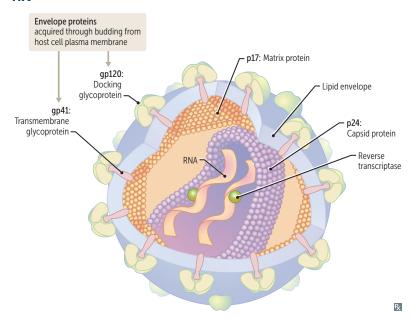
Anti-HAV (IgM)	IgM antibody to HAV; best test to detect acute hepatitis A.	
Anti-HAV (IgG)	IgG antibody indicates prior HAV infection and/or prior vaccination; protects against reinfection	
HBsAg	Antigen found on surface of HBV; indicates hepatitis B infection.	
Anti-HBs	Antibody to HBsAg; indicates immunity to hepatitis B due to vaccination or recovery from infection.	
HBcAg	Antigen associated with core of HBV.	
Anti-HBc	Antibody to HBcAg; $IgM = acute/recent$ infection; $IgG = prior$ exposure or chronic infection. $IgM$ anti-HBc may be the sole $\oplus$ marker of infection during window period.	
HBeAg	Secreted by infected hepatocyte into circulation. Not part of mature HBV virion. Indicates active viral replication and therefore high transmissibility and poorer prognosis.	
Anti-HBe	Antibody to HBeAg; indicates low transmissibility.	



HBsAg	Anti-HBs	HBeAg	Anti-HBe	Anti-HBc
✓		✓		IgM
			✓	IgM
✓		✓		IgG
✓			✓	IgG
	✓		✓	IgG
	✓			
	HBsAg ✓	HBsAg Anti-HBs  ✓  ✓  ✓  ✓  ✓	HBsAg Anti-HBs HBeAg	HBsAg Anti-HBs HBeAg Anti-HBe  /  /  /  /  /  /  /  /  /  /  /  /  /

FAS1\_2019\_03-Microbiology.indd 174 11/14/19 12:22 PM

#### HIV



Diploid genome (2 molecules of RNA). The 3 structural genes (protein coded for):

- *env* (gpl20 and gp41):
  - Formed from cleavage of gp160 to form envelope glycoproteins.
  - gp120—attachment to host CD4+ T cell.
  - gp4l—fusion and entry.
- gag (p24 and p17)—capsid and matrix proteins, respectively.
- pol—Reverse transcriptase, Integrase,
   Protease; RIP "Pol" (Paul)

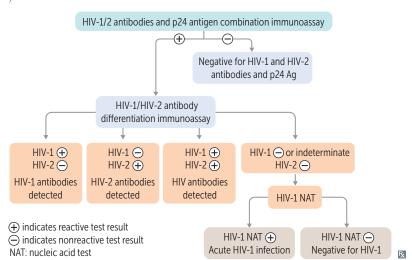
Reverse transcriptase synthesizes dsDNA from genomic RNA; dsDNA integrates into host genome.

Virus binds CD4 as well as a coreceptor, either CCR5 on macrophages (early infection) or CXCR4 on T cells (late infection).

Homozygous CCR5 mutation = immunity. Heterozygous CCR5 mutation = slower course.

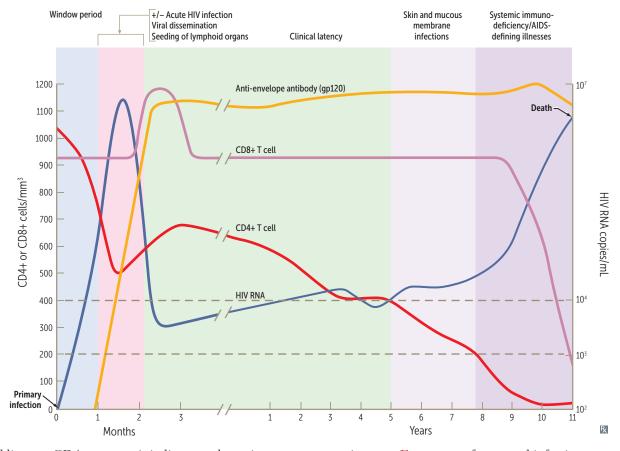
### **HIV diagnosis**

Presumptive diagnosis made with HIV-1/2 Ag/ Ab immunoassays. These immunoassays detect viral p24 Ag capsid protein and IgG Abs to HIV-1/2. Very high sensitivity/specificity. Viral load tests determine the amount of viral RNA in the plasma. High viral load associated with poor prognosis. Also use viral load to monitor effect of drug therapy. Use HIV genotyping to determine appropriate therapy. AIDS diagnosis: ≤ 200 CD4+ cells/mm³ (normal: 500–1500 cells/mm³) or HIV ⊕ with AIDS-defining condition (eg, *Pneumocystis* pneumonia). Western blot tests are no longer recommended by the CDC for confirmatory testing.
HIV-1/2 Ag/Ab testing is not recommended in babies with suspected HIV due to maternally transferred antibody. Use HIV viral load instead.



FAS1\_2019\_03-Microbiology.indd 175 11/14/19 12:22 PM

### Time course of untreated HIV infection



Dashed lines on CD4+ count axis indicate moderate immunocompromise (< 400 CD4+ cells/mm³) and when AIDS-defining illnesses emerge (< 200 CD4+ cells/mm³).

Most patients who do not receive treatment eventually die of complications of HIV infection.

Four stages of untreated infection:

- 1. Flu-like (acute)
- 2. **F**eeling fine (latent)
- 3. Falling count
- 4. Final crisis

During clinical latency phase, virus replicates in lymph nodes

FAS1\_2019\_03-Microbiology.indd 176 11/14/19 12:22 PM

SECTION II

### **Common diseases of HIV-positive adults**

↓ CD4+ cell count → reactivation of past infections (eg, TB, HSV, shingles), dissemination of bacterial infections and fungal infections (eg, coccidioidomycosis), and non-Hodgkin lymphomas.

PATHOGEN	PRESENTATION	FINDINGS
CD4+ cell count < 500/	mm³	
Candida albicans	Oral thrush	Scrapable white plaque, pseudohyphae on microscopy
EBV	Oral hairy leukoplakia	Unscrapable white plaque on lateral tongue
HHV-8	Kaposi sarcoma	Biopsy with lymphocytic inflammation
HPV	Squamous cell carcinoma, commonly of anus (men who have sex with men) or cervix	
CD4+ cell count < 200/	mm <sup>3</sup>	
Histoplasma capsulatum	Fever, weight loss, fatigue, cough, dyspnea, nausea, vomiting, diarrhea	Oval yeast cells within macrophages
HIV	Dementia	Cerebral atrophy on neuroimaging
JC virus (reactivation)	Progressive multifocal leukoencephalopathy	Nonenhancing areas of demyelination on MRI
Pneumocystis jirovecii	Pneumocystis pneumonia	"Ground-glass" opacities on chest imaging
CD4+ cell count < 100/	mm³	
Aspergillus fumigatus	Hemoptysis, pleuritic pain	Cavitation or infiltrates on chest imaging
Bartonella spp	Bacillary angiomatosis	Biopsy with neutrophilic inflammation
Candida albicans	Esophagitis	White plaques on endoscopy; yeast and pseudohyphae on biopsy
CMV	Colitis, Retinitis, Esophagitis, Encephalitis, Pneumonitis (CREEP)	Linear ulcers on endoscopy, cotton-wool spots on fundoscopy Biopsy reveals cells with intranuclear (owl eye) inclusion bodies
Cryptococcus neoformans	Meningitis	Encapsulated yeast on India ink stain or capsular antigen ⊕
Cryptosporidium spp	Chronic, watery diarrhea	Acid-fast oocysts in stool
EBV	B-cell lymphoma (eg, non-Hodgkin lymphoma, CNS lymphoma)	CNS lymphoma—ring enhancing, may be solitary (vs <i>Toxoplasma</i> )
Mycobacterium avium–intracellulare, Mycobacterium avium complex	Nonspecific systemic symptoms (fever, night sweats, weight loss) or focal lymphadenitis	Most common if CD4+ cell count < 50/mm <sup>3</sup>
Toxoplasma gondii	Brain abscesses	Multiple ring-enhancing lesions on MRI

FAS1\_2019\_03-Microbiology.indd 177 11/14/19 12:22 PM 178 **SECTION II** 

### MICROBIOLOGY ► MICROBIOLOGY—SYSTEMS

#### **Prions**

Prion diseases are caused by the conversion of a normal (predominantly  $\alpha$ -helical) protein termed prion protein (PrPc) to a β-pleated form (PrPsc), which is transmissible via CNS-related tissue (iatrogenic CJD) or food contaminated by BSE-infected animal products (variant CJD). PrPsc resists protease degradation and facilitates the conversion of still more PrPc to PrPsc. Resistant to standard sterilizing procedures, including standard autoclaving. Accumulation of PrPsc results in spongiform encephalopathy and dementia, ataxia, and death.

**Creutzfeldt-Jakob disease**—rapidly progressive dementia, typically sporadic (some familial forms).

Bovine spongiform encephalopathy—also called "mad cow disease."

Kuru—acquired prion disease noted in tribal populations practicing human cannibalism.

### ► MICROBIOLOGY—SYSTEMS

### **Normal flora:** dominant

Neonates delivered by C-section have no flora but are rapidly colonized after birth.

LOCATION	MICROORGANISM	
Skin	S epidermidis	
Nose	S epidermidis; colonized by S aureus	
Oropharynx	Viridans group streptococci	
Dental plaque	S mutans	
Colon	B fragilis > E coli	
Vagina	$Lactobacillus$ ; colonized by $E\ coli$ and group B strep	

### **Bugs causing food**borne illness

*S aureus* and *B cereus* food poisoning starts quickly and ends quickly.

SOURCE OF INFECTION	
Reheated rice. "Food poisoning from reheated rice? <b>Be serious</b> !" ( <b>B cereus</b> )	
Improperly canned foods (toxins), raw honey (spores)	
Reheated meat	
Undercooked meat	
Deli meats, soft cheeses	
Poultry, meat, and eggs	
Meats, mayonnaise, custard; preformed toxin	
Raw/undercooked seafood	

FAS1\_2019\_03-Microbiology.indd 178 11/14/19 12:22 PM

### **Bugs causing diarrhea**

Bloody diarrhea	
Campylobacter	Comma- or S-shaped organisms; growth at 42°C
E histolytica	Protozoan; amebic dysentery; liver abscess
Enterohemorrhagic <i>E coli</i>	O157:H7; can cause HUS; makes Shiga-like toxin
Enteroinvasive <i>E coli</i>	Invades colonic mucosa
Salmonella (non- typhoidal)	Lactose ⊖; flagellar motility; has animal reservoir, especially poultry and eggs
Shigella	Lactose ⊖; very low ID <sub>50</sub> ; produces Shiga toxin; human reservoir only; bacillary dysentery
Y enterocolitica	Day care outbreaks; pseudoappendicitis
Watery diarrhea	
C difficile	Pseudomembranous colitis; associated with antibiotics and PPIs; occasionally bloody diarrhea
C perfringens	Also causes gas gangrene
Enterotoxigenic <i>E coli</i>	Travelers' diarrhea; produces heat-labile (LT) and heat-stable (ST) toxins
Protozoa	Giardia, Cryptosporidium
V cholerae	Comma-shaped organisms; rice-water diarrhea; often from infected seafood
Viruses	Rotavirus, norovirus, enteric adenovirus

### Common causes of pneumonia

		ADULTS (18–40 YR)	ADULTS (40–65 YR)	ELDERLY	
Group B streptococci	Viruses (RSV)	Mycoplasma	S pneumoniae	S pneumoniae	
E coli	<b>M</b> ycoplasma	C pneumoniae	H influenzae	Influenza virus	
	C trachomatis	S pneumoniae	Anaerobes	Anaerobes	
	(infants-3 yr)	Viruses (eg, influenza)	Viruses	H influenzae	
	<b>C</b> pneumoniae		Mycoplasma	Gram ⊝ rods	
	(school-aged				
	children)				
	<b>S</b> pneumoniae				
	Runts May Cough				
	Chunky Sputum				
Special groups					
Alcoholic	Klebsiella, anaerobes usually due to aspiration (eg, Peptostreptococcus, Fusobacterium, Prevotella, Bacteroides)				
IV drug users	S pneumoniae, S aureus				
Aspiration	Anaerobes				
Atypical	Mycoplasma, Chlamydophila, Legionella, viruses (RSV, CMV, influenza, adenovirus)				
Cystic fibrosis	Pseudomonas, S aureus, S pneumoniae, Burkholderia cepacia				
Immunocompromised	S aureus, enteric gram ⊖ rods, fungi, viruses, P jirovecii (with HIV)				
Nosocomial (hospital acquired)	S aureus, Pseudomonas, other enteric gram $\ominus$ rods				
Postviral	S pneumoniae, S aurei	ıs, H influenzae			

11/14/19 12:22 PM FAS1\_2019\_03-Microbiology.indd 179

### **Common causes of meningitis**

NEWBORN (0-6 MO)	CHILDREN (6 MO-6 YR)	6-60 YR	60 YR +
Group B Streptococcus	S pneumoniae	N meningitidis	S pneumoniae
E coli	N meningitidis	S pneumoniae	N meningitidis
Listeria	H influenzae type b	Enteroviruses	H influenzae type b
	Group B Streptococcus	HSV	Group B Streptococcus
	Enteroviruses		Listeria

Give ceftriaxone and vancomycin empirically (add ampicillin if *Listeria* is suspected).

Viral causes of meningitis: enteroviruses (especially coxsackievirus), HSV-2 (HSV-1 = encephalitis), HIV, West Nile virus (also causes encephalitis), VZV.

In HIV: Cryptococcus spp.

Note: Incidence of Group B streptococcal meningitis in neonates has ↓ greatly due to screening and antibiotic prophylaxis in pregnancy. Incidence of *H influenzae* meningitis has ↓ greatly due to conjugate *H influenzae* vaccinations. Today, cases are usually seen in unimmunized children.

### **Cerebrospinal fluid findings in meningitis**

	OPENING PRESSURE	CELL TYPE	PROTEIN	GLUCOSE
Bacterial	<b>†</b>	† PMNs	<b>†</b>	<b>↓</b>
Fungal/TB	†	↑ lymphocytes	†	<b>†</b>
Viral	Normal/†	† lymphocytes	Normal/†	Normal

## Infections causing brain abscess

Most commonly viridans streptococci and *Staphylococcus aureus*. If dental infection or extraction precedes abscess, oral anaerobes commonly involved.

Multiple abscesses are usually from bacteremia; single lesions from contiguous sites: otitis media and mastoiditis → temporal lobe and cerebellum; sinusitis or dental infection → frontal lobe. *Toxoplasma* reactivation in AIDS.

### Osteomyelitis



ASSOCIATED INFECTION
S aureus (most common overall)
Neisseria gonorrhoeae (rare), septic arthritis more common
Salmonella and S aureus
S aureus and S epidermidis
S aureus, M tuberculosis (Pott disease)
Pasteurella multocida
S aureus; also Pseudomonas, Candida

Elevated ESR and CRP sensitive but not specific.

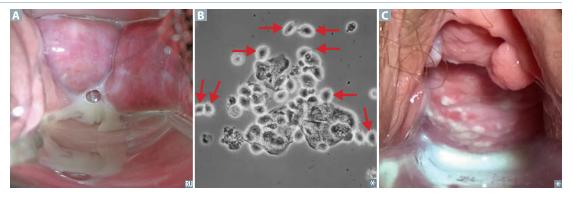
Radiographs are insensitive early but can be useful in chronic osteomyelitis (A, left). MRI is best for detecting acute infection and detailing anatomic involvement (A, right).

FAS1\_2019\_03-Microbiology.indd 180 11/14/19 12:22 PM

Urinary tract infections	Cystitis presents with dysuria, frequency, urgency, suprapubic pain, and WBCs (but not WBC casts) in urine. Primarily caused by ascension of microbes from urethra to bladder. Ascension to kidney results in pyelonephritis, which presents with fever, chills, flank pain, costovertebral angle tenderness, hematuria, and WBC casts.  Ten times more common in women (shorter urethras colonized by fecal flora).			
	Risk factors: obstruction (eg, kidney stones, enlarged prostate), kidney surgery, catheterization, congenital GU malformation (eg, vesicoureteral reflux), diabetes, pregnancy.			
SPECIES	FEATURES	COMMENTS		
Escherichia coli	Leading cause of UTI. Colonies show strong pink lactose-fermentation on MacConkey agar.	Diagnostic markers:  ① Leukocyte esterase = evidence of WBC activity.		
Staphylococcus saprophyticus	2nd leading cause of UTI in sexually active women.	<ul> <li>⊕ Nitrite test = reduction of urinary nitrates</li> <li>by gram ⊝ bacterial species (eg, E coli).</li> </ul>		
Klebsiella pneumoniae	3rd leading cause of UTI. Large mucoid capsule and viscous colonies.	<ul> <li>⊕ Urease test = urease-producing bugs (eg,</li> <li>S saprophyticus, Proteus, Klebsiella).</li> </ul>		
Serratia marcescens	Some strains produce a red pigment; often nosocomial and drug resistant.			
Enterococcus	Often nosocomial and drug resistant.			
Proteus mirabilis	Motility causes "swarming" on agar; associated with struvite stones.			
Pseudomonas aeruginosa	Blue-green pigment and fruity odor; usually nosocomial and drug resistant.			

### **Common vaginal infections**

	<b>Bacterial vaginosis</b>	Trichomonas vaginitis	Candida vulvovaginitis
SIGNS AND SYMPTOMS	No inflammation Thin, white discharge A with fishy odor	Inflammation ("strawberry cervix") Frothy, yellow-green, foul- smelling discharge	Inflammation Thick, white, "cottage cheese" discharge
LAB FINDINGS	Clue cells pH > 4.5 ⊕ KOH whiff test	Motile pear-shaped trichomonads B pH > 4.5	Pseudohyphae pH normal (4.0–4.5)
TREATMENT	Metronidazole or clindamycin	Metronidazole Treat sexual partner(s)	Azoles



FAS1\_2019\_03-Microbiology.indd 181 11/14/19 12:22 PM

### **TORCH infections**

Microbes that may pass from mother to fetus. Transmission is transplacental in most cases, or via delivery (especially HSV-2). Nonspecific signs common to many **ToRCHHeS** infections include hepatosplenomegaly, jaundice, thrombocytopenia, and growth retardation.

Other important infectious agents include *Streptococcus agalactiae* (group B streptococci), *E coli*, and *Listeria monocytogenes*—all causes of meningitis in neonates. Parvovirus B19 causes hydrops fetalis.

AGENT	MODES OF MATERNAL TRANSMISSION	MATERNAL MANIFESTATIONS	NEONATAL MANIFESTATIONS
Toxoplasma gondii	Cat feces or ingestion of undercooked meat	Usually asymptomatic; lymphadenopathy (rarely)	Classic triad: chorioretinitis, hydrocephalus, and intracranial calcifications, +/- "blueberry muffin" rash A
Rubella	Respiratory droplets	Rash, lymphadenopathy, polyarthritis, polyarthralgia	Classic triad: abnormalities of eye (cataracts ■) and ear (deafness) and congenital heart disease (PDA); +/- "blueberry muffin" rash. "I (eye) ▼ ruby (rubella) earrings"
Cytomegalovirus	Sexual contact, organ transplants	Usually asymptomatic; mononucleosis-like illness	Hearing loss, seizures, petechial rash, "blueberry muffin" rash, chorioretinitis, periventricular calcifications <b>C</b>
HIV	Sexual contact, needlestick	Variable presentation depending on CD4+ cell count	Recurrent infections, chronic diarrhea
Herpes simplex virus-2	Skin or mucous membrane contact	Usually asymptomatic; herpetic (vesicular) lesions	Meningoencephalitis, herpetic (vesicular) lesions
Syphilis	Sexual contact	Chancre (1°) and disseminated rash (2°) are the two stages likely to result in fetal infection	Often results in stillbirth, hydrops fetalis; if child survives, presents with facial abnormalities (eg, notched teeth, saddle nose, short maxilla), saber shins, CN VIII deafness







FAS1\_2019\_03-Microbiology.indd 182 11/14/19 12:22 PM

### **Red rashes of childhood**

AGENT	ASSOCIATED SYNDROME/DISEASE	CLINICAL PRESENTATION
Coxsackievirus type A	Hand-foot-mouth disease	Oval-shaped vesicles on palms and soles  A; vesicles and ulcers in oral mucosa (herpangina)
Human herpesvirus 6	Roseola (exanthem subitum)	Asymptomatic rose-colored macules appear on body after several days of high fever; can present with febrile seizures; usually affects infants
Measles virus	Measles (rubeola)	Confluent rash beginning at head and moving down; preceded by cough, coryza, conjunctivitis, and blue-white (Koplik) spots on buccal mucosa
Parvovirus B19	Erythema infectiosum (fifth disease)	"Slapped cheek" rash on face <b>B</b> (can cause hydrops fetalis in pregnant women)
Rubella virus	Rubella	Pink macules and papules begin at head and move down, remain discrete → fine desquamating truncal rash; postauricular lymphadenopathy
Streptococcus pyogenes	Scarlet fever	Flushed cheeks and circumoral pallor on face; erythematous, sandpaper-like rash from neck to trunk and extremities; fever, sore throat, strawberry tongue
Varicella-Zoster virus	Chickenpox	Vesicular rash begins on trunk; spreads to face and extremities with lesions of different stages









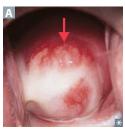
FAS1\_2019\_03-Microbiology.indd 183 11/14/19 12:22 PM

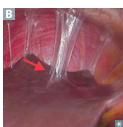
### **Sexually transmitted infections**

DISEASE	CLINICAL FEATURES	ORGANISM
AIDS	Opportunistic infections, Kaposi sarcoma, lymphoma	HIV
Chancroid A	Painful genital ulcer with exudate, inguinal adenopathy A	Haemophilus ducreyi (it's so painful, you "do cry")
Chlamydia	Urethritis, cervicitis, epididymitis, conjunctivitis, reactive arthritis, PID	Chlamydia trachomatis (D–K)
Condylomata acuminata	Genital warts, koilocytes	HPV-6 and -11
Genital herpes	Painful penile, vulvar, or cervical vesicles and ulcers; can cause systemic symptoms such as fever, headache, myalgia	HSV-2, less commonly HSV-1
Gonorrhea	Urethritis, cervicitis, PID, prostatitis, epididymitis, arthritis, creamy purulent discharge	Neisseria gonorrhoeae
Granuloma inguinale (Donovanosis)	Painless, beefy red ulcer that bleeds readily on contact  Uncommon in US	Klebsiella (Calymmatobacterium) granulomatis; cytoplasmic Donovan bodies (bipolar staining) seen on microscopy
Hepatitis B	Jaundice	HBV
Lymphogranuloma venereum	Infection of lymphatics; painless genital ulcers, painful lymphadenopathy (ie, buboes)	C trachomatis (L1–L3)
Primary syphilis	Painless chancre	Treponema pallidum
Secondary syphilis	Fever, lymphadenopathy, skin rashes, condylomata lata	
Tertiary syphilis	Gummas, tabes dorsalis, general paresis, aortitis, Argyll Robertson pupil	
Trichomoniasis	Vaginitis, strawberry cervix, motile in wet prep	Trichomonas vaginalis

FAS1\_2019\_03-Microbiology.indd 184 11/14/19 12:22 PM

## Pelvic inflammatory disease





Top bugs—*Chlamydia trachomatis* (subacute, often undiagnosed), *Neisseria gonorrhoeae* (acute).

C trachomatis—most common bacterial STI in the United States.

Signs include cervical motion tenderness, adnexal tenderness, purulent cervical discharge A.

PID may include salpingitis, endometritis, hydrosalpinx, and tubo-ovarian abscess.

Salpingitis is a risk factor for ectopic pregnancy, infertility, chronic pelvic pain, and adhesions. Can lead to perihepatitis (Fitz-Hugh-Curtis syndrome)—infection and inflammation of liver capsule and "violin string" adhesions of peritoneum to liver B.

RISK FACTOR	PATHOGEN	UNIQUE SIGNS/SYMPTOMS
Antibiotic use	Clostridium difficile	Watery diarrhea, leukocytosis
Aspiration (2° to altered mental status, old age)	Polymicrobial, gram ⊖ bacteria, often anaerobes	Right lower lobe infiltrate or right upper/ middle lobe (patient recumbent); purulent malodorous sputum
Decubitus ulcers, surgical wounds, drains	S aureus (including MRSA), gram ⊖ anaerobes (Bacteroides, Prevotella, Fusobacterium)	Erythema, tenderness, induration, drainage from surgical wound sites
Intravascular catheters	S aureus (including MRSA), S epidermidis (long term), Enterobacter	Erythema, induration, tenderness, drainage from access sites
Mechanical ventilation, endotracheal intubation	Late onset: P aeruginosa, Klebsiella, Acinetobacter, S aureus	New infiltrate on CXR, † sputum production sweet odor ( <i>Pseudomonas</i> )
Renal dialysis unit, needlestick	HBV, HCV	
Urinary catheterization	Proteus spp, E coli, Klebsiella (infections in your PEcKer)	Dysuria, leukocytosis, flank pain or costovertebral angle tenderness
Water aerosols	Legionella	Signs of pneumonia, GI symptoms (diarrhea, nausea, vomiting), neurologic abnormalities

FAS1\_2019\_03-Microbiology.indd 185 11/14/19 12:22 PM

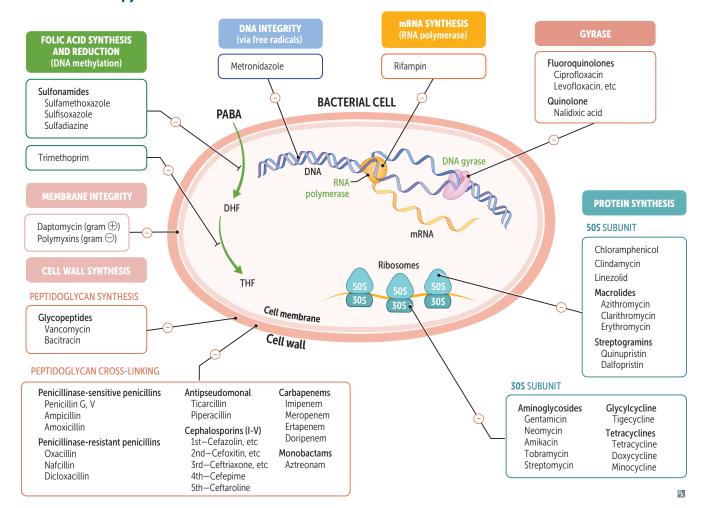
### **Bugs affecting unvaccinated children**

CLINICAL PRESENTATION	FINDINGS/LABS	PATHOGEN	
Dermatologic			
Rash	Beginning at head and moving down with postauricular lymphadenopathy	Rubella virus	
	Beginning at head and moving down; preceded by cough, coryza, conjunctivitis, and Koplik spots	Measles virus	
Neurologic			
Meningitis	Microbe colonizes nasopharynx	H influenzae type b	
	Can also lead to myalgia and paralysis	Poliovirus	
Tetanus	Muscle spasms and spastic paralysis (eg, lockjaw, opisthotonus)	Clostridium tetani	
Respiratory			
Epiglottitis	Fever with dysphagia, drooling, and difficulty breathing due to edema	H influenzae type b (also capable of causing epiglottitis in fully immunized children)	
Pertussis	Low-grade fevers, coryza → whooping cough, post-tussive vomiting → gradual recovery	Bordetella pertussis	
Pharyngitis	Grayish pseudomembranes (may obstruct airways)	Corynebacterium diphtheriae	
ug hints	CHARACTERISTIC	ORGANISM	
Š	Asplenic patients	Encapsulated microbes, especially <b>SHiN</b> ( <b>S</b> pneumoniae >> <b>H</b> influenzae type b > <b>N</b> meningitidis)	
	Branching rods in oral infection, sulfur granules	Actinomyces israelii	
	Chronic granulomatous disease	Catalase $\oplus$ microbes, especially $S$ aureus	
	"Currant jelly" sputum	Klebsiella	
	Dog or cat bite	Pasteurella multocida	
	Facial nerve palsy (typically bilateral)	Borrelia burgdorferi (Lyme disease)	
	Human bite	Human oral flora (eg, Eikenella, Fusobacterium	
	Neutropenic patients	Candida albicans (systemic), Aspergillus	
	Organ transplant recipient	CMV	
	PAS ⊕	Tropheryma whipplei (Whipple disease)	
	Pediatric infection	Haemophilus influenzae (including epiglottitis)	
	Pneumonia in cystic fibrosis, burn infection	Pseudomonas aeruginosa	
	Puncture wound, lockjaw	Clostridium tetani	
	Pus, empyema, abscess	S aureus	
	Rash on hands and feet	Coxsackie A, R rickettsii, Syphilis (CARS)	
	Sepsis/meningitis in newborn	Group B strep	
	Sinus/CNS infection in diabetics	Mucor or Rhizopus spp.	
	Surgical wound	S aureus	
	Traumatic open wound	Clostridium perfringens	

FAS1\_2019\_03-Microbiology.indd 186 11/14/19 12:22 PM

### ► MICROBIOLOGY — ANTIMICROBIALS

### **Antimicrobial therapy**



Penicillin G, V	Penicillin G (IV and IM form), penicillin V (oral). Prototype $\beta$ -lactam antibiotics.
MECHANISM	D-Ala-D-Ala structural analog. Bind penicillin-binding proteins (transpeptidases). Block transpeptidase cross-linking of peptidoglycan in cell wall. Activate autolytic enzymes.
CLINICAL USE	Mostly used for gram $\oplus$ organisms ( <i>S pneumoniae</i> , <i>S pyogenes</i> , <i>Actinomyces</i> ). Also used for gram $\ominus$ cocci (mainly <i>N meningitidis</i> ) and spirochetes (mainly <i>T pallidum</i> ). Bactericidal for gram $\oplus$ cocci, gram $\ominus$ cocci, and spirochetes. $\beta$ -lactamase sensitive.
ADVERSE EFFECTS	$Hypersensitivity\ reactions,\ direct\ Coombs\ \oplus\ hemolytic\ anemia,\ drug-induced\ interstitial\ nephritis.$
RESISTANCE	$\beta\mbox{-lactamase}$ cleaves the $\beta\mbox{-lactam}$ ring. Mutations in PBPs.

FAS1\_2019\_03-Microbiology.indd 187 11/14/19 12:22 PM

Penicillinase-sensitive penicillins	Amoxicillin, ampicillin; aminopenicillins.	
MECHANISM	Same as penicillin. Wider spectrum; penicillinase sensitive. Also combine with clavulanic acid to protect against destruction by β-lactamase.	AMinoPenicillins are AMPed-up penicillin. AmOxicillin has greater Oral bioavailability than ampicillin.
CLINICAL USE	Extended-spectrum penicillin— <i>H</i> influenzae, <i>H</i> pylori, <i>E</i> coli, <i>L</i> isteria monocytogenes, <i>Proteus mirabilis</i> , <i>Salmonella</i> , <i>Shigella</i> , enterococci.	Coverage: ampicillin/amoxicillin HHELPSS kill enterococci.
ADVERSE EFFECTS	Hypersensitivity reactions, rash, pseudomembranous colitis.	
MECHANISM OF RESISTANCE	Penicillinase (a type of $\beta$ -lactamase) cleaves $\beta$ -lactam ring.	
Penicillinase-resistant penicillins	Dicloxacillin, nafcillin, oxacillin.	
MECHANISM	Same as penicillin. Narrow spectrum; penicillinase resistant because bulky R group blocks access of β-lactamase to β-lactam ring.	
CLINICAL USE	S aureus (except MRSA).	"Use <b>naf</b> (nafcillin) for <b>staph</b> ."
ADVERSE EFFECTS	Hypersensitivity reactions, interstitial nephritis.	
MECHANISM OF RESISTANCE	MRSA has altered penicillin-binding protein target site.	
Antipseudomonal penicillins	Piperacillin, ticarcillin.	
MECHANISM	Same as penicillin. Extended spectrum. Penicilli	nase sensitive; use with $\beta$ -lactamase inhibitors.
CLINICAL USE	Pseudomonas spp. and gram ⊖ rods.	

FAS1\_2019\_03-Microbiology.indd 188 11/14/19 12:22 PM

_						
Ce	nh	al	ns	n	nri	ıns
	Р.,	•	-	Ρ,		

MECHANISM	β-lactam drugs that inhibit cell wall synthesis but are less susceptible to penicillinases. Bactericidal.	Organisms typically not covered by 1st–4th generation cephalosporins are LAME: Listeria, Atypicals (Chlamydia, Mycoplasma), MRSA, and Enterococci.
CLINICAL USE	lst generation (cefazolin, cephalexin)—gram ⊕ cocci, <b>P</b> roteus mirabilis, <b>E</b> coli, <b>K</b> lebsiella pneumoniae. Cefazolin used prior to surgery to prevent <i>S</i> aureus wound infections.	lst generation—⊕ PEcK.
	2nd generation (cefaclor, cefoxitin, cefuroxime, cefotetan)—gram ⊕ cocci, H influenzae, Enterobacter aerogenes, Neisseria spp., Serratia marcescens, Proteus mirabilis, E coli, Klebsiella pneumoniae.	<ul><li>2nd graders wear fake fox fur to tea parties.</li><li>2nd generation—⊕ HENS PEcK.</li></ul>
	3rd generation (ceftriaxone, cefotaxime, cefpodoxime, ceftazidime)—serious gram ⊖ infections resistant to other β-lactams.	Can cross blood-brain barrier. Ceftriaxone—meningitis, gonorrhea, disseminated Lyme disease. Ceftazidime— <i>Pseudomonas</i> .
	4th generation (cefepime)—gram ⊖ organisms, with ↑ activity against <i>Pseudomonas</i> and gram ⊕ organisms.	
	5th generation (ceftaroline)—broad gram ⊕ and gram ⊕ organism coverage; unlike 1st–4th generation cephalosporins, ceftaroline covers MRSA, and Enterococcus faecalis—does not cover Pseudomonas.	
ADVERSE EFFECTS	Hypersensitivity reactions, autoimmune hemolytic anemia, disulfiram-like reaction, vitamin K deficiency. Low rate of cross-reactivity even in penicillin-allergic patients.  † nephrotoxicity of aminoglycosides.	
MECHANISM OF RESISTANCE	Inactivated by cephalosporinases (a type of β-lactamase). Structural change in penicillin-binding proteins (transpeptidases).	
β-lactamase inhibitors	Include Clavulanic acid, Avibactam, Sulbactam, Tazobactam. Often added to penicillin antibiotics to protect the antibiotic from destruction by β-lactamase.	CAST (eg, amoxicillin-clavulanate, ceftazidime-avibactam, ampicillin-sulbactam, piperacillin-tazobactam).

11/14/19 12:22 PM FAS1\_2019\_03-Microbiology.indd 189

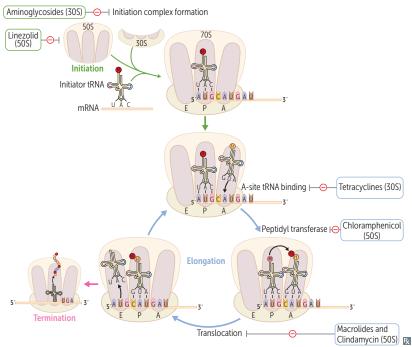
190 **SE** 

### SECTION II MICROBIOLOGY ➤ MICROBIOLOGY—ANTIMICROBIALS

Carbapenems	Doripenem, Imipenem, Meropenem, Ertapener 10/10 [life-threatening] infection).	m (DIME antibiotics are given when there is a
MECHANISM	Imipenem is a broad-spectrum, β-lactamase– resistant carbapenem. Always administered with cilastatin (inhibitor of renal dehydropeptidase I) to ↓ inactivation of drug in renal tubules.	With imipenem, "the kill is lastin' with cilastatin."  Newer carbapenems include ertapenem (limited Pseudomonas coverage) and doripenem.
CLINICAL USE	Gram ⊕ cocci, gram ⊖ rods, and anaerobes.  Wide spectrum and significant side effects limit use to life-threatening infections or after other drugs have failed. Meropenem has a ↓ risk of seizures and is stable to dehydropeptidase I.	
ADVERSE EFFECTS	GI distress, rash, and CNS toxicity (seizures) at high plasma levels.	
MECHANISM OF RESISTANCE	Inactivated by carbapenemases produced by, eg, <i>K pneumoniae</i> , <i>E coli</i> , <i>E aerogenes</i> .	
Monobactams	Aztreonam	
MECHANISM	Less susceptible to $\beta$ -lactamases. Prevents peptidoglycan cross-linking by binding to penicillinbinding protein 3. Synergistic with aminoglycosides. No cross-allergenicity with penicillins.	
CLINICAL USE	Gram ⊖ rods only—no activity against gram ⊕ rods or anaerobes. For penicillin-allergic patients and those with renal insufficiency who cannot tolerate aminoglycosides.	
ADVERSE EFFECTS	Usually nontoxic; occasional GI upset.	
Vancomycin		
MECHANISM	Inhibits cell wall peptidoglycan formation by binding D-Ala-D-Ala portion of cell wall precursors. Bactericidal against most bacteria (bacteriostatic against <i>C difficile</i> ). Not susceptible to β-lactamases.	
CLINICAL USE	Gram ⊕ bugs only—for serious, multidrug-resistant organisms, including MRSA, <i>S epidermidis</i> , sensitive <i>Enterococcus</i> species, and <i>Clostridium difficile</i> (oral dose for pseudomembranous colitis).	
ADVERSE EFFECTS	Well tolerated in general but <b>NOT</b> trouble <b>F</b> ree.	
A A A A A A A A A A A A A A A A A A A	Nephrotoxicity, Ototoxicity, Thrombophlebitis, or reaction largely preventable by pretreatment wi	diffuse Flushing (red man syndrome A idiopathic ith antihistamines), DRESS syndrome.
MECHANISM OF RESISTANCE	Occurs in bacteria (eg, <i>Enterococcus</i> ) via amino "If you <b>Lac</b> k a <b>D-Ala</b> (dollar), you can't ride the	acid modification of D-Ala-D-Ala to <b>D-Ala</b> -D <b>-Lac</b> . e van (vancomycin)."

FAS1\_2019\_03-Microbiology.indd 190 11/14/19 12:22 PM

### **Protein synthesis inhibitors**



Specifically target smaller bacterial ribosome (70S, made of 30S and 50S subunits), leaving human ribosome (80S) unaffected.

All are bacteriostatic, except aminoglycosides (bactericidal) and linezolid (variable).

### 30S inhibitors

Aminoglycosides
Tetracyclines

### 50S inhibitors

Chloramphenicol, Clindamycin Erythromycin (macrolides) Linezolid

"Buy **AT 30, CCEL** (sell) at **50**."

Aminoglycosides	Gentamicin, Neomycin, Amikacin, Tobramycin, Streptomycin.	"Mean" (aminoglycoside) GNATS caNNOT kill anaerobes.
MECHANISM	Bactericidal; irreversible inhibition of initiation complex through binding of the 30S subunit. Can cause misreading of mRNA. Also block translocation. Require O <sub>2</sub> for uptake; therefore ineffective against anaerobes.	
CLINICAL USE	Severe gram $\ominus$ rod infections. Synergistic with β-lactam antibiotics. Neomycin for bowel surgery.	
ADVERSE EFFECTS	Nephrotoxicity, Neuromuscular blockade (absolute contraindication with myasthenia gravis), Ototoxicity (especially with loop diuretics), Teratogenicity.	
MECHANISM OF RESISTANCE	Bacterial transferase enzymes inactivate the drug by acetylation, phosphorylation, or adenylation.	

FAS1\_2019\_03-Microbiology.indd 191 11/14/19 12:22 PM

Tetracyclines	Tetracycline, doxycycline, minocycline.	
MECHANISM	-	
CLINICAL USE	Borrelia burgdorferi, M pneumoniae. Drugs' ability to accumulate intracellularly makes them very effective against Rickettsia and Chlamydia. Also used to treat acne. Doxycycline effective against community-acquired MRSA.	
ADVERSE EFFECTS	GI distress, discoloration of teeth and inhibition Contraindicated in pregnancy.	n of bone growth in children, photosensitivity.
MECHANISM OF RESISTANCE	↓ uptake or ↑ efflux out of bacterial cells by plasmid-encoded transport pumps.	
Tigecycline		
MECHANISM	Tetracycline derivative. Binds to 30S, inhibiting	g protein synthesis. Generally bacteriostatic.
CLINICAL USE	Broad-spectrum anaerobic, gram ⊖, and gram ⊕ coverage. Multidrug-resistant organisms (MRSA, VRE) or infections requiring deep tissue penetration.	
ADVERSE EFFECTS	GI symptoms: nausea, vomiting.	
Chloramphenicol MECHANISM	Blocks peptidyltransferase at 50S ribosomal sub	punit. Bacteriostatic.
CLINICAL USE	Meningitis (Haemophilus influenzae, Neisseria rickettsial diseases (eg, Rocky Mountain spott Limited use due to toxicity but often still used	meningitidis, Streptococcus pneumoniae) and ted fever [Rickettsia rickettsii]).
ADVERSE EFFECTS	Anemia (dose dependent), aplastic anemia (dos infants because they lack liver UDP-glucuron	se independent), gray baby syndrome (in premature osyltransferase).
MECHANISM OF RESISTANCE	Plasmid-encoded acetyltransferase inactivates t	he drug.
Clindamycin		
MECHANISM	Blocks peptide transfer (translocation) at 50S ribosomal subunit. Bacteriostatic.	
CLINICAL USE	Anaerobic infections (eg, <i>Bacteroides</i> spp., <i>Clostridium perfringens</i> ) in aspiration pneumonia, lung abscesses, and oral infections. Also effective against invasive group A streptococcal infection.	Treats anaerobic infections <b>above</b> the diaphragm vs metronidazole (anaerobic infections <b>below</b> diaphragm).
ADVERSE EFFECTS	Pseudomembranous colitis ( <i>C difficile</i> overgrowth), fever, diarrhea.	

FAS1\_2019\_03-Microbiology.indd 192 11/14/19 12:22 PM

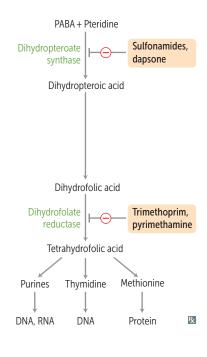
MECHANISM	Inhibits protein synthesis by binding to 50S subunit and preventing formation of the initiation complex.
CLINICAL USE	Gram ⊕ species including MRSA and VRE.
ADVERSE EFFECTS	Bone marrow suppression (especially thrombocytopenia), peripheral neuropathy, serotonin syndrome (due to partial MAO inhibition).
MECHANISM OF RESISTANCE	Point mutation of ribosomal RNA.
Macrolides	Azithromycin, clarithromycin, erythromycin.
MECHANISM	Inhibit protein synthesis by blocking translocation ("macroslides"); bind to the 23S rRNA of the 50S ribosomal subunit. Bacteriostatic.
CLINICAL USE	Atypical pneumonias ( <i>Mycoplasma</i> , <i>Chlamydia</i> , <i>Legionella</i> ), STIs ( <i>Chlamydia</i> ), gram ⊕ cocci (streptococcal infections in patients allergic to penicillin), and <i>B pertussis</i> .
ADVERSE EFFECTS	MACRO: Gastrointestinal Motility issues, Arrhythmia caused by prolonged QT interval, acute Cholestatic hepatitis, Rash, eOsinophilia. Increases serum concentration of theophylline, oral anticoagulants. Clarithromycin and erythromycin inhibit cytochrome P-450.
MECHANISM OF RESISTANCE	Methylation of 23S rRNA-binding site prevents binding of drug.
Polymyxins	Colistin (polymyxin E), polymyxin B.
MECHANISM	Cation polypeptides that bind to phospholipids on cell membrane of gram ⊖ bacteria. Disrupt cel membrane integrity → leakage of cellular components → cell death.
CLINICAL USE	Salvage therapy for multidrug-resistant gram $\ominus$ bacteria (eg, $P$ aeruginosa, $E$ coli, $K$ pneumoniae). Polymyxin B is a component of a triple antibiotic ointment used for superficial skin infections.
ADVERSE EFFECTS	Nephrotoxicity, neurotoxicity (eg, slurred speech, weakness, paresthesias), respiratory failure.

FAS1\_2019\_03-Microbiology.indd 193 11/14/19 12:22 PM

Sulfonamides	Sulfamethoxazole (SMX), sulfisoxazole, sulfadiazine.
MECHANISM	Inhibit dihydropteroate synthase, thus inhibiting folate synthesis. Bacteriostatic (bactericidal when combined with trimethoprim).
CLINICAL USE	Gram ⊕, gram ⊖, <i>Nocardia</i> . TMP-SMX for simple UTI.
ADVERSE EFFECTS	Hypersensitivity reactions, hemolysis if G6PD deficient, nephrotoxicity (tubulointerstitial nephritis), photosensitivity, Stevens-Johnson syndrome, kernicterus in infants, displace other drugs from albumin (eg, warfarin).
MECHANISM OF RESISTANCE	Altered enzyme (bacterial dihydropteroate synthase), ↓ uptake, or ↑ PABA synthesis.

Dapsone		
MECHANISM	Similar to sulfonamides, but structurally distinct agent.	
CLINICAL USE	Leprosy (lepromatous and tuberculoid), <i>Pneumocystis jirovecii</i> prophylaxis, or treatment when used in combination with TMP.	
ADVERSE EFFECTS	Hemolysis if G6PD deficient, methemoglobinemia, agranulocytosis.	

MECHANISM	Inhibits bacterial dihydrofolate reductase. Bacteriostatic.
CLINICAL USE	Used in combination with sulfonamides (trimethoprim-sulfamethoxazole [TMP-SMX]), causing sequential block of folate synthesis. Combination used for UTIs, Shigella, Salmonella, Pneumocystis jirovecii pneumonia treatment and prophylaxis, toxoplasmosis prophylaxis.
ADVERSE EFFECTS	Hyperkalemia (high doses), megaloblastic anemia, leukopenia, granulocytopenia, which may be avoided with coadministration of leucovorin (folinic acid). TMP Treats Marrow Poorly.



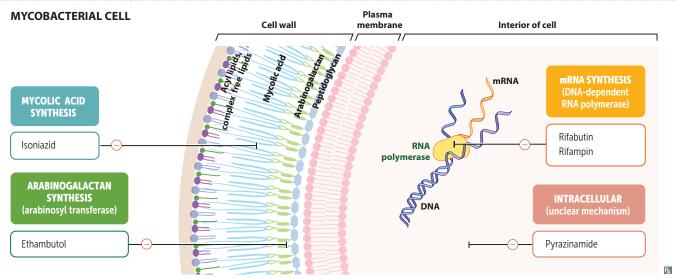
FAS1\_2019\_03-Microbiology.indd 194 11/14/19 12:22 PM

Fluoroquinolones	Ciprofloxacin, enoxacin, norfloxacin, ofloxacin; re levofloxacin, moxifloxacin.	espiratory fluoroquinolones—gemifloxacin,
MECHANISM	Inhibit prokaryotic enzymes topoisomerase II (DNA gyrase) and topoisomerase IV. Bactericidal. Must not be taken with antacids.	
CLINICAL USE	Gram $\ominus$ rods of urinary and GI tracts (including <i>Pseudomonas</i> ), some gram $\oplus$ organisms, otitis externa.	
ADVERSE EFFECTS	GI upset, superinfections, skin rashes, headache, dizziness. Less commonly, can cause leg cramps and myalgias.  Contraindicated in pregnant women, nursing mothers, and children < 18 years old due to possible damage to cartilage. Some may prolong QT interval.  May cause tendonitis or tendon rupture in people > 60 years old and in patients taking prednisone. Ciprofloxacin inhibits cytochrome P-450.	Fluoroquinolones hurt attachments to your bones.
MECHANISM OF RESISTANCE	Chromosome-encoded mutation in DNA gyrase, plasmid-mediated resistance, efflux pumps.	
Daptomycin		
MECHANISM	Lipopeptide that disrupts cell membranes of gram ⊕ cocci by creating transmembrane channels.	
CLINICAL USE	S aureus skin infections (especially MRSA), bacteremia, endocarditis, VRE.	Not used for pneumonia (avidly binds to and is inactivated by surfactant). "Daptomyskin" is used for skin infections.
ADVERSE EFFECTS	Myopathy, rhabdomyolysis.	
Metronidazole		
MECHANISM	Forms toxic free radical metabolites in the bacterial cell that damage DNA. Bactericidal, antiprotozoal.	
CLINICAL USE	Treats <i>Giardia</i> , <i>Entamoeba</i> , <i>Trichomonas</i> , <i>Gardnerella vaginalis</i> , <i>A</i> naerobes ( <i>Bacteroides</i> , <i>C difficile</i> ). Can be used in place of amoxicillin in <i>H pylori</i> "triple therapy" in case of penicillin allergy.	GET GAP on the Metro with metronidazole! Treats anaerobic infection below the diaphragm vs clindamycin (anaerobic infections above diaphragm).
ADVERSE EFFECTS	Disulfiram-like reaction (severe flushing, tachycardia, hypotension) with alcohol; headache, metallic taste.	

11/14/19 12:22 PM FAS1\_2019\_03-Microbiology.indd 195

### **Antimycobacterial therapy**

BACTERIUM	PROPHYLAXIS	TREATMENT
M tuberculosis	Isoniazid	Rifampin, Isoniazid, Pyrazinamide, Ethambutol (RIPE for treatment)
M avium–intracellulare	Azithromycin, rifabutin	Azithromycin or clarithromycin + ethambutol Can add rifabutin or ciprofloxacin
M leprae	N/A	Long-term treatment with dapsone and rifampin for tuberculoid form Add clofazimine for lepromatous form



Rifamycins	Rifampin, rifabutin.	
MECHANISM	Inhibit DNA-dependent RNA polymerase.	Rifampin's 4 R's:
CLINICAL USE	Mycobacterium tuberculosis; delay resistance to dapsone when used for leprosy. Used for meningococcal prophylaxis and chemoprophylaxis in contacts of children with H influenzae type b.	RNA polymerase inhibitor Ramps up microsomal cytochrome P-450 Red/orange body fluids Rapid resistance if used alone Rifampin ramps up cytochrome P-450, but
ADVERSE EFFECTS	Minor hepatotoxicity and drug interactions († cytochrome P-450); orange body fluids (nonhazardous side effect). Rifabutin favored over rifampin in patients with HIV infection due to less cytochrome P-450 stimulation.	rifa <b>but</b> in does not.
MECHANISM OF RESISTANCE	Mutations reduce drug binding to RNA polymerase. Monotherapy rapidly leads to resistance.	

FAS1\_2019\_03-Microbiology.indd 196 11/14/19 12:22 PM

MECHANISM	↓ synthesis of mycolic acids. Bacterial catalase- peroxidase (encoded by KatG) needed to convert INH to active metabolite.	
CLINICAL USE	Mycobacterium tuberculosis. The only agent used as solo prophylaxis against TB. Also used as monotherapy for latent TB.	Different INH half-lives in fast vs slow acetylators.
ADVERSE EFFECTS	Hepatotoxicity, cytochrome P-450 inhibition, drug-induced SLE, anion gap metabolic acidosis, vitamin B <sub>6</sub> deficiency (peripheral neuropathy, sideroblastic anemia), seizures (in high doses, refractory to benzodiazepines). Administer with pyridoxine (B <sub>6</sub> ).	INH Injures Neurons and Hepatocytes.
MECHANISM OF RESISTANCE	Mutations leading to underexpression of KatG.	
Pyrazinamide		
MECHANISM	Mechanism uncertain. Pyrazinamide is a prodrug pyrazinoic acid. Works best at acidic pH (eg, in	
CLINICAL USE	Mycobacterium tuberculosis.	
ADVERSE EFFECTS	Hyperuricemia, hepatotoxicity.	
Ethambutol		
MECHANISM	↓ carbohydrate polymerization of mycobacterium	cell wall by blocking arabinosyltransferase.
CLINICAL USE	Mycobacterium tuberculosis.	
ADVERSE EFFECTS	Optic neuropathy (red-green color blindness, usu	ally reversible). Pronounce " <mark>eye</mark> thambutol."
Streptomycin		
MECHANISM	Interferes with 30S component of ribosome.	
CLINICAL USE	Mycobacterium tuberculosis (2nd line).	
ADVERSE EFFECTS	Tinnitus, vertigo, ataxia, nephrotoxicity.	

11/14/19 12:22 PM FAS1\_2019\_03-Microbiology.indd 197

# Antimicrobial prophylaxis

CLINICAL SCENARIO	MEDICATION
Exposure to meningococcal infection	Ceftriaxone, ciprofloxacin, or rifampin
High risk for endocarditis and undergoing surgical or dental procedures	Amoxicillin
History of recurrent UTIs	TMP-SMX
Malaria prophylaxis for travelers	Atovaquone-proguanil, mefloquine, doxycycline, primaquine, or chloroquine (for areas with sensitive species)
Pregnant woman carrying group B strep	Intrapartum penicillin G or ampicillin
Prevention of gonococcal conjunctivitis in newborn	Erythromycin ointment on eyes
Prevention of postsurgical infection due to S aureus	Cefazolin
Prophylaxis of strep pharyngitis in child with prior rheumatic fever	Benzathine penicillin G or oral penicillin V

### **Prophylaxis in HIV/AIDS patients**

<u> </u>	•	
CELL COUNT	PROPHYLAXIS	INFECTION
CD4 < 200 cells/mm <sup>3</sup>	TMP-SMX	Pneumocystis pneumonia
CD4 < 100 cells/mm <sup>3</sup>	TMP-SMX	Pneumocystis pneumonia and toxoplasmosis
CD4 < 50 cells/mm <sup>3</sup>	Azithromycin or clarithromycin	Mycobacterium avium complex

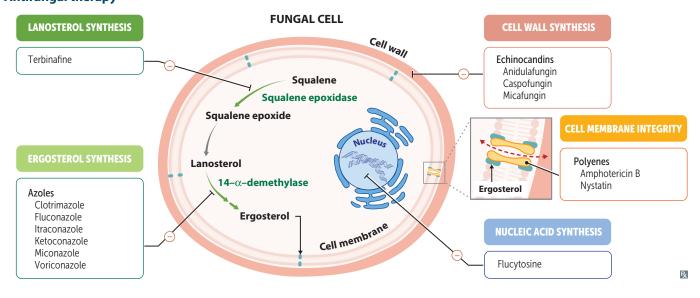
## Treatment of highly resistant bacteria

MRSA: vancomycin, daptomycin, linezolid, tigecycline, ceftaroline, doxycycline.

VRE: linezolid, tigecycline, and streptogramins (quinupristin, dalfopristin).

Multidrug-resistant P aeruginosa, multidrug-resistant Acinetobacter baumannii: polymyxins B and E (colistin).

### **Antifungal therapy**



FAS1\_2019\_03-Microbiology.indd 198 11/14/19 12:22 PM

MECHANISM	Binds ergosterol (unique to fungi); forms membrane pores that allow leakage of electrolytes.	Amphotericin "tears" holes in the fungal membrane by forming pores.
CLINICAL USE	Serious, systemic mycoses. <i>Cryptococcus</i> (amphotericin B with +/– without flucytosine for cryptococcal meningitis), <i>Blastomyces</i> , <i>Coccidioides</i> , <i>Histoplasma</i> , <i>Candida</i> , <i>Mucor</i> . Intrathecally for coccidioidal meningitis.	Supplement K <sup>+</sup> and Mg <sup>2+</sup> because of altered renal tubule permeability.
ADVERSE EFFECTS	Fever/chills ("shake and bake"), hypotension, nephrotoxicity, arrhythmias, anemia, IV phlebitis ("amphoterrible"). Hydration ↓ nephrotoxicity. Liposomal amphotericin ↓ toxicity.	
Nystatin		
MECHANISM	Same as amphotericin B. Topical use only as too	toxic for systemic use.
CLINICAL USE	"Swish and swallow" for oral candidiasis (thrush)	; topical for diaper rash or vaginal candidiasis.
Flucytosine		
MECHANISM	Inhibits DNA and RNA biosynthesis by conversion to 5-fluorouracil by cytosine deaminase.	
CLINICAL USE	Systemic fungal infections (especially meningitis amphotericin B.	s caused by <i>Cryptococcus</i> ) in combination with
ADVERSE EFFECTS	Bone marrow suppression.	
Azoles	Clotrimazole, fluconazole, isavuconazole, itracon	nazole, ketoconazole, miconazole, voriconazole.
MECHANISM	Inhibit fungal sterol (ergosterol) synthesis by inhi lanosterol to ergosterol.	biting the cytochrome P-450 enzyme that converts
CLINICAL USE	Local and less serious systemic mycoses. Flucona meningitis in AIDS patients and candidal infect Blastomyces, Coccidioides, Histoplasma, Sporota topical fungal infections. Voriconazole for Aspe serious Aspergillus and Mucor infections.	etions of all types. Itraconazole may be used for hrix schenckii. Clotrimazole and miconazole for
ADVERSE EFFECTS	Testosterone synthesis inhibition (gynecomastia, (inhibits cytochrome P-450).	especially with ketoconazole), liver dysfunction
Terbinafine		
MECHANISM	Inhibits the fungal enzyme squalene epoxidase.	
CLINICAL USE	Dermatophytoses (especially onychomycosis—fu	ngal infection of finger or toe nails).
ADVERSE EFFECTS	GI upset, headaches, hepatotoxicity, taste disturb	ance.

FAS1\_2019\_03-Microbiology.indd 199 11/14/19 12:22 PM

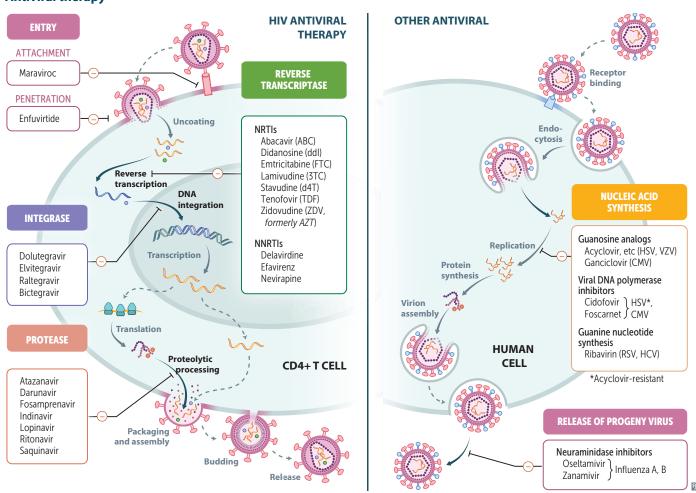
200

### SECTION II MICROBIOLOGY ➤ MICROBIOLOGY—ANTIMICROBIALS

Echinocandins	Anidulafungin, caspofungin, micafungin.		
MECHANISM	Inhibit cell wall synthesis by inhibiting synthesis of β-glucan.		
CLINICAL USE	Invasive aspergillosis, Candida.		
ADVERSE EFFECTS	GI upset, flushing (by histamine release).		
Griseofulvin			
MECHANISM	Interferes with microtubule function; disrupts mitosis. Deposits in keratin-containing tissues (eg, nails).		
CLINICAL USE	Oral treatment of superficial infections; inhibits growth of dermatophytes (tinea, ringworm).		
ADVERSE EFFECTS	Teratogenic, carcinogenic, confusion, headaches, disulfiram-like reaction, † cytochrome P-450 and warfarin metabolism.		
Antiprotozoal therapy	Pyrimethamine (toxoplasmosis), suramin and melarsoprol ( <i>Trypanosoma brucei</i> ), nifurtimox ( <i>T cruzi</i> ), sodium stibogluconate (leishmaniasis).		
Anti-mite/louse therapy	Permethrin (inhibits Na <sup>+</sup> channel deactivation $\rightarrow$ neuronal membrane depolarization), malathion (acetylcholinesterase inhibitor), topical +/- oral ivermectin. Used to treat scabies ( <i>Sarcoptes scabiei</i> ) and lice ( <i>Pediculus</i> and <i>Pthirus</i> ).		
Chloroquine			
MECHANISM	Blocks detoxification of heme into hemozoin. Heme accumulates and is toxic to plasmodia.		
CLINICAL USE	Treatment of plasmodial species other than <i>P falciparum</i> (frequency of resistance in <i>P falciparum</i> is too high). Resistance due to membrane pump that \(\psi\) intracellular concentration of drug. Treat <i>P falciparum</i> with artemether/lumefantrine or atovaquone/proguanil. For life-threatening malaria, use quinidine in US (quinine elsewhere) or artesunate.		
ADVERSE EFFECTS	Retinopathy; pruritus (especially in dark-skinned individuals).		
Antihelminthic therapy	Pyrantel pamoate, Ivermectin, Mebendazole (microtubule inhibitor), Praziquantel († Ca <sup>2+</sup> permeability, † vacuolization), Diethylcarbamazine. Helminths get PIMP'D.		

11/14/19 12:22 PM FAS1\_2019\_03-Microbiology.indd 200

### **Antiviral therapy**



### Oseltamivir, zanamivir

MECHANISM	Inhibit influenza neuraminidase → ↓ release of progeny virus.
CLINICAL USE	Treatment and prevention of influenza A and B. Beginning therapy within 48 hours of symptom onset may shorten duration of illness.

### Acyclovir, famciclovir, valacyclovir

MECHANISM	Guanosine analogs. Monophosphorylated by HSV/VZV thymidine kinase and not phosphorylated in uninfected cells → few adverse effects. Triphosphate formed by cellular enzymes. Preferentially inhibit viral DNA polymerase by chain termination.	
CLINICAL USE	HSV and VZV. Weak activity against EBV. No activity against CMV. Used for HSV-induced mucocutaneous and genital lesions as well as for encephalitis. Prophylaxis in immunocompromised patients. No effect on latent forms of HSV and VZV. Valacyclovir, a prodrug of acyclovir, has better oral bioavailability.  For herpes zoster, use famciclovir.	
ADVERSE EFFECTS	Obstructive crystalline nephropathy and acute kidney injury if not adequately hydrated.	
MECHANISM OF RESISTANCE	Mutated viral thymidine kinase.	

FAS1\_2019\_03-Microbiology.indd 201 11/14/19 12:22 PM

_				•
Ga	no	ic	l٥١	/ir

Ganciciovir			
MECHANISM	5'-monophosphate formed by a CMV viral kinase. Guanosine analog. Triphosphate formed by cellular kinases. Preferentially inhibits viral DNA polymerase.		
CLINICAL USE	CMV, especially in immunocompromised patients. Valganciclovir, a prodrug of ganciclovir, has better oral bioavailability.		
ADVERSE EFFECTS	Bone marrow suppression (leukopenia, neutropenia, thrombocytopenia), renal toxicity. More toxic to host enzymes than acyclovir.		
MECHANISM OF RESISTANCE	Mutated viral kinase.		
Foscarnet			
MECHANISM	Viral DNA/RNA polymerase inhibitor and HIV reverse transcriptase inhibitor. Binds to pyrophosphate-binding site of enzyme. Does not require any kinase activation.	Foscarnet = pyrofosphate analog.	
CLINICAL USE	CMV retinitis in immunocompromised patients when ganciclovir fails; acyclovir-resistant HSV.		
ADVERSE EFFECTS	Nephrotoxicity, electrolyte abnormalities (hypo- or hypercalcemia, hypo- or hyperphosphatemia, hypokalemia, hypomagnesemia) can lead to seizures.		
MECHANISM OF RESISTANCE	Mutated DNA polymerase.		
Cidofovir			
MECHANISM	Preferentially inhibits viral DNA polymerase. Does not require phosphorylation by viral kinase.		
CLINICAL USE	CMV retinitis in immunocompromised patients;	acyclovir-resistant HSV. Long half-life.	
ADVERSE EFFECTS	Nephrotoxicity (coadminister with probenecid an	d IV saline to 1 toxicity).	

FAS1\_2019\_03-Microbiology.indd 202 11/14/19 12:22 PM

**HIV** therapy

Antiretroviral therapy (ART): often initiated at the time of HIV diagnosis.

	Strongest indication for use with patients presentic counts (< 500 cells/mm³), or high viral load. Reg 2 NRTIs and preferably an integrase inhibitor. All ARTs are active against HIV-1 and HIV-2 with	ing with AIDS-defining illness, low CD4+ cell gimen consists of 3 drugs to prevent resistance:
DRUG	MECHANISM	TOXICITY
NRTIs		
Abacavir (ABC) Didanosine (ddl) Emtricitabine (FTC) Lamivudine (3TC) Stavudine (d4T) Tenofovir (TDF) Zidovudine (ZDV, formerly AZT)	Competitively inhibit nucleotide binding to reverse transcriptase and terminate the DNA chain (lack a 3' OH group). Tenofovir is a nucleoTide; the others are nucleosides. All need to be phosphorylated to be active.  ZDV can be used for general prophylaxis and during pregnancy to \$\dagger\$ risk of fetal transmission. Have you dined (vudine) with my nuclear (nucleosides) family?	Bone marrow suppression (can be reversed with granulocyte colony-stimulating factor [G-CSF] and erythropoietin), peripheral neuropathy, lactic acidosis (nucleosides), anemia (ZDV), pancreatitis (didanosine).  Abacavir contraindicated if patient has HLA-B*5701 mutation due to † risk of hypersensitivity.
NNRTIs		
Delavirdine Efavirenz Nevirapine	Bind to reverse transcriptase at site different from NRTIs. Do not require phosphorylation to be active or compete with nucleotides.	Rash and hepatotoxicity are common to all NNRTIs. Vivid dreams and CNS symptoms are common with efavirenz.
Integrase inhibitors		
Bictegravir Dolutegravir Elvitegravir Raltegravir	Inhibits HIV genome integration into host cell chromosome by reversibly inhibiting HIV integrase.	† creatine kinase.
<b>Protease</b> inhibitors		
Atazanavir Darunavir Fosamprenavir Indinavir Lopinavir Ritonavir Saquinavir	Assembly of virions depends on HIV-1 protease (pol gene), which cleaves the polypeptide products of HIV mRNA into their functional parts. Thus, protease inhibitors prevent maturation of new viruses.  Ritonavir can "boost" other drug concentrations by inhibiting cytochrome P-450.  Navir (never) tease a protease.	Hyperglycemia, GI intolerance (nausea, diarrhea), lipodystrophy (Cushing-like syndrome).  Nephropathy, hematuria, thrombocytopenia (indinavir).  Rifampin (potent CYP/UGT inducer) reduces protease inhibitor concentrations; use rifabutin instead.
Entry inhibitors		
Enfuvirtide	Binds gp41, inhibiting viral entry.	Skin reaction at injection sites. En <b>fu</b> virtide inhibits <b>fu</b> sion.
Maraviroc	Binds CCR-5 on surface of T cells/monocytes, inhibiting interaction with gpl20.	Maraviroc inhibits docking.

FAS1\_2019\_03-Microbiology.indd 203 11/14/19 12:22 PM

Hepatitis C therapy	Chronic HCV infection treated with multidrug therapy that targets specific steps within HCV replication cycle (HCV-encoded proteins). Examples of drugs are provided.		
DRUG	MECHANISM TOXICITY		
NS5A inhibitors			
Ledipasvir Ombitasvir Velpatasvir	Inhibits NS5A, a viral phosphoprotein that plays a key role in RNA replication  Exact mechanism unknown	Headache, diarrhea	
NS5B inhibitors			
Sofos <mark>buvir</mark> Dasa <mark>buvir</mark>	Inhibits NS5B, an RNA-dependent RNA polymerase acting as a chain terminator Prevents viral RNA replication	Fatigue, headache	
NS3/4A inhibitors			
Grazoprevir Simeprevir	Inhibits NS3/4A, a viral protease, preventing viral replication	Grazoprevir: headache, fatigue Simeprevir: photosensitivity reactions, rash	
Alternative drugs			
Ribavirin	Inhibits synthesis of guanine nucleotides by competitively inhibiting IMP dehydrogenase Used as adjunct in cases refractory to newer medications  Hemolytic anemia, severe teratog		
Disinfection and sterilization	Goals include the reduction of pathogenic organi inactivation of all microbes including spores (ste		
Autoclave	Pressurized steam at > 120°C. Sporicidal. May not reliably inactivate prions.		
Alcohols	Denature proteins and disrupt cell membranes. Not sporicidal.		
Chlorhexidine	Denatures proteins and disrupts cell membranes. Not sporicidal.		
Chlorine	Oxidizes and denatures proteins. Sporicidal.		
Ethylene oxide	Alkylating agent. Sporicidal.		
Hydrogen peroxide	Free radical oxidation. Sporicidal.		
lodine and iodophors	Halogenation of DNA, RNA, and proteins. May l	oe sporicidal.	
Quaternary amines	Impair permeability of cell membranes. Not sport	icidal.	
Antimicrobials to	ANTIMICROBIAL	ADVERSE EFFECT	
avoid in pregnancy	Sulfonamides	Kernicterus	
	Aminoglycosides	Ototoxicity	
	Fluoroquinolones	Cartilage damage	
	Clarithromycin	Embryotoxic	
	Tetracyclines	Discolored teeth, inhibition of bone growth	
	Ribavirin	Teratogenic	
	Griseofulvin	Teratogenic	

FAS1\_2019\_03-Microbiology.indd 204 11/14/19 12:22 PM

### HIGH-YIELD PRINCIPLES IN

# **Pathology**

"Digressions, objections, delight in mockery, carefree mistrust are signs of health; everything unconditional belongs in pathology."

-Friedrich Nietzsche

"You cannot separate passion from pathology any more than you can separate a person's spirit from his body."

-Richard Selzer

The fundamental principles of pathology are key to understanding diseases in all organ systems. Major topics such as inflammation and neoplasia appear frequently in questions across different organ systems, and such topics are definitely high yield. For example, the concepts of cell injury and inflammation are key to understanding the inflammatory response that follows myocardial infarction, a very common subject of board questions. Similarly, a familiarity with the early cellular changes that culminate in the development of neoplasias—for example, esophageal or colon cancer—is critical. Finally, make sure you recognize the major tumor-associated genes and are comfortable with key cancer concepts such as tumor staging and metastasis.

► Cellular Injury 206 ► Inflammation 213

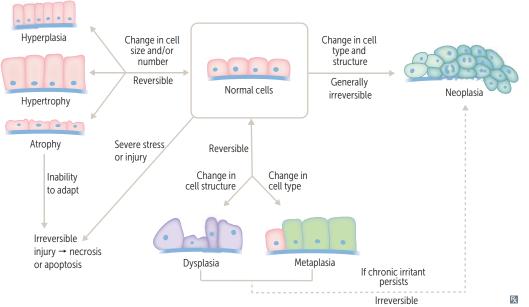
▶ Neoplasia 219

205

FAS1\_2019\_04-Pathol.indd 205 11/7/19 4:02 PM

### ▶ PATHOLOGY—CELLULAR INJURY

Cellular adaptations	Reversible changes that can be physiologic (eg, uterine enlargement during pregnancy) or pathologic (eg, myocardial hypertrophy $2^{\circ}$ to systemic HTN). If stress is excessive or persistent, adaptations can progress to cell injury (eg, significant LV hypertrophy $\rightarrow$ injury to myofibrils $\rightarrow$ HF).
Hypertrophy	↑ structural proteins and organelles → ↑ in size of cells. Example: cardiac hypertrophy.
Hyperplasia	Controlled proliferation of stem cells and differentiated cells → ↑ in number of cells. Excessive stimulation → pathologic hyperplasia (eg, endometrial hyperplasia), which may progress to dysplasia and cancer. Example: benign prostatic hyperplasia.
Atrophy	↓ in tissue mass due to ↓ in size († cytoskeleton degradation via ubiquitin-proteasome pathway and autophagy; ↓ protein synthesis) and/or number of cells (apoptosis). Causes include disuse, denervation, loss of blood supply, loss of hormonal stimulation, poor nutrition.
Metaplasia	Reprogramming of stem cells → replacement of one cell type by another that can adapt to a new stress. Usually due to exposure to an irritant, such as gastric acid (→ Barrett esophagus) or cigarette smoke (→ respiratory ciliated columnar epithelium replaced by stratified squamous epithelium). May progress to dysplasia → malignant transformation with persistent insult (eg, Barrett esophagus → esophageal adenocarcinoma). Metaplasia of connective tissue can also occur (eg, myositis ossificans, the formation of bone within muscle after trauma).
Dysplasia	Disordered, precancerous epithelial cell growth; not considered a true adaptive response.  Characterized by loss of uniformity of cell size and shape (pleomorphism); loss of tissue orientation; nuclear changes (eg, † nuclear:cytoplasmic ratio and clumped chromatin). Mild and moderate dysplasias (ie, do not involve entire thickness of epithelium) may regress with alleviation of inciting cause. Severe dysplasia often becomes irreversible and progresses to carcinoma in situ. Usually preceded by persistent metaplasia or pathologic hyperplasia.



FAS1\_2019\_04-Pathol.indd 206 11/7/19 4:02 PM

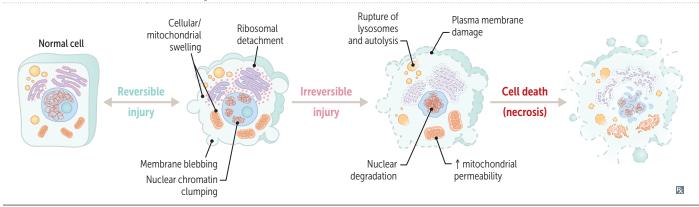
### **Cell injury**

### Reversible cell injury

- ↓ ATP → ↓ activity of Ca<sup>2+</sup> and Na<sup>+</sup>/K<sup>+</sup> pumps → cellular swelling (earliest morphologic manifestation), mitochondrial swelling
- Ribosomal/polysomal detachment → ↓ protein synthesis
- Plasma membrane changes (eg, blebbing)
- Nuclear changes (eg, chromatin clumping)
- Rapid loss of function (eg, myocardial cells are noncontractile after 1-2 minutes of ischemia)
- Myelin figures (aggregation of peroxidized lipids)

### Irreversible cell injury

- Breakdown of plasma membrane → cytosolic enzymes (eg, troponin) leak outside of cell, influx of Ca<sup>2+</sup> → activation of degradative enzymes
- Mitochondrial damage/dysfunction → loss of electron transport chain → ↓ ATP
- Cytoplasmic vacuolization accompanies programmed cell death (apoptosis)
- Rupture of lysosomes → autolysis
- Nuclear degradation: pyknosis (nuclear condensation) → karyorrhexis (nuclear fragmentation caused by endonuclease-mediated cleavage) → karyolysis (nuclear dissolution)
- Amorphous densities/inclusions in mitochondria



FAS1\_2019\_04-Pathol.indd 207 11/7/19 4:02 PM

### **Apoptosis**

ATP-dependent programmed cell death.

Intrinsic and extrinsic pathways; both pathways activate caspases (cytosolic proteases) → cellular breakdown including cell shrinkage, chromatin condensation, membrane blebbing, and formation of apoptotic bodies, which are then phagocytosed.

Characterized by deeply eosinophilic cytoplasm and basophilic nucleus, pyknosis, and karyorrhexis. Cell membrane typically remains intact without significant inflammation (unlike necrosis). DNA laddering (fragments in multiples of 180 bp) is a sensitive indicator of apoptosis.

### Intrinsic (mitochondrial) pathway

Involved in tissue remodeling in embryogenesis. Occurs when a regulating factor is withdrawn from a proliferating cell population (eg, ↓ IL-2 after a completed immunologic reaction → apoptosis of proliferating effector cells). Also occurs after exposure to injurious stimuli (eg, radiation, toxins, hypoxia).

Regulated by Bcl-2 family of proteins. BAX and BAK are proapoptotic, while Bcl-2 and Bcl-xL are antiapoptotic.

BAX and BAK form pores in the mitochondrial membrane → release of cytochrome C from inner mitochondrial membrane into the cytoplasm → activation of caspases.

Bcl-2 keeps the mitochondrial membrane impermeable, thereby preventing cytochrome C release. Bcl-2 overexpression (eg, follicular lymphoma t[14;18]) → ↓ caspase activation → tumorigenesis.

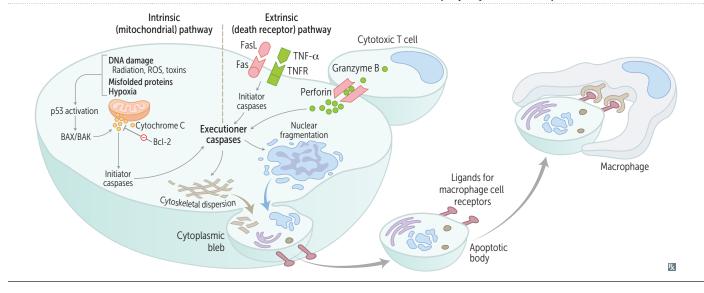
# Extrinsic (death receptor) pathway

2 pathways:

- Ligand receptor interactions (FasL binding to Fas [CD95] or TNF-α binding to its receptor)
- Immune cell (cytotoxic T-cell release of perforin and granzyme B)

Fas-FasL interaction is necessary in thymic medullary negative selection.

Fas mutations † numbers of circulating self-reacting lymphocytes due to failure of clonal deletion. Defective Fas-FasL interactions cause autoimmune lymphoproliferative syndrome.



FAS1 2019 04-Pathol.indd 208 11/7/19 4:02 PM

ТҮРЕ	SEEN IN	ar components leak → local in	HISTOLOGY
Coagulative	Ischemia/infarcts in most tissues (except brain)	Ischemia or infarction; injury denatures enzymes → proteolysis blocked	Preserved cellular architecture (cell outlines seen), but nuclei disappear;  ↑ cytoplasmic binding of eosin stain  (→ ↑ eosinophilia; red/pink color) A
Liquefactive	Bacterial abscesses, brain infarcts	Neutrophils release lysosomal enzymes that digest the tissue B	Early: cellular debris and macrophages Late: cystic spaces and cavitation (brain) Neutrophils and cell debris seen with bacterial infection
Caseous	TB, systemic fungi (eg, Histoplasma capsulatum), Nocardia	Macrophages wall off the infecting microorganism → granular debris C	Fragmented cells and debris surrounded by lymphocytes and macrophages (granuloma)
Fat	Enzymatic: acute pancreatitis (saponification of peripancreatic fat) Nonenzymatic: traumatic (eg, injury to breast tissue)	Damaged pancreatic cells release lipase, which breaks down triglycerides; liberated fatty acids bind calcium → saponification (chalkywhite appearance)	Outlines of dead fat cells without peripheral nuclei; saponification of fat (combined with Ca <sup>2+</sup> ) appears dark blue on H&E stain D
Fibrinoid	Immune vascular reactions (eg, PAN) Nonimmune vascular reactions (eg, hypertensive emergency, preeclampsia)	Immune complex deposition (type III hypersensitivity reaction) and/or plasma protein (eg, fibrin) leakage from damaged vessel	Vessel walls are thick and pink <b>E</b>
Gangrenous	Distal extremity and	Dry: ischemia <b>F</b>	Coagulative
	GI tract, after chronic ischemia	Wet: superinfection	Liquefactive superimposed on coagulative
	D	E E	

FAS1\_2019\_04-Pathol.indd 209 11/7/19 4:02 PM

#### Ischemia



Inadequate blood supply to meet demand. Mechanisms include ↓ arterial perfusion (eg, atherosclerosis), ↓ venous drainage (eg, testicular torsion, Budd-Chiari syndrome), shock. Regions most vulnerable to hypoxia/ischemia and subsequent infarction:

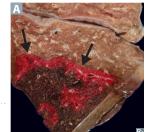
ORGAN	REGION	
Brain	ACA/MCA/PCA boundary areas <sup>a,b</sup>	
Heart	Subendocardium (LV) 🖪	
Kidney	Straight segment of proximal tubule (medulla) Thick ascending limb (medulla)	
Liver	Area around central vein (zone III)	
Colon	Splenic flexure (Griffith point), <sup>a</sup> rectosigmoid junction (Sudeck point) <sup>a</sup>	

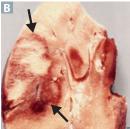
<sup>&</sup>lt;sup>a</sup>Watershed areas (border zones) receive blood supply from most distal branches of 2 arteries with limited collateral vascularity. These areas are susceptible to ischemia from hypoperfusion.

#### **Types of infarcts**

#### **Red** infarct

Occurs in venous occlusion and tissues with multiple blood supplies (eg, liver, lung A, intestine, testes), and with reperfusion (eg, after angioplasty). Reperfusion injury is due to damage by free radicals.





#### **Pale infarct**

Occurs in solid organs with a single (endarterial) blood supply (eg, heart, kidney **B**).

#### Free radical injury

Free radicals damage cells via membrane lipid peroxidation, protein modification, DNA breakage. Initiated via radiation exposure (eg, cancer therapy), metabolism of drugs (phase I), redox reactions, nitric oxide (eg, inflammation), transition metals, WBC (eg, neutrophils, macrophages) oxidative burst.

Free radicals can be eliminated by scavenging enzymes (eg, catalase, superoxide dismutase, glutathione peroxidase), spontaneous decay, antioxidants (eg, vitamins A, C, E), and certain metal carrier proteins (eg, transferrin, ceruloplasmin).

#### Examples:

- Oxygen toxicity: retinopathy of prematurity (abnormal vascularization), bronchopulmonary dysplasia, reperfusion injury after thrombolytic therapy
- Drug/chemical toxicity: acetaminophen overdose (hepatotoxicity), carbon tetrachloride (converted by cytochrome P-450 into CCl₃ free radical → fatty liver [cell injury
- → ↓ apolipoprotein synthesis → fatty change], centrilobular necrosis)
- Metal storage diseases: hemochromatosis (iron) and Wilson disease (copper)

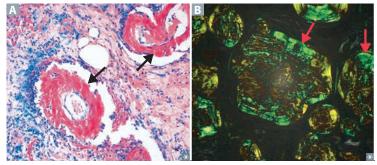
FAS1\_2019\_04-Pathol.indd 210 11/7/19 4:02 PM

<sup>&</sup>lt;sup>b</sup>Neurons most vulnerable to hypoxic-ischemic insults include Purkinje cells of the cerebellum and pyramidal cells of the hippocampus and neocortex (zones 3, 5, 6).

Types of calcification	Calcium deposits appear deeply basophilic (arrow	in 🗚) on H&E stain.
	Dystrophic calcification	Metastatic calcification
Ca <sup>2+</sup> DEPOSITION	In abnormal (Diseased) tissues	In normal tissues
EXTENT	Tends to be localized (eg, calcific aortic stenosis)	Widespread (ie, diffuse, metastatic)
ASSOCIATED CONDITIONS  A	TB (lung and pericardium) and other granulomatous infections, liquefactive necrosis of chronic abscesses, fat necrosis, infarcts, thrombi, schistosomiasis, congenital CMV, toxoplasmosis, rubella, psammoma bodies, CREST syndrome, atherosclerotic plaques can become calcified	Predominantly in interstitial tissues of kidney, lung, and gastric mucosa (these tissues lose acid quickly; † pH favors Ca <sup>2+</sup> deposition)  Nephrocalcinosis of collecting ducts may lead to nephrogenic diabetes insipidus and renal failure
ETIOLOGY	2° to injury or necrosis	2° to hypercalcemia (eg, 1° hyperparathyroidism, sarcoidosis, hypervitaminosis D) or high calcium-phosphate product levels (eg, chronic kidney disease with 2° hyperparathyroidism, long-term dialysis, calciphylaxis, multiple myeloma)
SERUM Ca <sup>2+</sup> LEVELS	Normal	Usually abnormal
Lipofuscin	A yellow-brown "wear and tear" pigment A associated with normal aging.  Composed of polymers of lipids and phospholipids complexed with protein. May be derived through lipid peroxidation of polyunsaturated lipids of subcellular membranes.  Autopsy of elderly person will reveal deposits in heart, colon, liver, kidney, eye, and other organs.	

FAS1\_2019\_04-Pathol.indd 211 11/7/19 4:02 PM

Amyloidosis	fibrils → cellular damage a (red/orange on nonpolarize	teins (or their fragments) into β-pleate and apoptosis. Amyloid deposits visuali d light [arrows in A]), (apple-green bi ain (shows deposits in glomerular mean light microscopy.	zed by Congo red stain refringence on polarized light	
COMMON TYPES	FIBRIL PROTEIN	DESCRIPTION		
Systemic				
Primary amyloidosis	AL (from Ig Light chains)	Seen in Plasma cell disorders (eg, multiple myeloma)	Manifestations include:  • Cardiac (eg, restrictive	
Secondary amyloidosis	Serum <b>A</b> myloid <b>A</b> ( <b>AA</b> )	Seen in chronic inflammatory conditions, (eg, rheumatoid arthritis, IBD, familial Mediterranean fever, protracted infection)	cardiomyopathy)  GI (eg, macroglossia, hepatomegaly)  Renal (eg, nephrotic syndrome)	
Dialysis-related amyloidosis	$eta_2$ -microglobulin	Seen in patients with ESRD and/or on long-term dialysis	<ul> <li>Hematologic (eg, easy bruising, splenomegaly)</li> <li>Neurologic (eg, neuropathy)</li> <li>Musculoskeletal (eg, carpal tunnel syndrome)</li> </ul>	
Localized				
Alzheimer disease	β-amyloid protein	Cleaved from amyloid precursor protein (APP)		
Type 2 diabetes mellitus	Islet amyloid polypeptide (IAPP)	Caused by deposition of amylin in pancreatic islets		
Medullary thyroid cancer	Calcitonin			
Isolated atrial amyloidosis	ANP	Common in normal aging † risk of atrial fibrillation		
Systemic senile (age- related) amyloidosis	Normal (wild-type) transthyretin (TTR)	Seen predominantly in cardiac ventricles	Cardiac dysfunction more insidious than in AL amyloidosis	
Hereditary				
Familial amyloid cardiomyopathy	Mutated transthyretin (ATTR)	Ventricular endomyocardium deposition → restrictive cardiomyopathy, arrhythmias	5% of African Americans are carriers of mutant allele	
Familial amyloid polyneuropathies	Mutated transthyretin (ATTR)	Due to transthyretin gene mutation		
	A	В		



FAS1\_2019\_04-Pathol.indd 212 11/7/19 4:02 PM

nflammation	Response to eliminate initial cause of cell injury, original insult, and to initiate tissue repair. Divid response itself can be harmful to the host if the (eg, persistent infections such as TB), or inappro	ded into acute and chronic. The inflammatory reaction is excessive (eg, septic shock), prolonged
Cardinal signs	MECHANICA	нгриторс
SIGN	MECHANISM	MEDIATORS
Rubor (redness), calor (warmth)	Vasodilation (relaxation of arteriolar smooth muscle) → ↑ blood flow	Histamine, prostaglandins, bradykinin, NO
Tumor (swelling)	Endothelial contraction/disruption (eg, from tissue damage) → ↑ vascular permeability → leakage of protein-rich fluid from postcapillary venules into interstitial space (exudate) → ↑ interstitial oncotic pressure	Endothelial contraction: leukotrienes ( $C_4$ , $D_4$ , $E_4$ ), histamine, serotonin
Dolor (pain)	Sensitization of sensory nerve endings	Bradykinin, PGE <sub>2</sub> , histamine
Functio laesa (loss of function)	Cardinal signs above impair function (eg, inability to make fist with hand that has cellulitis)	
Systemic manifestations	(acute-phase reaction)	
Fever	Pyrogens (eg, LPS) induce macrophages to release IL-1 and TNF → ↑ COX activity in perivascular cells of hypothalamus → ↑ PGE <sub>2</sub> → ↑ temperature set point	
Leukocytosis	Elevation of WBC count; type of cell that is predominantly elevated depends on the inciting agent or injury (eg, bacteria → ↑ neutrophils)	
† plasma acute-phase proteins	Factors whose serum concentrations change significantly in response to inflammation Produced by the liver in both acute and chronic inflammatory states	Notably induced by IL-6
Acute phase reactants	More FFiSH in the C (sea).	
POSITIVE (UPREGULATED)	D: 1 1	·
Ferritin	Binds and sequesters iron to inhibit microbial iron	
Fibrinogen	Coagulation factor; promotes endothelial repair; o	correlates with ESK.
Serum amyloid A	Prolonged elevation can lead to amyloidosis.	
Hepcidin	↓ iron absorption (by degrading ferroportin) and ↓ iron release (from macrophages) → anemia of chronic disease.	
C-reactive protein	Opsonin; fixes complement and facilitates phagocytosis.  Measured clinically as a nonspecific sign of ongoing inflammation.	
NEGATIVE (DOWNREGULATED)	D.1.	
Albumin	Reduction conserves amino acids for positive reac	tants.
Transferrin	Internalized by macrophages to sequester iron.	

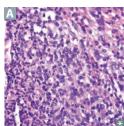
FAS1\_2019\_04-Pathol.indd 213 11/7/19 4:02 PM

### **Erythrocyte** sedimentation rate

RBCs normally remain separated via ⊖ charges. Products of inflammation (eg, fibrinogen) coat RBCs → ↓ ⊖ charge → ↑ RBC aggregation. Denser RBC aggregates fall at a faster rate within a pipette tube → ↑ ESR. Often co-tested with CRP (more specific marker of inflammation).

† ESR	↓ ESR
Most anemias	Sickle cell anemia (altered shape)
Infections	Polycythemia († RBCs "dilute" aggregation
Inflammation (eg, giant cell [temporal] arteritis,	factors)
polymyalgia rheumatica)	HF
Cancer (eg, metastases, multiple myeloma)	Microcytosis
Renal disease (end-stage or nephrotic syndrome)	Hypofibrinogenemia
Pregnancy	

#### **Acute inflammation**



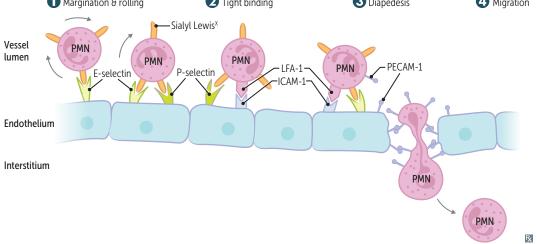
Transient and early response to injury or infection. Characterized by neutrophils in tissue A, often with associated edema. Rapid onset (seconds to minutes) and short duration (minutes to days). Represents a reaction of the innate immune system (ie, less specific response than chronic inflammation).

STIMULI	Infections, trauma, necrosis, foreign bodies.	
MEDIATORS	Toll-like receptors, arachidonic acid metabolites, neutrophils, eosinophils, antibodies (preexisting), mast cells, basophils, complement, Hageman factor (factor XII).	Inflammasome—Cytoplasmic protein complex that recognizes products of dead cells, microbial products, and crystals (eg, uric acid crystals) → activation of IL-l and inflammatory response.
COMPONENTS	<ul> <li>Vascular: vasodilation (→ ↑ blood flow and stasis) and ↑ endothelial permeability</li> <li>Cellular: extravasation of leukocytes (mainly neutrophils) from postcapillary venules and accumulation in the focus of injury followed by leukocyte activation</li> </ul>	To bring cells and proteins to site of injury or infection.  Leukocyte extravasation has 4 steps: margination and rolling, adhesion, transmigration, and migration (chemoattraction).
OUTCOMES	<ul> <li>Resolution and healing (IL-10, TGF-β)</li> <li>Persistent acute inflammation (IL-8)</li> <li>Abscess (acute inflammation walled off by fibrosis)</li> <li>Chronic inflammation (antigen presentation by macrophages and other APCs         → activation of CD4<sup>+</sup> Th cells)</li> <li>Scarring</li> </ul>	Macrophages predominate in the late stages of acute inflammation (peak 2–3 days after onset) and influence outcome by secreting cytokines.

FAS1\_2019\_04-Pathol.indd 214 11/7/19 4:02 PM

#### Leukocyte extravasation

EP	VASCULATURE/STROMA	LEUKOCYTE
Margination and rolling— defective in leukocyte adhesion	E-selectin (upregulated by TNF and IL-1)	Sialyl Lewis <sup>X</sup>
deficiency type 2 ( Sialyl Lewis <sup>X</sup> )	P-selectin (released from Weibel-Palade bodies)	Sialyl Lewis <sup>X</sup>
	GlyCAM-1, CD34	L-selectin
Tight binding (adhesion)— defective in leukocyte adhesion	ICAM-1 (CD54)	CD11/18 integrins (LFA-1, Mac-1)
deficiency type 1 (\$\ddot CD18 integrin subunit)	VCAM-1 (CD106)	VLA-4 integrin
Diapedesis (transmigration)— WBC travels between endothelial cells and exits blood vessel	PECAM-1 (CD31)	PECAM-1 (CD31)
Migration—WBC travels through interstitium to site of injury or infection guided by chemotactic signals	Chemotactic factors: C5a, IL-8, LTB <sub>4</sub> , kallikrein, platelet-activating factor	Various
■ Margination & rolling	2 Tight binding 3 Diapedesis	4 Migration
/essel PMN Sialyl Le	wis <sup>x</sup>	



FAS1\_2019\_04-Pathol.indd 215 11/7/19 4:02 PM

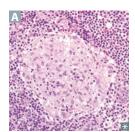
Chronic inflammation	Prolonged inflammation characterized by mononuclear infiltration (macrophages, lymphocytes, plasma cells), which leads to simultaneous tissue destruction and repair (including angiogenesis and fibrosis). May be preceded by acute inflammation.	
STIMULI	Persistent infections (eg, TB, <i>T pallidum</i> , certain fungi and viruses) → type IV hypersensitivity, autoimmune diseases, prolonged exposure to toxic agents (eg, silica) and foreign material.	
MEDIATORS	<ul> <li>Macrophages are the dominant cells. Interaction of macrophages and T lymphocytes → chronic inflammation.</li> <li>Th1 cells secrete IFN-γ → macrophage classical activation (proinflammatory)</li> <li>Th2 cells secrete IL-4 and IL-13 → macrophage alternative activation (repair and anti-inflammatory)</li> </ul>	
OUTCOMES	Scarring, amyloidosis, and neoplastic transformation (eg, chronic HCV infection → chronic inflammation → hepatocellular carcinoma; <i>Helicobacter pylori</i> infection → chronic gastritis → gastric adenocarcinoma).	
Wound healing		
Tissue mediators	MEDIATOR	ROLE
	FGF	Stimulates angiogenesis
	TGF-β	Angiogenesis, fibrosis
	VEGF	Stimulates angiogenesis
	PDGF	Secreted by activated platelets and macrophages Induces vascular remodeling and smooth muscle cell migration Stimulates fibroblast growth for collagen synthesis
	Metalloproteinases	Tissue remodeling
	EGF	Stimulates cell growth via tyrosine kinases (eg, EGFR/ErbB1)
PHASE OF WOUND HEALING	EFFECTOR CELLS	CHARACTERISTICS
Inflammatory (up to 3 days after wound)	Platelets, neutrophils, macrophages	Clot formation, † vessel permeability and neutrophil migration into tissue; macrophages clear debris 2 days later
Proliferative (day 3–weeks after wound)	Fibroblasts, myofibroblasts, endothelial cells, keratinocytes, macrophages	Deposition of granulation tissue and type III collagen, angiogenesis, epithelial cell proliferation, dissolution of clot, and wound contraction (mediated by myofibroblasts) Delayed second phase of wound healing in vitamin C and copper deficiency
Remodeling (1 week–6+ months after wound)	Fibroblasts	Type III collagen replaced by type I collagen,  ↑ tensile strength of tissue  Collagenases (require zinc to function) break down type III collagen  Zinc deficiency → delayed wound healing

FAS1\_2019\_04-Pathol.indd 216 11/7/19 4:02 PM

### **Granulomatous** inflammation

A pattern of chronic inflammation. Can be induced by persistent T-cell response to certain infections (eg, TB), immune-mediated diseases, and foreign bodies. Granulomas "wall off" a resistant stimulus without completely eradicating or degrading it → persistent inflammation→ fibrosis, organ damage.

#### HISTOLOGY



Focus of epithelioid cells (activated macrophages with abundant pink cytoplasm) surrounded by lymphocytes and multinucleated giant cells (formed by fusion of several activated macrophages). Two types:

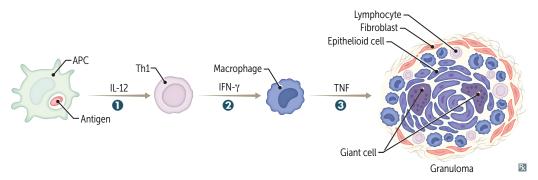
Caseating: associated with Central necrosis. Seen with infectious etiologies (eg, TB, fungal). Noncaseating A: no central necrosis. Seen with autoimmune diseases (eg, sarcoidosis, Crohn disease).

MECHANISM

- APCs present antigens to CD4+ Th cells and secrete IL-12 → CD4+ Th cells differentiate into Th1 cells
- 2 Thl secretes IFN- $\gamma \rightarrow$  macrophage activation
- Macrophages ↑ cytokine secretion (eg, TNF) → formation of epithelioid macrophages and giant cells

Anti-TNF therapy can cause sequestering granulomas to break down → disseminated disease. Always test for latent TB before starting anti-TNF therapy.

Associated with hypercalcemia due to  $\uparrow 1\alpha$ -hydroxylase activity in activated macrophages, resulting in  $\uparrow$  vitamin D activity.



#### ETIOLOGIES

#### INFECTIOUS

Bacterial: *Mycobacteria* (tuberculosis, leprosy), *Bartonella henselae* (cat scratch disease; stellate necrotizing granulomas), *Listeria monocytogenes* (granulomatosis infantiseptica), *Treponema pallidum* (3° syphilis)

Fungal: endemic mycoses (eg, histoplasmosis) Parasitic: schistosomiasis

#### NONINFECTIOUS

Immune-mediated: sarcoidosis, Crohn disease, 1° biliary cholangitis, subacute (de Quervain/granulomatous) thyroiditis

Vasculitis: granulomatosis with polyangiitis (Wegener), eosinophilic granulomatosis with polyangiitis (Churg-Strauss), giant cell (temporal) arteritis, Takayasu arteritis

Foreign bodies: berylliosis, talcosis, hypersensitivity pneumonitis

Chronic granulomatous disease

FAS1\_2019\_04-Pathol.indd 217 11/7/19 4:02 PM

Scar formation	Occurs when repair cannot be accomplished by cell regeneration alone. Nonregenerated cells (2° to severe acute or chronic injury) are replaced by connective tissue. 70–80% of tensile strength regained at 3 months; little tensile strength regained thereafter. Associated with excess TGF-β.	
SCAR TYPE	Hypertrophic A	Keloid B
COLLAGEN SYNTHESIS	† (type III collagen)	††† (types I and III collagen)
COLLAGEN ORGANIZATION	Parallel	Disorganized
EXTENT OF SCAR	Confined to borders of original wound	Extends beyond borders of original wound with "claw-like" projections typically on earlobes, face, upper extremities
RECURRENCE	Infrequent	Frequent
PREDISPOSITION	None	↑ incidence in ethnic groups with darker skin



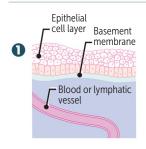


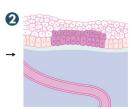
FAS1\_2019\_04-Pathol.indd 218 11/7/19 4:02 PM

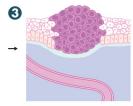
#### ▶ PATHOLOGY—NEOPLASIA

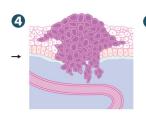
#### **Neoplasia** and neoplastic progression

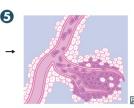
Uncontrolled, monoclonal proliferation of cells. Can be benign or malignant. Any neoplastic growth has two components: parenchyma (neoplastic cells) and supporting stroma (nonneoplastic; eg, blood vessels, connective tissue).











#### **Normal cells**

Normal cells with basal → apical polarity. See cervical example A, which shows normal cells and spectrum of dysplasia, as discussed below.

#### Dysplasia

Loss of uniformity in cell size and shape (pleomorphism); loss of tissue orientation; nuclear changes (eg, † nuclear:cytoplasmic ratio) A.

#### Carcinoma in situ/ preinvasive

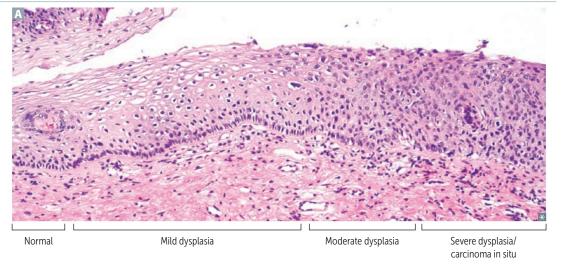
3 Irreversible severe dysplasia that involves the entire thickness of epithelium but does not penetrate the intact basement membrane A.

#### **Invasive carcinoma**

4 Cells have invaded basement membrane using collagenases and hydrolases (metalloproteinases). Cell-cell contacts lost by inactivation of E-cadherin.

#### Metastasis

Spread to distant organ(s) via lymphatics or blood.



FAS1\_2019\_04-Pathol.indd 219 11/7/19 4:02 PM 220

SECTION II

### PATHOLOGY ► PATHOLOGY—NEOPLASIA

Tumor nomenclature		erentiation, erratic growth, local invasion,  hamartoma (disorganized overgrowth of tissues in and choristoma (normal tissue in a foreign location,
CELL TYPE	BENIGN	MALIGNANT
Epithelium	Adenoma, papilloma	Adenocarcinoma, papillary carcinoma
Mesenchyme		
Blood cells		Leukemia, lymphoma
Blood vessels	Hemangioma	Angiosarcoma
Smooth muscle	Leiomyoma	Leiomyosarcoma
Striated muscle	Rhabdomyoma	Rhabdomyosarcoma
Connective tissue	Fibroma	Fibrosarcoma
Bone	Osteoma	Osteosarcoma
Fat	Lipoma	Liposarcoma
Melanocyte	Nevus/mole	Melanoma
Tumor grade vs stage		bles its tissue of origin. Well-differentiated tumors sue of origin, whereas poorly differentiated tumors ells in a malignant neoplasm.
Grade	Degree of cellular differentiation and mitotic activity on histology. Ranges from low grade (well-differentiated) to high grade (poorly differentiated, undifferentiated, or anaplastic).	Low grade High grade 🕟
Stage	Degree of localization/spread based on site and size of 1° lesion, spread to regional lymph nodes, presence of metastases. Based on clinical (c) or pathologic (p) findings. Stage generally has more prognostic value than grade (eg, a high-stage yet low-grade tumor is usually worse than a low-stage yet high-grade tumor). Stage determines Survival.  TNM staging system (Stage = Spread):  T = Tumor size/invasiveness, N = Node involvement, M = Metastases, eg, cT3N1M0.  Each TNM factor has independent prognostic value; N and M are often most important.	Lymph node  N M Blood or lymphatic vessel Spread to other organs and tissues

FAS1\_2019\_04-Pathol.indd 220 11/7/19 4:02 PM

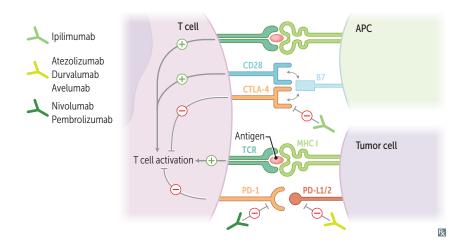
Hallmarks of cancer	Cancer is caused by (mostly acquired) DNA mutations that affect fundamental cellular processes (eg, growth, DNA repair, survival).	
HALLMARK	MECHANISM	
Growth signal self-sufficiency	<ul> <li>Mutations in genes encoding:</li> <li>Proto-oncogenes → ↑ growth factors → autocrine loop (eg, ↑ PDGF in brain tumors)</li> <li>Growth factor receptors → constitutive signalling (eg, HER2/neu in breast cancer)</li> <li>Signaling molecules (eg, RAS)</li> <li>Transcription factors (eg, MYC)</li> <li>Cell cycle regulators (eg, cyclins, CDKs)</li> </ul>	
Anti-growth signal insensitivity	<ul> <li>Mutations in tumor suppressor genes (eg, Rb)</li> <li>Loss of E-cadherin function → loss of contact inhibition (eg, NF2 mutations)</li> </ul>	
<b>Evasion of apoptosis</b>	Mutations in genes that regulate apoptosis (eg, $TP53$ , $BCL2 \rightarrow$ follicular B cell lymphoma).	
Limitless replicative potential	Reactivation of telomerase → maintenance and lengthening of telomeres → prevention of chromosome shortening and cell aging.	
Sustained angiogenesis	↑ pro-angiogenic factors (eg, VEGF) or ↓ inhibitory factors. Factors may be produced by tumor or stromal cells. Vessels can sprout from existing capillaries (neoangiogenesis) or endothelial cells are recruited from bone marrow (vasculogenesis). Vessels may be leaky and/or dilated.	
Tissue invasion	Loss of E-cadherin function → loosening of intercellular junctions → metalloproteinases degrade basement membrane and ECM → cells attach to ECM proteins (eg, laminin, fibronectin) → cells migrate through degraded ECM ("locomotion") → vascular dissemination.	
Metastasis	Tumor cells or emboli spread via lymphatics or blood → adhesion to endothelium → extravasation and homing. Site of metastasis can be predicted by site of 1° tumor, as the target organ is often the first-encountered capillary bed. Some cancers show organ tropism (eg, lung cancers commonly metastasize to adrenals).	
Warburg effect	Shift of glucose metabolism away from mitochondrial oxidative phosphorylation toward glycolysis.	
Immune evasion in cancer	<ul> <li>Normally, immune cells can recognize and attack tumor cells. For successful tumorigenesis, tumor cells must evade the immune system. Multiple escape mechanisms exist:</li> <li>↓ MHC class I expression by tumor cells → cytotoxic T cells are unable to recognize tumor cells.</li> <li>Tumor cells secrete immunosuppressive factors (eg, TGF-β) and recruit regulatory T cells to down regulate immune response.</li> <li>Tumor cells up regulate immune checkpoint molecules, which inhibit immune response.</li> </ul>	

FAS1\_2019\_04-Pathol.indd 221 11/7/19 4:02 PM

### Immune checkpoint interactions

Signals that modulate T cell activation and function → ↓ immune response against tumor cells. Targeted by several cancer immunotherapies. Examples:

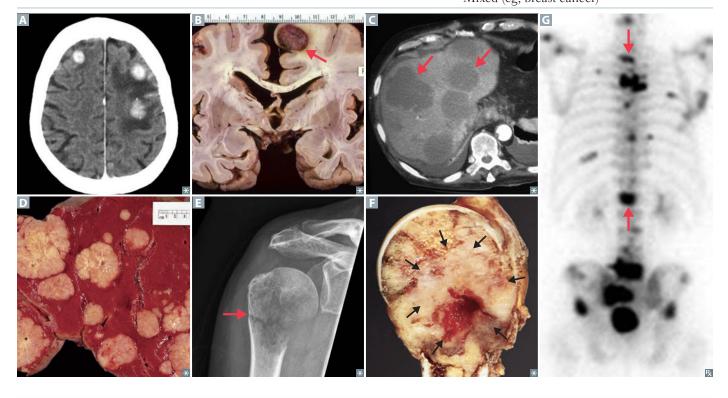
- Interaction between PD-1 (on T cells) and PD-L1/2 (on tumor cells or immune cells in tumor microenvironment) → T cell dysfunction (exhaustion). Inhibited by antibodies against PD-1 (eg, pembrolizumab, nivolumab) or PD-L1 (eg, atezolizumab, durvalumab, avelumab).
- CTLA-4 on T cells outcompetes CD28 for B7 on APCs → loss of T cell costimulatory signal. Inhibited by ipilimumab (anti-CTLA-4 antibody).



Cancer epidemiology	Skin cancer (basal :	> squamous >> meland	oma) is the most commo	on cancer (not included below).
	MEN	WOMEN	CHILDREN (AGE 0-14)	NOTES
Cancer incidence	<ol> <li>Prostate</li> <li>Lung</li> <li>Colon/rectum</li> </ol>	<ol> <li>Breast</li> <li>Lung</li> <li>Colon/rectum</li> </ol>	1. Leukemia 2. CNS 3. Neuroblastoma	Lung cancer incidence has ↓ in men, but has not changed significantly in women.
Cancer mortality	1. Lung 2. Prostate 3. Colon/rectum	<ol> <li>Lung</li> <li>Breast</li> <li>Colon/rectum</li> </ol>	<ol> <li>Leukemia</li> <li>CNS</li> <li>Neuroblastoma</li> </ol>	Cancer is the 2nd leading cause of death in the United States (heart disease is 1st).

FAS1\_2019\_04-Pathol.indd 222 11/7/19 4:02 PM

Common metastases	Most sarcomas spread hematogenously; most carcinomas spread via lymphatics. However Carcinomas Route Hematogenously: Follicular thyroid carcinoma, Choriocarcinoma, carcinoma, and Hepatocellular carcinoma.		
SITE OF METASTASIS	1º TUMOR	NOTES	
Brain	Lung > breast > melanoma, colon, kidney	50% of brain tumors are from metastases A B Commonly seen as multiple well-circumscribed tumors at gray/white matter junction	
Liver	Colon >> Stomach > Pancreas (Cancer Sometimes Penetrates liver)	Liver  and lung are the most common sites of metastasis after the regional lymph nodes	
Bone	Prostate, Breast > Kidney, Thyroid, Lung (Painful Bones Kill The Lungs)	Bone metastasis	



FAS1\_2019\_04-Pathol.indd 223 11/7/19 4:02 PM

	Gain of function mutation converts proto-oncogene (normal gene) to oncogene → Requires damage to only one allele of a proto-oncogene.		
GENE	GENE PRODUCT	ASSOCIATED NEOPLASM	
ALK	Receptor tyrosine Kinase	Lung Adenocarcinoma (Adenocarcinoma of the Lung Kinase)	
BCR-ABL	Non-receptor tyrosine kinase	CML, ALL	
BCL-2	Antiapoptotic molecule (inhibits apoptosis)	Follicular and diffuse large B Cell Lymphomas	
BRAF	Serine/threonine kinase	Melanoma, non-Hodgkin lymphoma, papillary thyroid carcinoma, hairy cell leukemia	
c-KIT	CytoKIne receptor	Gastrointestinal stromal tumor (GIST)	
c-MYC	Transcription factor	Burkitt lymphoma	
HER2/neu (c-erbB2)	Receptor tyrosine kinase	Breast and gastric carcinomas	
JAK2	Tyrosine kinase	Chronic myeloproliferative disorders	
KRAS	GTPase	Colon cancer, lung cancer, pancreatic cancer	
MYCL1	Transcription factor	Lung tumor	
N-myc (MYCN)	Transcription factor	Neuroblastoma	
RET	Receptor tyrosine kinase	MEN 2A and 2B, papillary thyroid carcinoma, pheochromocytoma	
Tumor suppressor	Loss of function → ↑ cancer risk; both (two) allele	es of a tumor suppressor gene must be lost for	
Tumor suppressor genes	Loss of function → † cancer risk; both (two) allele expression of disease.	es of a <b>tu</b> mor suppressor gene must be lost for	
genes GENE	expression of disease.  GENE PRODUCT	ASSOCIATED CONDITION	
genes GENE APC	expression of disease.	ASSOCIATED CONDITION  Colorectal cancer (associated with FAP)	
GENE APC BRCA1/BRCA2	expression of disease.  GENE PRODUCT  Negative regulator of β-catenin/WNT pathway  BRCA1/BRCA2 proteins	ASSOCIATED CONDITION  Colorectal cancer (associated with FAP)  Breast, ovarian, and pancreatic cancers	
genes GENE APC	expression of disease.  GENE PRODUCT  Negative regulator of $\beta$ -catenin/WNT pathway  BRCA1/BRCA2 proteins  pl6, blocks $G_1 \rightarrow S$ phase	ASSOCIATED CONDITION  Colorectal cancer (associated with FAP)  Breast, ovarian, and pancreatic cancers  Melanoma, pancreatic cancer	
GENE APC BRCA1/BRCA2 CDKN2A DCC	expression of disease.  GENE PRODUCT  Negative regulator of $\beta$ -catenin/WNT pathway  BRCA1/BRCA2 proteins  pl6, blocks $G_1 \rightarrow S$ phase  DCC—Deleted in Colon Cancer	ASSOCIATED CONDITION  Colorectal cancer (associated with FAP)  Breast, ovarian, and pancreatic cancers  Melanoma, pancreatic cancer  Colon cancer	
GENE APC BRCA1/BRCA2 CDKN2A	expression of disease.  GENE PRODUCT  Negative regulator of β-catenin/WNT pathway  BRCA1/BRCA2 proteins  pl6, blocks G <sub>1</sub> → S phase  DCC—Deleted in Colon Cancer  DPC—Deleted in Pancreatic Cancer	ASSOCIATED CONDITION  Colorectal cancer (associated with FAP)  Breast, ovarian, and pancreatic cancers  Melanoma, pancreatic cancer  Colon cancer  Pancreatic cancer	
GENE APC BRCA1/BRCA2 CDKN2A DCC	expression of disease.  GENE PRODUCT  Negative regulator of $\beta$ -catenin/WNT pathway  BRCA1/BRCA2 proteins  pl6, blocks $G_1 \rightarrow S$ phase  DCC—Deleted in Colon Cancer	ASSOCIATED CONDITION  Colorectal cancer (associated with FAP)  Breast, ovarian, and pancreatic cancers  Melanoma, pancreatic cancer  Colon cancer	
GENE APC BRCA1/BRCA2 CDKN2A DCC SMAD4 (DPC4)	expression of disease.  GENE PRODUCT  Negative regulator of β-catenin/WNT pathway  BRCA1/BRCA2 proteins  pl6, blocks G <sub>1</sub> → S phase  DCC—Deleted in Colon Cancer  DPC—Deleted in Pancreatic Cancer	ASSOCIATED CONDITION  Colorectal cancer (associated with FAP)  Breast, ovarian, and pancreatic cancers  Melanoma, pancreatic cancer  Colon cancer  Pancreatic cancer	
GENE APC BRCA1/BRCA2 CDKN2A DCC SMAD4 (DPC4) MEN1	expression of disease.  GENE PRODUCT  Negative regulator of β-catenin/WNT pathway  BRCA1/BRCA2 proteins  pl6, blocks G <sub>1</sub> → S phase  DCC—Deleted in Colon Cancer  DPC—Deleted in Pancreatic Cancer  Menin	ASSOCIATED CONDITION  Colorectal cancer (associated with FAP)  Breast, ovarian, and pancreatic cancers  Melanoma, pancreatic cancer  Colon cancer  Pancreatic cancer  Multiple Endocrine Neoplasia type 1	
GENE APC BRCA1/BRCA2 CDKN2A DCC SMAD4 (DPC4) MEN1 NF1	expression of disease.  GENE PRODUCT  Negative regulator of $\beta$ -catenin/WNT pathway  BRCA1/BRCA2 proteins  pl6, blocks $G_1 \rightarrow S$ phase  DCC—Deleted in Colon Cancer  DPC—Deleted in Pancreatic Cancer  Menin  Neurofibromin (Ras GTPase activating protein)	ASSOCIATED CONDITION  Colorectal cancer (associated with FAP)  Breast, ovarian, and pancreatic cancers  Melanoma, pancreatic cancer  Colon cancer  Pancreatic cancer  Multiple Endocrine Neoplasia type 1  Neurofibromatosis type 1	
genes  GENE  APC  BRCA1/BRCA2  CDKN2A  DCC  SMAD4 (DPC4)  MEN1  NF1  NF2  PTEN	expression of disease.  GENE PRODUCT  Negative regulator of β-catenin/WNT pathway  BRCA1/BRCA2 proteins  pl6, blocks G <sub>1</sub> → S phase  DCC—Deleted in Colon Cancer  DPC—Deleted in Pancreatic Cancer  Menin  Neurofibromin (Ras GTPase activating protein)  Merlin (schwannomin) protein	ASSOCIATED CONDITION  Colorectal cancer (associated with FAP)  Breast, ovarian, and pancreatic cancers  Melanoma, pancreatic cancer  Colon cancer  Pancreatic cancer  Multiple Endocrine Neoplasia type 1  Neurofibromatosis type 1  Neurofibromatosis type 2	
GENE APC BRCA1/BRCA2 CDKN2A DCC SMAD4 (DPC4) MEN1 NF1 NF2	expression of disease.  GENE PRODUCT  Negative regulator of β-catenin/WNT pathway  BRCA1/BRCA2 proteins  pl6, blocks G <sub>1</sub> → S phase  DCC—Deleted in Colon Cancer  DPC—Deleted in Pancreatic Cancer  Menin  Neurofibromin (Ras GTPase activating protein)  Merlin (schwannomin) protein  Negative regulator of PI3k/AKT pathway	ASSOCIATED CONDITION  Colorectal cancer (associated with FAP)  Breast, ovarian, and pancreatic cancers  Melanoma, pancreatic cancer  Colon cancer  Pancreatic cancer  Multiple Endocrine Neoplasia type 1  Neurofibromatosis type 1  Neurofibromatosis type 2  Prostate, breasT, and ENdometrial cancers  Retinoblastoma, osteosarcoma (bone cancer)  Most human cancers, Li-Fraumeni syndrome (multiple malignancies at early age, aka, SBLA	
genes  GENE  APC  BRCA1/BRCA2  CDKN2A  DCC  SMAD4 (DPC4)  MEN1  NF1  NF2  PTEN  Rb	expression of disease.  GENE PRODUCT  Negative regulator of β-catenin/WNT pathway  BRCA1/BRCA2 proteins  pl6, blocks G <sub>1</sub> → S phase  DCC—Deleted in Colon Cancer  DPC—Deleted in Pancreatic Cancer  Menin  Neurofibromin (Ras GTPase activating protein)  Merlin (schwannomin) protein  Negative regulator of PI3k/AKT pathway  Inhibits E2F; blocks G <sub>1</sub> → S phase	ASSOCIATED CONDITION  Colorectal cancer (associated with FAP)  Breast, ovarian, and pancreatic cancers  Melanoma, pancreatic cancer  Colon cancer  Pancreatic cancer  Multiple Endocrine Neoplasia type 1  Neurofibromatosis type 1  Neurofibromatosis type 2  Prostate, breasT, and ENdometrial cancers  Retinoblastoma, osteosarcoma (bone cancer)  Most human cancers, Li-Fraumeni syndrome (multiple malignancies at early age, aka, SBLA cancer syndrome: Sarcoma, Breast, Leukemia	
GENE APC BRCA1/BRCA2 CDKN2A DCC SMAD4 (DPC4) MEN1 NF1 NF2 PTEN Rb TP53	expression of disease.  GENE PRODUCT  Negative regulator of β-catenin/WNT pathway BRCA1/BRCA2 proteins pl6, blocks G <sub>1</sub> → S phase  DCC—Deleted in Colon Cancer  DPC—Deleted in Pancreatic Cancer  Menin  Neurofibromin (Ras GTPase activating protein)  Merlin (schwannomin) protein  Negative regulator of PI3k/AKT pathway  Inhibits E2F; blocks G <sub>1</sub> → S phase p53, activates p21, blocks G <sub>1</sub> → S phase	ASSOCIATED CONDITION  Colorectal cancer (associated with FAP)  Breast, ovarian, and pancreatic cancers  Melanoma, pancreatic cancer  Colon cancer  Pancreatic cancer  Multiple Endocrine Neoplasia type 1  Neurofibromatosis type 1  Neurofibromatosis type 2  Prostate, breasT, and ENdometrial cancers  Retinoblastoma, osteosarcoma (bone cancer)  Most human cancers, Li-Fraumeni syndrome (multiple malignancies at early age, aka, SBLA cancer syndrome: Sarcoma, Breast, Leukemia, Adrenal gland)	
genes  GENE  APC  BRCA1/BRCA2  CDKN2A  DCC  SMAD4 (DPC4)  MEN1  NF1  NF2  PTEN  Rb  TP53	expression of disease.  GENE PRODUCT  Negative regulator of β-catenin/WNT pathway  BRCA1/BRCA2 proteins  pl6, blocks G <sub>1</sub> → S phase  DCC—Deleted in Colon Cancer  DPC—Deleted in Pancreatic Cancer  Menin  Neurofibromin (Ras GTPase activating protein)  Merlin (schwannomin) protein  Negative regulator of PI3k/AKT pathway  Inhibits E2F; blocks G <sub>1</sub> → S phase  p53, activates p21, blocks G <sub>1</sub> → S phase	Colorectal cancer (associated with FAP)  Breast, ovarian, and pancreatic cancers  Melanoma, pancreatic cancer  Colon cancer  Pancreatic cancer  Multiple Endocrine Neoplasia type 1  Neurofibromatosis type 1  Neurofibromatosis type 2  Prostate, breasT, and ENdometrial cancers  Retinoblastoma, osteosarcoma (bone cancer)  Most human cancers, Li-Fraumeni syndrome (multiple malignancies at early age, aka, SBLA cancer syndrome: Sarcoma, Breast, Leukemia, Adrenal gland)  Tuberous sclerosis	

FAS1\_2019\_04-Pathol.indd 224 11/7/19 4:02 PM

### PATHOLOGY → PATHOLOGY—NEOPLASIA SECTION II

#### Carcinogens

TOXIN	EXPOSURE	ORGAN	IMPACT
Aflatoxins (Aspergillus)	Stored grains and nuts	Liver	Hepatocellular carcinoma
Alkylating agents	Oncologic chemotherapy	Blood	Leukemia/lymphoma
Aromatic amines (eg, benzidine, 2-naphthylamine)	Textile industry (dyes), cigarette smoke (2-naphthylamine)	Bladder	Transitional cell carcinoma
Arsenic	Herbicides (vineyard workers), metal smelting	Liver Lung Skin	Angiosarcoma Lung cancer Squamous cell carcinoma
Asbestos	Old roofing material, shipyard workers	Lung	Bronchogenic carcinoma > mesothelioma
Cigarette smoke		Bladder Cervix Esophagus	Transitional cell carcinoma Squamous cell carcinoma Squamous cell carcinoma/ adenocarcinoma
		Kidney Larynx Lung	Renal cell carcinoma Squamous cell carcinoma Squamous cell and small cell carcinoma
		Oropharynx Pancreas	Oropharyngeal cancer Pancreatic adenocarcinoma
Ethanol		Esophagus Liver	Squamous cell carcinoma Hepatocellular carcinoma
lonizing radiation		Thyroid	Papillary thyroid carcinoma, leukemias
Nickel, chromium, beryllium, silica	Occupational exposure	Lung	Lung cancer
Nitrosamines	Smoked foods	Stomach	Gastric cancer
Radon	Byproduct of uranium decay, accumulates in basements	Lung	Lung cancer (2nd leading cause after cigarette smoke)
Vinyl chloride	Used to make PVC pipes (plumbers)	Liver	Angiosarcoma

FAS1\_2019\_04-Pathol.indd 225 11/7/19 4:02 PM

#### **Oncogenic microbes**

	Microbe	Associated cancer
	EBV	Burkitt lymphoma, Hodgkin lymphoma, nasopharyngeal carcinoma, 1° CNS lymphoma (in immunocompromised patients)
	HBV, HCV	Hepatocellular carcinoma
	HHV-8	Kaposi sarcoma
	HPV	Cervical and penile/anal carcinoma (types 16, 18), head and neck cancer
	H pylori	Gastric adenocarcinoma and MALT lymphoma
	HTLV-1	Adult <b>T</b> -cell <b>L</b> eukemia/ <b>L</b> ymphoma
	Liver fluke (Clonorchis sinensis)	Cholangiocarcinoma
	Schistosoma haematobium	<b>S</b> quamous cell bladder cancer
Serum tumor markers	Tumor markers should not be used as the 1° tool used to monitor tumor recurrence and response biopsy. Some can be associated with non-neopla IMPORTANT ASSOCIATIONS	to therapy, but definitive diagnosis is made via
Alkaline phosphatase	Metastases to bone or liver, Paget disease of	Exclude hepatic origin by checking LFTs and
Alkalille phospilatase	bone, seminoma (placental ALP).	GGT levels.
α-fetoprotein	Hepatocellular carcinoma, Endodermal sinus (yolk sac) tumor, Mixed germ cell tumor, Ataxia-telangiectasia, Neural tube defects. (HE-MAN is the alpha male!)	Normally made by fetus. Transiently elevated in pregnancy. High levels associated with neural tube and abdominal wall defects, low levels associated with Down syndrome.
hCG	Hydatidiform moles and Choriocarcinomas (Gestational trophoblastic disease), testicular cancer, mixed germ cell tumor.	Produced by syncytiotrophoblasts of the placenta.
CA 15-3/CA 27-29	Breast cancer.	
CA 19-9	Pancreatic adenocarcinoma.	
CA 125	Ovarian cancer.	
Calcitonin	Medullary thyroid carcinoma (alone and in MEN2A, MEN2B).	
CEA	Colorectal and pancreatic cancers. Minor associations: gastric, breast, and medullary thyroid carcinomas.	Carcinoembryonic antigen. Very nonspecific.
Chromogranin	Neuroendocrine tumors.	
LDH	Testicular germ cell tumors, ovarian dysgerminoma, other cancers.	Can be used as an indicator of tumor burden.
Neuron-specific enolase	Neuroendocrine tumors (eg, small cell lung cancer, carcinoid tumor, neuroblastoma)	
PSA	Prostate cancer.	Prostate-specific antigen. Also elevated in BPH

FAS1\_2019\_04-Pathol.indd 226 11/7/19 4:02 PM

# Important immunohistochemical stains

Determine primary site of origin for metastatic tumors and characterize tumors that are difficult to classify. Can have prognostic and predictive value.

STAIN	TARGET	TUMORS IDENTIFIED
Chromogranin and synaptophysin	Neuroendocrine cells	Small cell carcinoma of the lung, carcinoid tumor
Cytokeratin	Epithelial cells	Epithelial tumors (eg, squamous cell carcinoma)
Des <mark>M</mark> in	<b>M</b> uscle	Muscle tumors (eg, rhabdomyosarcoma)
GFAP	NeuroGlia (eg, astrocytes, Schwann cells, oligodendrocytes)	Astrocytoma, Glioblastoma
Neurofilament	Neurons	Neuronal tumors (eg, neuroblastoma)
PSA	Prostatic epithelium	Prostate cancer
S-100	Neural crest cells	Melanoma, schwannoma, Langerhans cell histiocytosis
TRAP	Tartrate-resistant acid phosphatase	Hairy cell leukemia
Vimentin	<b>Me</b> senchymal tissue (eg, fibroblasts, endothelial cells, macrophages)	Mesenchymal tumors (eg, sarcoma), but also many other tumors (eg, endometrial carcinoma, renal cell carcinoma, meningioma)

#### **P-glycoprotein**

Also known as multidrug resistance protein 1 (MDR1). Classically seen in adrenocortical carcinoma but also expressed by other cancer cells (eg, colon, liver). Used to pump out toxins, including chemotherapeutic agents (one mechanism of \$\frac{1}{2}\$ responsiveness or resistance to chemotherapy over time).

#### **Psammoma bodies**

Laminated, concentric spherules with dystrophic calcification A, PSaMMOMa bodies are seen in:



- Somatostatinoma
- Meningioma
- Malignant Mesothelioma
- Ovarian serous papillary cystadenocarcinoma
- Prolactinoma (Milk)

#### Cachexia

Weight loss, muscle atrophy, and fatigue that occur in chronic disease (eg, cancer, AIDS, heart failure, COPD). Mediated by TNF- $\alpha$ , IFN- $\gamma$ , IL-1, and IL-6.

FAS1\_2019\_04-Pathol.indd 227 11/7/19 4:02 PM

#### **Paraneoplastic syndromes**

MANIFESTATION	DESCRIPTION/MECHANISM	MOST COMMONLY ASSOCIATED TUMOR(S)
Musculoskeletal and cuta	aneous	
Dermatomyositis	Progressive proximal muscle weakness, Gottron papules, heliotrope rash	Adenocarcinomas, especially ovarian
Acanthosis nigricans	Hyperpigmented velvety plaques in axilla and neck	Gastric adenocarcinoma and other visceral malignancies
Sign of Leser-Trélat	Sudden onset of multiple seborrheic keratoses	GI adenocarcinomas and other visceral malignancies
Hypertrophic osteoarthropathy	Abnormal proliferation of skin and bone at distal extremities → clubbing, arthralgia, joint effusions, periostosis of tubular bones	Adenocarcinoma of the lung
Endocrine		
Hypercalcemia	PTHrP  1,25-(OH) <sub>2</sub> vitamin D <sub>3</sub> (calcitriol)	Squamous cell carcinomas of lung, head, and neck; renal, bladder, breast, and ovarian carcinomas  Lymphoma
Cushing syndrome	† ACTH	2,111,1101111
Hyponatremia (SIADH)	† ADH	Small cell lung cancer
Hematologic	1711211	
Polycythemia	↑ Erythropoietin	Pheochromocytoma, renal cell carcinoma,
. o.yeyarenna	Paraneoplastic rise to high hematocrit levels	HCC, hemangioblastoma, leiomyoma
Pure red cell aplasia	Anemia with low reticulocytes	
Good syndrome	Hypogammaglobulinemia	Thymoma
Trousseau syndrome	Migratory superficial thrombophlebitis	
Nonbacterial thrombotic (marantic) endocarditis	Deposition of sterile platelet thrombi on heart valves	Adenocarcinomas, especially pancreatic
Neuromuscular		
Anti-NMDA receptor encephalitis	Psychiatric disturbance, memory deficits, seizures, dyskinesias, autonomic instability, language dysfunction	Ovarian teratoma
Opsoclonus- myoclonus ataxia syndrome	"Dancing eyes, dancing feet"	Neuroblastoma (children), small cell lung cancer (adults)
Paraneoplastic cerebellar degeneration	Antibodies against antigens in Purkinje cells	Small cell lung cancer (anti-Hu), gynecologic and breast cancers (anti-Yo), and Hodgkin lymphoma (anti-Tr)
Paraneoplastic encephalomyelitis	Antibodies against Hu antigens in neurons	Small cell lung canaca
Lambert-Eaton myasthenic syndrome	Antibodies against presynaptic (P/Q-type) Ca <sup>2+</sup> channels at NMJ	Small cell lung cancer
Myasthenia gravis	Antibodies against postsynaptic ACh receptors at NMJ	Thymoma

FAS1\_2019\_04-Pathol.indd 228 11/7/19 4:02 PM

### HIGH-YIELD PRINCIPLES IN

## **Pharmacology**

"One pill makes you larger, and one pill makes you small."

-Grace Slick

"I was under medication when I made the decision not to burn the tapes."

—Richard Nixon

"I wondher why ye can always read a doctor's bill an' ye niver can read his purscription."

-Finley Peter Dunne

"One of the first duties of the physician is to educate the masses not to take medicine."

-William Osler

Preparation for pharmacology questions is straightforward. Know all the mechanisms, clinical use, and important adverse effects of key drugs and their major variants. Obscure derivatives are low-yield. Learn their classic and distinguishing toxicities as well as major drug-drug interactions. Reviewing associated biochemistry, physiology, and microbiology concepts can be useful while studying pharmacology. The exam has a strong emphasis on ANS, CNS, antimicrobial, and cardiovascular agents as well as on NSAIDs, which are covered throughout the text. Specific drug dosages or trade names are generally not testable. The exam may use graphs to test various pharmacology content, so make sure you are comfortable interpreting them.

- ▶ Pharmacokinetics and Pharmacodynamics 230
- ▶ Autonomic Drugs 236
- ► Toxicities and Side Effects
- 248
- ► Miscellaneous 253

229

#### ▶ PHARMACOLOGY—PHARMACOKINETICS AND PHARMACODYNAMICS

#### **Enzyme kinetics**

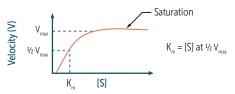
#### Michaelis-Menten kinetics

K<sub>m</sub> is inversely related to the affinity of the enzyme for its substrate.

 $V_{max}$  is directly proportional to the enzyme concentration.

Most enzymatic reactions follow a hyperbolic curve (ie, Michaelis-Menten kinetics); however, enzymatic reactions that exhibit a sigmoid curve usually indicate cooperative kinetics (eg, hemoglobin).

[S] = concentration of substrate; V = velocity.



#### Effects of enzyme inhibition



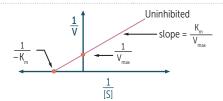
#### Lineweaver-Burk plot

The closer to 0 on the Y-axis, the higher the  $V_{\text{max}}$ .

The closer to 0 on the X-axis, the higher the  $K_m$ . The higher the K<sub>m</sub>, the lower the affinity.

Competitive inhibitors cross each other, whereas **no**ncompetitive inhibitors do **no**t.

Kompetitive inhibitors increase  $K_m$ .



#### Effects of enzyme inhibition



	Competitive inhibitors, reversible	Competitive inhibitors, irreversible	Noncompetitive inhibitors
Resemble substrate	Yes	Yes	No
Overcome by † [S]	Yes	No	No
Bind active site	Yes	Yes	No
Effect on V <sub>max</sub>	Unchanged	Ţ	<b>†</b>
Effect on K <sub>m</sub>	1	Unchanged	Unchanged
Pharmacodynamics	↓ potency	↓ efficacy	↓ efficacy

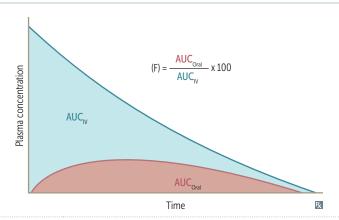
FAS1\_2019\_05-Pharmacology.indd 230 11/7/19 4:08 PM

#### **Pharmacokinetics**

#### Bioavailability (F)

Fraction of administered drug reaching systemic circulation unchanged. For an IV dose, F = 100%.

Orally: F typically < 100% due to incomplete absorption and first-pass metabolism. Can be calculated from the area under the curve in a plot of plasma concentration over time.



### Volume of distribution (V<sub>d</sub>)

Theoretical volume occupied by the total amount of drug in the body relative to its plasma concentration. Apparent  $V_d$  of plasma protein—bound drugs can be altered by liver and kidney disease ( $\downarrow$  protein binding,  $\uparrow$   $V_d$ ). Drugs may distribute in more than one compartment.

$$V_d = \frac{\text{amount of drug in the body}}{\text{plasma drug concentration}}$$

V <sub>d</sub>	COMPARTMENT	DRUG TYPES
Low	Intravascular	Large/charged molecules; plasma protein bound
Medium	ECF	Small hydrophilic molecules
High	All tissues including fat	Small lipophilic molecules, especially if bound to tissue protein

#### Clearance (CL)

The volume of plasma cleared of drug per unit time. Clearance may be impaired with defects in cardiac, hepatic, or renal function.

$$CL = \frac{rate \ of \ elimination \ of \ drug}{plasma \ drug \ concentration} \ = V_d \times \ K_e \ (elimination \ constant)$$

#### Half-life (t<sub>1/2</sub>)

The time required to change the amount of drug in the body by  $\frac{1}{2}$  during elimination.

In first-order kinetics, a drug infused at a constant rate takes 4–5 half-lives to reach steady state. It takes 3.3 half-lives to reach 90% of the steady-state level.

$$t_{1/2} = \frac{0.7 \times V_d}{CL}$$
 in first-order elimination

# of half-lives	1	2	3	4
% remaining	50%	25%	12.5%	6.25%

#### **Dosage calculations**

$$Loading \ dose = \frac{C_p \times V_d}{F}$$

$$Maintenance \; dose = \frac{C_p \times CL \times \tau}{F}$$

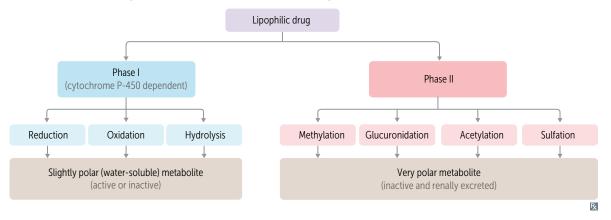
 $C_p$  = target plasma concentration at steady state au = dosage interval (time between doses), if not administered continuously

In renal or liver disease, maintenance dose ↓ and loading dose is usually unchanged.

Time to steady state depends primarily on  $t_{1/2}$  and is independent of dose and dosing frequency.

#### **Drug metabolism**

Geriatric patients lose phase I first. Patients who are slow acetylators have † side effects from certain drugs because of ‡ rate of metabolism (eg, isoniazid).



#### **Elimination of drugs**

### Zero-order elimination

Rate of elimination is constant regardless of  $C_p$  (ie, constant **amount** of drug eliminated per unit time).  $C_p \downarrow$  linearly with time. Examples of drugs—Phenytoin, Ethanol, and Aspirin (at high or toxic concentrations).

Capacity-limited elimination.

PEA (a pea is round, shaped like the "0" in

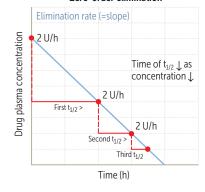
**PEA** (a pea is round, shaped like the "0" is zero-order).

#### First-order elimination

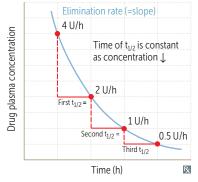
Rate of First-order elimination is directly proportional to the drug concentration (ie, constant Fraction of drug eliminated per unit time).  $C_p \downarrow$  exponentially with time. Applies to most drugs.

Flow-dependent elimination.

#### Zero-order elimination



#### First-order elimination

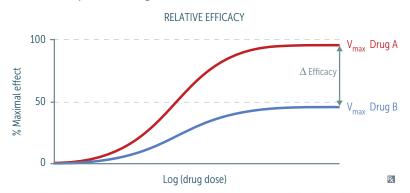


Urine pH and drug elimination	Ionized species are trapped in urine and cleared quickly. Neutral forms can be reabsorbed.		
Weak acids	Examples: phenobarbital, methotrexate, aspirin (salicylates). Trapped in basic environments. Treat overdose with sodium bicarbonate to alkalinize urine.		
	$\begin{array}{ccc} RCOOH & \rightleftharpoons & RCOO^- + H^+ \\ \text{(lipid soluble)} & & \text{(trapped)} \end{array}$		
Weak bases	Examples: TCAs, amphetamines. Trapped in acidic environments. Treat overdose with ammonium chloride to acidify urine.		
	$RNH_3^+ \rightleftharpoons RNH_2 + H^+$		
	(trapped) (lipid soluble)		
	TCA toxicity is generally treated with sodium bicarbonate to overcome the sodium channel-blocking activity of TCAs, but not for accelerating drug elimination.		
рКа	pH at which drugs (weak acid or base) are 50% ionized and 50% nonionized. The pKa represent the strength of the weak acid or base.		

#### **Efficacy vs potency**

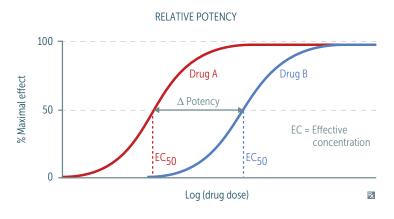
#### **Efficacy**

Maximal effect a drug can produce. Represented by the y-value  $(V_{max})$ . † y-value = †  $V_{max}$  = † efficacy. Unrelated to potency (ie, efficacious drugs can have high or low potency). Partial agonists have less efficacy than full agonists.



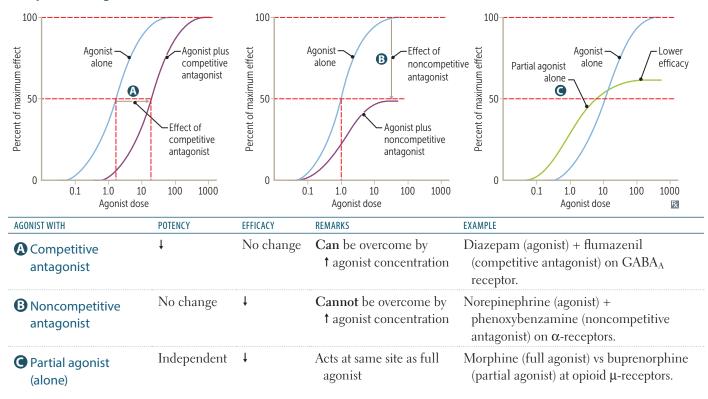
#### **Potency**

Amount of drug needed for a given effect. Represented by the x-value (EC<sub>50</sub>). Left shifting =  $\downarrow$  EC<sub>50</sub> =  $\uparrow$  potency =  $\downarrow$  drug needed. Unrelated to efficacy (ie, potent drugs can have high or low efficacy).



FAS1\_2019\_05-Pharmacology.indd 233

#### **Receptor binding**



#### Therapeutic index

Measurement of drug safety.

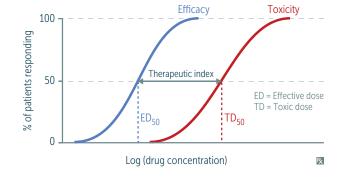
 $\frac{\text{TD}_{50}}{\text{ED}_{50}} = \frac{\text{median toxic dose}}{\text{median effective dose}}$ 

Therapeutic window—dosage range that can safely and effectively treat disease.

TITE: Therapeutic Index = TD<sub>50</sub> / ED<sub>50</sub>.

Safer drugs have higher TI values. Drugs with lower TI values frequently require monitoring (eg, Warfarin, Theophylline, Digoxin, Antiepileptic drugs, Lithium; Warning! These Drugs Are Lethal!).

 $LD_{50}$  (lethal median dose) often replaces  $TD_{50}$  in animal studies.



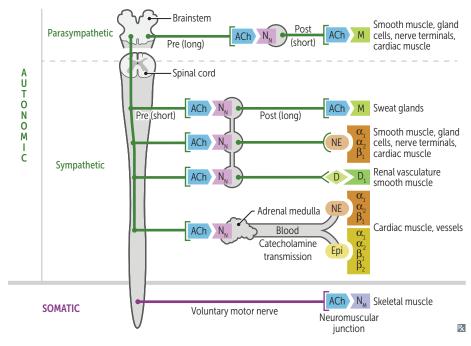
#### **Types of drug interactions**

TERM	DEFINITION	EXAMPLE
Additive	Effect of substances A and B together is equal to the sum of their individual effects	Aspirin and acetaminophen $2 + 2 = 4$ "
Permissive	Presence of substance A is required for the full effects of substance B	Cortisol on catecholamine responsiveness
Synergistic	Effect of substances A and B together is greater than the sum of their individual effects	Clopidogrel with aspirin "2 + 2 > 4"
Potentiation	Similar to synergism, but drug B with no therapeutic action enhances the therapeutic action of drug A	Carbidopa only blocks enzyme to prevent peripheral conversion of levodopa " $2 + 0 > 2$ "
Antagonistic	Effect of substances A and B together is less than the sum of their individual effects	Ethanol antidote for methanol toxicity " $2 + 2 < 4$ "
Tachyphylactic	Acute decrease in response to a drug after initial/repeated administration	Nitrates, niacin, phenylephrine, LSD, MDMA

FAS1\_2019\_05-Pharmacology.indd 235 11/7/19 4:08 PM

#### ▶ PHARMACOLOGY—AUTONOMIC DRUGS

#### **Autonomic receptors**



Pelvic splanchnic nerves and CNs III, VII, IX and X are part of the parasympathetic nervous system. Adrenal medulla is directly innervated by preganglionic sympathetic fibers.

Sweat glands are part of the sympathetic pathway but are innervated by cholinergic fibers (sympathetic nervous system results in a "chold" sweat).

### Acetylcholine receptors

Nicotinic ACh receptors are ligand-gated  $Na^+/K^+$  channels. Two subtypes:  $N_N$  (found in autonomic ganglia, adrenal medulla) and  $N_M$  (found in neuromuscular junction of skeletal muscle). Muscarinic ACh receptors are G-protein–coupled receptors that usually act through 2nd messengers. 5 subtypes:  $M_{1-5}$  found in heart, smooth muscle, brain, exocrine glands, and on sweat glands (cholinergic sympathetic).

FAS1\_2019\_05-Pharmacology.indd 236 11/7/19 4:08 PM

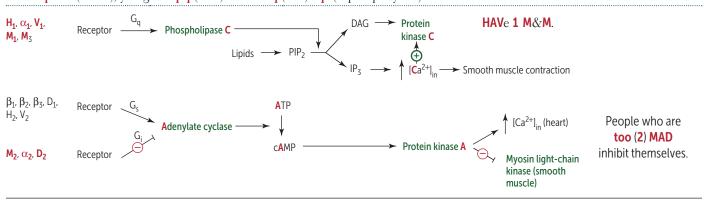
Micturition control	Micturition center in pons regulates involuntary bladder function via coordination of sympathetic and parasympathetic nervous systems.  ■ ⊕ sympathetic → ↑ urinary retention  ■ ⊕ parasympathetic → ↑ urine voiding. Some autonomic drugs act on smooth muscle receptors to treat bladder dysfunction.	Pelvic nerve (parasympathetic input)  Hypogastric nerve (sympathetic input)  Pudendal nerve (somatic input)  Pudendal nerve (somatic input)  Nicotinic receptor
DRUGS	MECHANISM	USE
Muscarinic antagonists (eg, oxybutynin)	⊕ M <sub>3</sub> receptor → relaxation of detrusor smooth muscle → ↓ detrusor overactivity	Urgency incontinence
Muscarinic agonists (eg, bethanechol)	<ul> <li>⊕ M<sub>3</sub> receptor → contraction of detrusor smooth muscle → ↑ bladder emptying</li> </ul>	Urinary retention
<b>2</b> Sympathomimetics (eg, mirabegron)	⊕ β₃ receptor → relaxation of detrusor smooth muscle → ↑ bladder capacity	Urgency incontinence
<b>3</b> α <sub>1</sub> -blockers (eg, tamsulosin)		ВРН

FAS1\_2019\_05-Pharmacology.indd 237 11/7/19 4:08 PM

#### **G-protein-linked second messengers**

RECEPTOR	G-PROTEIN CLASS	MAJOR FUNCTIONS
Adrenergic		
$\alpha_1$	q	↑ vascular smooth muscle contraction, ↑ pupillary dilator muscle contraction (mydriasis), ↑ intestinal and bladder sphincter muscle contraction
$lpha_2$	i	↓ sympathetic (adrenergic) outflow, ↓ insulin release, ↓ lipolysis, ↑ platelet aggregation, ↓ aqueous humor production
$\beta_1$	S	↑ heart rate, ↑ contractility (one heart), ↑ renin release, ↑ lipolysis
$\beta_2$	S	Vasodilation, bronchodilation (two lungs), ↑ lipolysis, ↑ insulin release, ↑ glycogenolysis, ↓ uterine tone (tocolysis), ↑ aqueous humor production, ↑ cellular K <sup>+</sup> uptake
β <sub>3</sub>	S	↑ lipolysis, ↑ thermogenesis in skeletal muscle, ↑ bladder relaxation
Cholinergic		
$M_1$	q	Mediates higher cognitive functions, stimulates enteric nervous system
M <sub>2</sub>	i	↓ heart rate and contractility of atria
M <sub>3</sub>	q	† exocrine gland secretions (eg, lacrimal, sweat, salivary, gastric acid), † gut peristalsis, † bladder contraction, bronchoconstriction, † pupillary sphincter muscle contraction (miosis), ciliary muscle contraction (accommodation), † insulin release, endothelium-mediated vasodilation
Dopamine		
D <sub>1</sub>	S	Relaxes renal vascular smooth muscle, activates direct pathway of striatum
D <sub>2</sub>	i	Modulates transmitter release, especially in brain, inhibits indirect pathway of striatum
Histamine		
H <sub>1</sub>	q	↑ nasal and bronchial mucus production, ↑ vascular permeability, bronchoconstriction, pruritus, pain
H <sub>2</sub>	S	↑ gastric acid secretion
Vasopressin		
$V_1$	q	↑ vascular smooth muscle contraction
V <sub>2</sub>	S	↑ H <sub>2</sub> O permeability and reabsorption via upregulating aquaporin-2 in collecting twobules (tubules) of kidney, ↑ release of vWF

"After qisses (kisses), you get a qiq (kick) out of siq (sick) sqs (super qinky sex)."



FAS1\_2019\_05-Pharmacology.indd 238 11/7/19 4:08 PM

#### **Autonomic drugs**

Release of norepinephrine from a sympathetic nerve ending is modulated by NE itself, acting on presynaptic α<sub>2</sub>-autoreceptors → negative feedback.

Amphetamines use the NE transporter (NET) to enter the presynaptic terminal, where they utilize the vesicular monoamine transporter (VMAT) to enter neurosecretory vesicles. This displaces NE from the vesicles. Once NE reaches a concentration threshold within the presynaptic terminal, the action of NET is reversed, and NE is expelled into the synaptic cleft, contributing to the characteristics and effects of † NE observed in patients taking amphetamines.

#### **CHOLINERGIC NORADRENERGIC AXON AXON Tyrosine** Choline Tyrosine Choline+ DOPA Acetyl-CoA Dopamine ChAT **VMAT** Reserpine Release-modulating ACh 📷 receptors II TA Amphetamine, ephedrine Reuptake Botulinum Negative feedback Cocaine, TCAs, Choline + amphetamine NE 🔾 acetate Diffusion, metabolism ACh receptor **AChE** inhibitors **AChE** Adrenore ceptors $\alpha$ or $\beta$ POSTSYNAPTIC MEMBRANE **POSTSYNAPTIC MEMBRANE** Ŗ

represents transporters.

FAS1\_2019\_05-Pharmacology.indd 239 11/7/19 4:08 PM

ACTION	APPLICATIONS
Activates bladder smooth muscle; resistant to AChE. No nicotinic activity. "Bethany, call me to activate your bladder."	Urinary retention.
Carbon copy of acetylcholine (but resistant to AChE).	Constricts pupil and relieves intraocular pressure in open-angle glaucoma.
Stimulates muscarinic receptors in airway when Challenge test for diagnosis of a inhaled.	
Contracts ciliary muscle of eye (open-angle glaucoma), pupillary sphincter (closed-angle glaucoma); resistant to AChE, can cross bloodbrain barrier (tertiary amine). "You cry, drool, and sweat on your 'pilow."	
cholinesterases)	
† ACh.	lst line for Alzheimer disease ( <b>Dona Riva</b> dances at the <b>gala</b> ).
↑ ACh.	Historically used to diagnose myasthenia gravis; replaced by anti-AChR Ab (anti-acetylcholine receptor antibody) test.
† ACh.  Neo CNS = No CNS penetration (quaternary amine).	Postoperative and neurogenic ileus and urinary retention, myasthenia gravis, reversal of neuromuscular junction blockade (postoperative).
† ACh. Phreely (freely) crosses blood-brain barrier → CNS (tertiary amine).	Antidote for anticholinergic toxicity; physostigmine "phyxes" atropine overdose.
† ACh; † muscle strength. Used with glycopyrrolate, hyoscyamine, or propantheline to control pyridostigmine side effects.  Pyridostigmine gets rid of myasthenia gravis.	Myasthenia gravis (long acting); does not penetrate CNS (quaternary amine).
Often due to organophosphates (eg, parathion) that irreversibly inhibit AChE. Organophosphates commonly used as insecticides; poisoning usually seen in farmers.	
Diarrhea, Urination, Miosis, Bronchospasm, Bradycardia, Emesis, Lacrimation, Sweating, Salivation.	DUMBBELSS. Reversed by atropine, a competitive inhibitor. Atropine can cross BBB to relieve CNS symptoms.
Neuromuscular blockade (mechanism similar to succinylcholine).	Reversed by pralidoxime, regenerates AChE via dephosphorylation if given early.  Pralidoxime (quaternary amine) does not readily cross BBB.
	Activates bladder smooth muscle; resistant to AChE. No nicotinic activity. "Bethany, call me to activate your bladder."  Carbon copy of acetylcholine (but resistant to AChE).  Stimulates muscarinic receptors in airway when inhaled.  Contracts ciliary muscle of eye (open-angle glaucoma), pupillary sphincter (closed-angle glaucoma), resistant to AChE, can cross blood- brain barrier (tertiary amine). "You cry, drool, and sweat on your 'pilow.'"  cholinesterases)  † ACh.  ACh.  Neo CNS = No CNS penetration (quaternary amine).  † ACh. Phreely (freely) crosses blood-brain barrier → CNS (tertiary amine).  † ACh; † muscle strength. Used with glycopyrrolate, hyoscyamine, or propantheline to control pyridostigmine side effects. Pyridostigmine gets rid of myasthenia gravis.  Often due to organophosphates (eg, parathion) tha commonly used as insecticides; poisoning usually Diarrhea, Urination, Miosis, Bronchospasm, Bradycardia, Emesis, Lacrimation, Sweating, Salivation.

FAS1\_2019\_05-Pharmacology.indd 240 11/7/19 4:08 PM

#### **Muscarinic antagonists**

DRUGS	ORGAN SYSTEMS	APPLICATIONS	
Atropine, homatropine, tropicamide	Eye	Produce mydriasis and cycloplegia.	
Benztropine, trihexyphenidyl	CNS	Parkinson disease ("park my Benz"). Acute dystonia.	
Glycopyrrolate	GI, respiratory	Parenteral: preoperative use to reduce airway secretions. Oral: drooling, peptic ulcer.	
Hyoscyamine, dicyclomine	GI	Antispasmodics for irritable bowel syndrome.	
Ipratropium, tiotropium	Respiratory	COPD, asthma ("I pray I can breathe soon!").	
Oxybutynin, solifenacin, tolterodine	Genitourinary	Reduce bladder spasms and urge urinary incontinence (overactive bladder).	
Scopolamine	CNS	Motion sickness.	
Atropine	Muscarinic antagonist. Used to treat bradycardia	and for ophthalmic applications.	
ORGAN SYSTEM	ACTION NOTES		
Eye	↑ pupil dilation, cycloplegia	Blocks muscarinic effects (DUMBBELSS)	
Airway	Bronchodilation, ↓ secretions	of anticholinesterases, but not the nicotinic	
Stomach		effects.	
Stolliacii	↓ acid secretion	епестя.	
Gut	↓ acid secretion ↓ motility	effects.	
		effects.	

FAS1\_2019\_05-Pharmacology.indd 241 11/7/19 4:08 PM

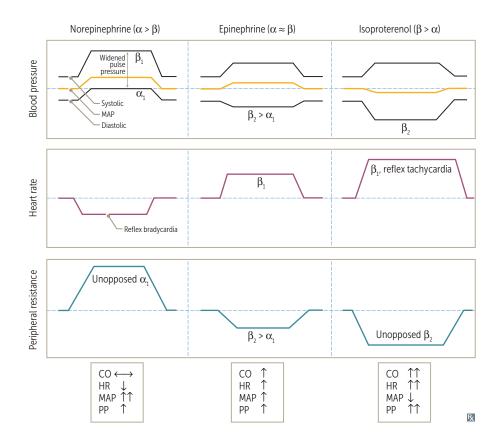
#### **Sympathomimetics**

DRUG	ACTION	HEMODYNAMIC CHANGES	APPLICATIONS
Direct sympathomimeti	CS		
Albuterol, salmeterol, terbutaline	$\beta_2 > \beta_1$	† HR (little effect)	Albuterol for Acute asthma/COPD. Salmeterol for Serial (long-term) asthma/COPD.  Terbutaline for acute bronchospasm in asthma and tocolysis.
Dobutamine	$\beta_1 > \beta_2,  \alpha$	↔/↓ BP, ↑ HR, ↑ CO	Heart failure (HF), cardiogenic shock (inotropic > chronotropic), cardiac stress testing.
Dopamine	$D_1 = D_2 > \beta > \alpha$	† BP (high dose), † HR, † CO	Unstable bradycardia, HF, shock; inotropic and chronotropic effects at lower doses due to $\beta$ effects; vasoconstriction at high doses due to $\alpha$ effects.
Epinephrine	$\beta > \alpha$	† BP (high dose), † HR, † CO	Anaphylaxis, asthma, open-angle glaucoma; α effects predominate at high doses. Significantly stronger effect at β <sub>2</sub> -receptor than norepinephrine.
Fenoldopam	$D_1$	<ul><li>♣ BP (vasodilation), ↑ HR,</li><li>↑ CO</li></ul>	Postoperative hypertension, hypertensive crisis. Vasodilator (coronary, peripheral, renal, and splanchnic). Promotes natriuresis. Can cause hypotension and tachycardia.
Isoproterenol	$\beta_1 = \beta_2$	<ul><li>↓ BP (vasodilation), ↑ HR,</li><li>↑ CO</li></ul>	Electrophysiologic evaluation of tachyarrhythmias. Can worsen ischemia. Has negligible α effect.
Midodrine	$lpha_{ m l}$	↑ BP (vasoconstriction), ↓ HR, ↔/↓ CO	Autonomic insufficiency and postural hypotension. May exacerbate supine hypertension.
Mirabegron	β <sub>3</sub>		Urinary urgency or incontinence or overactive bladder. Think "mirab3gron."
Norepinephrine	$\alpha_1>\alpha_2>\beta_1$	† BP, † HR, ↔/† CO	Hypotension, septic shock.
Phenylephrine	$\alpha_1 > \alpha_2$	† BP (vasoconstriction), ↓ HR, ↔/↓ CO	Hypotension (vasoconstrictor), ocular procedures (mydriatic), rhinitis (decongestant), ischemic priapism.
Indirect sympathomime	tics		
Amphetamine	Indirect general agonist, reuptake inhibitor, also releases stored catecholamines		Narcolepsy, obesity, ADHD.
Cocaine	Indirect general agonist, reuptake inhibitor		Causes vasoconstriction and local anesthesia. Caution when giving β-blockers if cocaine intoxication is suspected (can lead to unopposed α₁ activation → extreme hypertension, coronary vasospasm).
Ephedrine	Indirect general a catecholamines	gonist, releases stored	Nasal decongestion (pseudoephedrine), urinary incontinence, hypotension.

FAS1\_2019\_05-Pharmacology.indd 242 11/7/19 4:08 PM

### Norepinephrine vs isoproterenol

NE  $\uparrow$  systolic and diastolic pressures as a result of  $\alpha_1$ -mediated vasoconstriction  $\rightarrow \uparrow$  mean arterial pressure  $\rightarrow$  reflex bradycardia. However, isoproterenol (rarely used) has little  $\alpha$  effect but causes  $\beta_2$ -mediated vasodilation, resulting in  $\downarrow$  mean arterial pressure and  $\uparrow$  heart rate through  $\beta_1$  and reflex activity.



#### Sympatholytics (α<sub>2</sub>-agonists)

DRUG	APPLICATIONS	ADVERSE EFFECTS	
Clonidine, guanfacine	Hypertensive urgency (limited situations), ADHD, Tourette syndrome, symptom control in opioid withdrawal	CNS depression, bradycardia, hypotension, respiratory depression, miosis, rebound hypertension with abrupt cessation	
<b>α</b> -methyldopa	Hypertension in pregnancy	Direct Coombs ⊕ hemolysis, drug-induced lupus, hyperprolactinemia	
Tizanidine	Relief of spasticity	Hypotension, weakness, xerostomia	

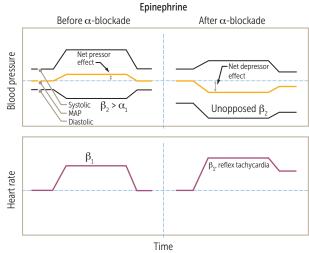
FAS1\_2019\_05-Pharmacology.indd 243 11/7/19 4:08 PM

#### α-blockers

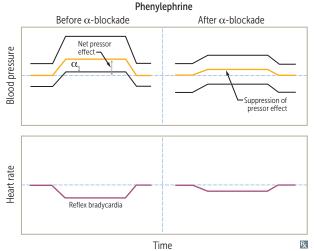
DRUG	APPLICATIONS	ADVERSE EFFECTS	
Nonselective			
Phenoxybenzamine	Irreversible. Pheochromocytoma (used preoperatively) to prevent catecholamine (hypertensive) crisis		
Phentolamine	Reversible. Given to patients on MAO inhibitors who eat tyramine-containing foods and for severe cocaine-induced hypertension (2nd line)	Orthostatic hypotension, reflex tachycardia	
$\alpha_1$ selective (-osin endir	ng)		
Prazosin, terazosin, doxazosin, tamsulosin	Urinary symptoms of BPH; PTSD (prazosin); hypertension (except tamsulosin)	lst-dose orthostatic hypotension, dizziness, headache	
$\alpha_2$ selective			
Mirtazapine	Depression	Sedation 1 serum cholesterol 1 appetite	

#### Mirtazapine Depression





Epinephrine response exhibits reversal of mean arterial pressure from a net increase (the  $\alpha$  response) to a net decrease (the  $\beta_2$  response).



Phenylephrine response is suppressed but not reversed because it is a "pure"  $\alpha$ -agonist (lacks  $\beta$ -agonist properties).

FAS1\_2019\_05-Pharmacology.indd 244 11/7/19 4:08 PM

β-blockers	Acebutolol, atenolol, betaxolol, bisoprolol, carvedilol, esmolol, labetalol, metoprolol, nadolol, nebivolol, pindolol, propranolol, timolol.		
APPLICATION	ACTIONS	NOTES/EXAMPLES	
Angina pectoris	↓ heart rate and contractility → ↓ O <sub>2</sub> consumption		
Glaucoma	↓ production of aqueous humor	Timolol	
Heart failure	↓ mortality	Bisoprolol, Carvedilol, Metoprolol (β-blockers Curb Mortality)	
Hypertension	↓ cardiac output, ↓ renin secretion (due to β₁- receptor blockade on JG cells)		
Hyperthyroidism/ thyroid storm	Symptom control (↓ heart rate, ↓ tremor)	Propranolol	
Hypertrophic cardiomyopathy	↓ heart rate → ↑ filling time, relieving obstruction		
Myocardial infarction	↓ O <sub>2</sub> demand (short-term), ↓ mortality (long-term)		
Supraventricular tachycardia	↓ AV conduction velocity (class II antiarrhythmic)	Metoprolol, esmolol	
Variceal bleeding	↓ hepatic venous pressure gradient and portal hypertension (prophylactic use)	Nadolol, propranolol, carvedilol	
ADVERSE EFFECTS	Erectile dysfunction, cardiovascular (bradycardia, AV block, HF), CNS (seizures, sleep alterations), dyslipidemia (metoprolol), and asthma/COPD exacerbations	Use of β-blockers for acute cocaine-associated chest pain remains controversial due to unsubstantiated concern for unopposed α-adrenergic stimulation	
SELECTIVITY	$\beta_1$ -selective antagonists ( $\beta_1 > \beta_2$ )—acebutolol (partial agonist), atenolol, betaxolol, bisoprolol, esmolol, metoprolol	Selective antagonists mostly go from $A$ to $M$ ( $\beta_l$ with $lst$ half of alphabet)	
	Nonselective antagonists $(\beta_1 = \beta_2)$ —nadolol, pindolol (partial agonist), propranolol, timolol	NonZelective antagonists mostly go from $N$ to $Z$ ( $\beta_2$ with 2nd half of alphabet)	
	Nonselective $\alpha$ - and $\beta$ -antagonists—carvedilol, labetalol	Nonselective $\alpha$ - and $\beta$ -antagonists have modified suffixes (instead of "-olol")	
	Nebivolol combines cardiac-selective β <sub>1</sub> -adrenergic blockade with stimulation of β <sub>3</sub> -receptors (activate nitric oxide synthase in the vasculature and ↓ SVR)	Nebivolol increases NO	

11/7/19 4:08 PM FAS1\_2019\_05-Pharmacology.indd 245

# Phosphodiesterase inhibitors

Phosphodiesterase (PDE) inhibitors inhibit PDE, which catalyzes the hydrolysis of cAMP and/or cGMP, and thereby increase cAMP and/or cGMP. These inhibitors have varying specificity for PDE isoforms and thus have different clinical uses.

TYPE OF INHIBITOR	MECHANISM OF ACTION	CLINICAL USES	ADVERSE EFFECTS
Nonspecific PDE inhibitor Theophylline	↓ cAMP hydrolysis → ↑ cAMP     → bronchial smooth muscle     relaxation → bronchodilation	COPD/asthma (rarely used)	Cardiotoxicity (eg, tachycardia, arrhythmia), neurotoxicity (eg, headache), abdominal pain
PDE-5 inhibitors Sildenafil, vardenafil, tadalafil, avanafil	<ul> <li>I hydrolysis of cGMP</li> <li>→ ↑ cGMP → ↑ smooth muscle relaxation by enhancing NO activity</li> <li>→ pulmonary vasodilation and ↑ blood flow in corpus cavernosum fills the penis</li> </ul>	Erectile dysfunction Pulmonary hypertension BPH (tadalafil only)	Facial flushing, headache, dyspepsia, hypotension in patients taking nitrates; "Hot and sweaty," then Headache, Heartburn, Hypotension Sildenafil only: cyanopia (bluetinted vision) via inhibition of PDE-6 in retina
PDE-4 inhibitor Roflumilast	† cAMP in neutrophils, granulocytes, and bronchial epithelium	Severe COPD	Abdominal pain, weight loss, mental disorders (eg, depression)
PDE-3 inhibitor Milrinone	In cardiomyocytes:  ↑ cAMP → ↑ Ca <sup>2+</sup> influx  → ↑ ionotropy and chronotropy In vascular smooth muscle:  ↑ cAMP → MLCK inhibition  → vasodilation → ↓ preload and afterload	Acute decompensated HF with cardiogenic shock	Tachycardia, ventricular arrhythmias (thus not for chronic use), hypotension
<b>"Platelet inhibitors"</b> Cilostazol <sup>a</sup> Dipyridamole <sup>b</sup>	In platelets: ↑ cAMP  → inhibition of platelet aggregation	Intermittent claudication Stroke or TIA prevention (with aspirin) Cardiac stress testing (dipyridamole only, due to coronary vasodilation) Prevention of coronary stent restenosis	Nausea, headache, facial flushing, hypotension, abdominal pain

<sup>&</sup>lt;sup>a</sup>Cilostazol is a PDE-3 inhibitor, but due to its indications is categorized as a platelet inhibitor together with dipyridamole.

FAS1\_2019\_05-Pharmacology.indd 246 11/7/19 4:08 PM

<sup>&</sup>lt;sup>b</sup>Dipyridamole is a nonspecific PDE inhibitor, leading to inhibition of platelet aggregation. It also prevents adenosine reuptake by platelets → ↑ extracellular adenosine → ↑ vasodilation.

# Ingested seafood toxins

Toxin actions include **H**istamine release, **T**otal block of Na<sup>+</sup> channels, or opening of Na<sup>+</sup> channels to Cause depolarization.

TOXIN	SOURCE	ACTION	SYMPTOMS	TREATMENT
Histamine (scombroid poisoning)	Spoiled dark-meat fish such as tuna, mahi- mahi, mackerel, and bonito	Bacterial histidine decarboxylase converts histidine to histamine Frequently misdiagnosed as fish allergy	Mimics anaphylaxis: acute burning sensation of mouth, flushing of face, erythema, urticaria, itching May progress to bronchospasm, angioedema, hypotension	Antihistamines Albuterol and epinephrine if needed
Tetrodotoxin	Pufferfish	Highly potent toxin; binds fast voltage-gated Na <sup>+</sup> channels in nerve tissue, preventing depolarization	Nausea, diarrhea, paresthesias, weakness, dizziness, loss of reflexes	Supportive
Ciguatoxin	Reef fish such as barracuda, snapper, and moray eel	Opens Na <sup>+</sup> channels, causing depolarization	Nausea, vomiting, diarrhea; perioral numbness; reversal of hot and cold sensations; bradycardia, heart block, hypotension	Supportive

#### **Beers criteria**

Widely used criteria developed to reduce potentially inappropriate prescribing and harmful polypharmacy in the geriatric population. Includes > 50 medications that should be avoided in elderly patients due to \$\ddot\$ efficacy and/or \$\ddot\$ risk of adverse events. Examples:

- α-blockers († risk of hypotension)
- Anticholinergics, antidepressants, antihistamines, opioids († risk of delirium, sedation, falls, constipation, urinary retention)
- Benzodiazepines († risk of delirium, sedation, falls)
- NSAIDs († risk of GI bleeding, especially with concomitant anticoagulation)
- PPIs († risk of *C difficile* infection)

FAS1\_2019\_05-Pharmacology.indd 247 11/7/19 4:08 PM

# ► PHARMACOLOGY—TOXICITIES AND SIDE EFFECTS

# Specific toxicity treatments

TOXIN	TREATMENT
Acetaminophen	N-acetylcysteine (replenishes glutathione)
AChE inhibitors, organophosphates	Atropine > pralidoxime
Antimuscarinic, anticholinergic agents	Physostigmine (crosses BBB), control hyperthermia
Arsenic	Dimercaprol, succimer
Benzodiazepines	Flumazenil
β-blockers	Atropine, glucagon, saline
Carbon monoxide	100% O <sub>2</sub> , hyperbaric O <sub>2</sub>
Copper	"Penny" cillamine (penicillamine), trientine (copper penny × 3)
Cyanide	Hydroxocobalamin, nitrites + sodium thiosulfate
Digitalis (digoxin)	Digoxin-specific antibody fragments
Heparin	Protamine sulfate
Iron ( <b>Fe</b> )	Deferoxamine, deferasirox, deferiprone
Lead	Calcium disodium EDTA, dimercaprol, succimer, penicillamine
<b>Mer</b> cury	Dimercaprol, succimer
Methanol, ethylene glycol (antifreeze)	Fomepizole > ethanol, dialysis
<b>Meth</b> emoglobin	Methylene blue, vitamin C (reducing agent)
<b>O</b> pi <b>O</b> ids	Nal <mark>OxO</mark> ne
Salicylates	NaHCO3 (alkalinize urine), dialysis
TCAs	NaHCO3 (stabilizes cardiac cell membrane)
Warfarin	Vitamin K (delayed effect), PCC (prothrombin complex concentrate)/FFP (immediate effect)

#### Drug reactions—cardiovascular

DRUG REACTION	CAUSAL AGENTS	
Coronary vasospasm	Cocaine, Amphetamines, Sumatriptan, Ergot alkaloids (CASE)	
Cutaneous <mark>flush</mark> ing	Vancomycin, Adenosine, Niacin, Ca <sup>2+</sup> channel blockers, Echinocandins, Nitrates (flushed from VANCEN [dancing])	
	Red man syndrome—rate-dependent infusion reaction to vancomycin causing widespread prurition erythema due to histamine release. Manage with diphenhydramine, slower infusion rate.	
Dilated cardiomyopathy	Anthracyclines (eg, Doxorubicin, Daunorubicin); prevent with Dexrazoxane	
Torsades de pointes	Agents that prolong QT interval: antiArrhythmics (class IA, III), antiBiotics (eg, macrolides), anti"C"ychotics (eg, ziprasidone), antiDepressants (eg, TCAs), antiEmetics (eg, ondansetron) (ABCDE)	

FAS1\_2019\_05-Pharmacology.indd 248 11/7/19 4:08 PM

# Drug reactions—endocrine/reproductive

DRUG REACTION	CAUSAL AGENTS	NOTES
Adrenocortical insufficiency	HPA suppression 2° to glucocorticoid withdrawal	
Diabetes insipidus	Lithium, demeclocycline	
Hot flashes	SERMs (eg, tamoxifen, clomiphene, raloxifene)	
Hyperglycemia	Tacrolimus, Protease inhibitors, Niacin, HCTZ, Corticosteroids	The People Need Hard Candies
Hyperprolactinemia	Typical antipsychotics (eg, haloperidol), atypical antipsychotics (eg, risperidone), metoclopramide, methyldopa, reserpine	Presents with hypogonadism (eg, infertility, amenorrhea, erectile dysfunction) and galactorrhea
Hyperthyroidism	Amiodarone, iodine	
Hypothyroidism	AMiodarone, SUlfonamides, Lithium	I <mark>AM SU</mark> ddenly <mark>L</mark> ethargic
SIADH	Carbamazepine, Cyclophosphamide, SSRIs	Can't Concentrate Serum Sodium

# **Drug reactions—gastrointestinal**

DRUG REACTION	CAUSAL AGENTS	NOTES
Acute cholestatic hepatitis, jaundice	Macrolides (eg, erythromycin)	
Diarrhea	Acamprosate, antidiabetic agents (acarbose, metformin, pramlintide), colchicine, cholinesterase inhibitors, lipid-lowering agents (eg, ezetimibe, orlistat), macrolides (eg, erythromycin), SSRIs, chemotherapy (eg, irinotecan)	
Focal to massive hepatic necrosis	Halothane, <i>Amanita phalloides</i> (death cap mushroom), Valproic acid, <i>Ac</i> etaminophen	Liver "HAVAc"
Hepatitis	Rifampin, isoniazid, pyrazinamide, statins, fibrates	
Pancreatitis	Didanosine, Corticosteroids, Alcohol, Valproic acid, Azathioprine, Diuretics (eg, furosemide, HCTZ)	Drugs Causing A Violent Abdominal Distress
Pill-induced esophagitis	Bisphosphonates, ferrous sulfate, NSAIDs, potassium chloride, tetracyclines	Caustic effect minimized with upright posture and adequate water ingestion
Pseudomembranous colitis	Ampicillin, cephalosporins, clindamycin, fluoroquinolones, PPIs	Antibiotics predispose to superinfection by resistant <i>C difficile</i>

FAS1\_2019\_05-Pharmacology.indd 249 11/7/19 4:08 PM

# **Drug reactions—hematologic**

DRUG REACTION	CAUSAL AGENTS	NOTES
Agranulocytosis	Dapsone, Clozapine, Carbamazepine, Propylthiouracil, Methimazole, Colchicine, Ganciclovir	Drugs Can Cause Pretty Major Collapse of Granulocytes
Aplastic anemia	Carbamazepine, Methimazole, NSAIDs, Benzene, Chloramphenicol, Propylthiouracil	Can't Make New Blood Cells Properly
Direct Coombs ⊕ hemolytic anemia	Penicillin, methylDopa, Cephalosporins	P Diddy Coombs
Drug reaction with eosinophilia and systemic symptoms (DRESS)	Allopurinol, anticonvulsants, antibiotics, sulfa drugs	Potentially fatal delayed hypersensitivity reaction. Latency period (2- 8 weeks), then fever, morbilliform skin rash, frequent multiorgan involvement. Treatment: withdrawal of offending drug, corticosteroids
Gray baby syndrome	Chloramphenicol	
Hemolysis in G6PD deficiency	Isoniazid, Sulfonamides, Dapsone, Primaquine, Aspirin, Ibuprofen, Nitrofurantoin	Hemolysis <mark>IS D PAIN</mark>
Megaloblastic anemia	Hydrox <b>yur</b> ea, <b>P</b> henytoin, <b>M</b> ethotrexate, <b>S</b> ulfa drugs	You're having a mega blast with PMS
Thrombocytopenia	Heparin, vancomycin, linezolid, quinidine, indinavir, ganciclovir, abciximab	
Thrombotic complications	Combined oral contraceptives, hormone replacement therapy, SERMs (eg, tamoxifen)	Estrogen-mediated side effect

#### Drug reactions—musculoskeletal/skin/connective tissue

DRUG REACTION	CAUSAL AGENTS	NOTES
Drug-induced <mark>lupus</mark>	Methyldopa, Minocycline, Hydralazine, Isoniazid, Phenytoin, Sulfa drugs, Etanercept, Procainamide	Lupus Makes My HIPS Extremely Painful
Fat redistribution	Protease inhibitors, Glucocorticoids	Fat PiG
Gingival hyperplasia	Cyclosporine, Ca <sup>2+</sup> channel blockers, Phenytoin	Can Cause Puffy gums
Hyperuricemia (gout)	Pyrazinamide, Thiazides, Furosemide, Niacin, Cyclosporine	Painful Tophi and Feet Need Care
Myopathy	Statins, fibrates, niacin, colchicine, daptomycin, hydroxychloroquine, interferon-α, penicillamine, glucocorticoids	
Osteoporosis	Corticosteroids, depot medroxyprogesterone acetate, GnRH agonists, aromatase inhibitors, anticonvulsants, heparin, PPIs	
Photosensitivity	Sulfonamides, Amiodarone, Tetracyclines, 5-FU	SAT For Photo
Rash ( <mark>Stevens-Johnson</mark> syndrome)	Anti-epileptic drugs (especially lamotrigine), allopurinol, sulfa drugs, penicillin	Steven Johnson has epileptic allergy to sulfadrugs and penicillin
Teeth discoloration	<b>Tet</b> racyclines	Teethracyclines
Tendon/cartilage damage	Fluoroquinolones	

FAS1\_2019\_05-Pharmacology.indd 250 11/7/19 4:08 PM

# **Drug reactions—neurologic**

DRUG REACTION	CAUSAL AGENTS	NOTES
Cinchonism	Quinidine, quinine	Can present with tinnitus, hearing/vision loss, psychosis, and cognitive impairment
Parkinson-like syndrome	Antipsychotics, Reserpine, Metoclopramide	Cogwheel rigidity of <b>ARM</b>
Peripheral neuropathy	Isoniazid, phenytoin, platinum agents (eg, cisplatin), vincristine	
Idiopathic intracranial hypertension	Growth hormones, tetracyclines, vitamin A	
Seizures	Isoniazid, Bupropion, Imipenem/cilastatin, Tramadol, Enflurane	With seizures, I BITE my tongue
Tardive dyskinesia	Antipsychotics, metoclopramide	
Visual disturbance	Topiramate (blurred vision/diplopia, haloes), Digoxin (yellow-tinged vision), Isoniazid (optic neuritis), Vigabatrin (bilateral visual field defects), PDE-5 inhibitors (blue-tinged vision), Ethambutol (color vision changes)	These Drugs Irritate Very Precious Eyes

## **Drug reactions—renal/genitourinary**

DRUG REACTION	CAUSAL AGENTS	NOTES
Fanconi syndrome	Cisplatin, ifosfamide, expired tetracyclines, tenofovir	
Hemorrhagic cystitis	Cyclophosphamide, ifosfamide	Prevent by coadministering with mesna
Interstitial nephritis	Diuretics (Pee), NSAIDs (Pain-free), Penicillins and cephalosporins, PPIs, rifamPin, and sulfa drugs	Remember the <b>5 P</b> 's

# **Drug reactions—respiratory**

DRUG REACTION	CAUSAL AGENTS	NOTES
Dry cough	ACE inhibitors	
Pulmonary fibrosis	Methotrexate, Nitrofurantoin, Carmustine, Bleomycin, Busulfan, Amiodarone	My Nose Cannot Breathe Bad Air

## **Drug reactions—multiorgan**

DRUG REACTION	CAUSAL AGENTS	NOTES
Antimuscarinic	Atropine, TCAs, H <sub>1</sub> -blockers, antipsychotics	
Disulfiram-like reaction	lst-generation Sulfonylureas, Procarbazine, certain Cephalosporins, Griseofulvin, Metronidazole	Sorry Pals, Can't Go Mingle
Nephrotoxicity/ ototoxicity	Loop diuretics, Aminoglycosides, cisPlatin, Vancomycin, amphoTERicin B	Listen And Pee Very TERriBly Cisplatin toxicity may respond to amifostine

FAS1\_2019\_05-Pharmacology.indd 251 11/7/19 4:08 PM

## **Drugs affecting pupil size**

† pupil size	↓ pupil size
Anticholinergics (eg, atropine, TCAs, tropicamide, scopolamine, antihistamines)	Sympatholytics (eg, $\alpha_2$ -agonists)
Drugs of abuse (eg, amphetamines, cocaine, LSD), meperidine	Drugs of abuse (eg, heroin/opioids)
Sympathomimetics	Parasympathomimetics (eg, pilocarpine), organophosphates

## **Cytochrome P-450 interactions (selected)**

Inducers (+)	Substrates	Inhibitors (-)
<b>Mo</b> dafinil	Warfarin	Sodium valproate
Chronic alcohol use	Anti-epileptics	<b>I</b> soniazid
St. John's wort	<b>The</b> ophylline	Cimetidine
Phenytoin	OCPs	Ketoconazole
Phenobarbital Phenobarbital		<b>F</b> luconazole
<b>Nev</b> irapine		Acute alcohol abuse
<b>R</b> ifampin		Chloramphenicol
Griseofulvin		Erythromycin/clarithromycin
Carbamazepine		Sulfonamides
		Ciprofloxacin
		Omeprazole
		<b>M</b> etronidazole
		<b>Am</b> iodarone
		Ritonavir
		Grapefruit juice
Most chronic alcoholics	War Against The OCPs	SICKFACES.COM (when
Steal Phen-Phen and Never	<u> </u>	I <b>Am R</b> eally drinking
Refuse Greasy Carbs		Grapefruit juice)

# Sulfa drugs

Sulfonamide antibiotics, Sulfasalazine, Probenecid, Furosemide, Acetazolamide, Celecoxib, Thiazides, Sulfonylureas.
Patients with sulfa allergies may develop fever, urinary tract infection, Stevens-Johnson syndrome, hemolytic anemia, thrombocytopenia, agranulocytosis, acute interstitial nephritis, and urticaria (hives).

Scary Sulfa Pharm FACTS

FAS1\_2019\_05-Pharmacology.indd 252 11/7/19 4:08 PM

# ▶ PHARMACOLOGY—MISCELLANEOUS

ENDING	CATEGORY	EXAMPLE
Antimicrobial		
-bendazole	Antiparasitic/antihelminthic	Mebendazole
-cillin	Transpeptidase inhibitor	Ampicillin
-conazole	Ergosterol synthesis inhibitor	Ketoconazole
-cycline	Protein synthesis inhibitor	Tetracycline
-ivir	Neuraminidase inhibitor	Oseltamivir
-navir	Protease inhibitor	Ritonavir
-ovir	Viral DNA polymerase inhibitor	Acyclovir
tegravir	Integrase inhibitor	Elvitegravir, raltegravir
thromycin	Macrolide antibiotic	Azithromycin
CNS		
-apine, -idone	Atypical antipsychotic	Quetiapine, risperidone
-azine	Typical antipsychotic	Thioridazine
barbital	Barbiturate	Phenobarbital
ipramine, -triptyline	TCA	Imipramine, amitriptyline
triptan	5-HT <sub>1B/1D</sub> agonist	Sumatriptan
zepam, -zolam	Benzodiazepine	Diazepam, alprazolam
Autonomic		
chol	Cholinergic agonist	Bethanechol, carbachol
olol	β-blocker	Propranolol
stigmine	AChE inhibitor	Neostigmine
terol	β2-agonist	Albuterol
zosin	α <sub>1</sub> -blocker	Prazosin
Cardiovascular		
afil	PDE-5 inhibitor	Sildenafil
dipine	Dihydropyridine Ca <sup>2+</sup> channel blocker	Amlodipine
pril	ACE inhibitor	Captopril
sartan	Angiotensin-II receptor blocker	Losartan
xaban	Direct factor <mark>Xa</mark> inhibitor	Api <mark>xa</mark> ban, edo <mark>xa</mark> ban, rivaro <b>xa</b> ban
Metabolic		
gliflozin	SGLT-2 inhibitor	Dapagliflozin, canagliflozin
-glinide	Meglitinide	Repaglinide, nateglinide
-gliptin	DPP-4 inhibitor	Sitagliptin
-glitazone	PPAR-γ activator	Rosiglitazone
-glutide	GLP-1 analog	Liraglutide, albiglutide

11/7/19 4:08 PM FAS1\_2019\_05-Pharmacology.indd 253

254 SECTION II

# PHARMACOLOGY → PHARMACOLOGY—MISCELLANEOUS

# **Drug names** (continued)

ENDING	CATEGORY	EXAMPLE
Other		
-dronate	Bisphosphonate	Alendronate
-prazole	Proton pump inhibitor	Omeprazole
-prost	Prostaglandin analog	Latanoprost
-sentan	Endothelin receptor antagonist	Bosentan
-tidine	H <sub>2</sub> -antagonist	Cimetidine
-vaptan	ADH antagonist	Tolvaptan

# **Biologic agents**

ENDING	CATEGORY	EXAMPLE
Monoclonal ant	ibodies (-mab)—target overexpressed cell surface rece	ptors
-ximab	Chimeric human-mouse monoclonal antibody	Rituximab
-zumab	Humanized mouse monoclonal antibody	Bevacizumab
-umab	Human monoclonal antibody	Denosumab
Small molecule	inhibitors (-ib)—target intracellular molecules	
-tinib	Tyrosine kinase inhibitor	Imatinib
-zomib	Proteasome inhibitor	Bortezomib
-ciclib	Cyclin-dependent kinase inhibitor	Palbociclib
Receptor fusion	proteins (-cept)	
-cept	TNF- $\alpha$ antagonist	Etanercept
Interleukin rece	ptor modulators (-kin)—agonists and antagonists of inf	terleukin receptors
-leukin	IL-2 agonist/analog	Aldesleukin
-kinra	Interleukin receptor antagonist	Anakinra

FAS1\_2019\_05-Pharmacology.indd 254 11/7/19 4:08 PM

# HIGH-YIELD PRINCIPLES IN

# **Public Health Sciences**

"Medicine is a science of uncertainty and an art of probability."

-William Osler

"There are two kinds of statistics: the kind you look up and the kind you make up."

-Rex Stout

"On a long enough timeline, the survival rate for everyone drops to zero."

—Chuck Palahniuk

"There are three kinds of lies: lies, damned lies, and statistics."

-Mark Twain

A heterogenous mix of epidemiology, biostatistics, ethics, law, healthcare delivery, patient safety, quality improvement, and more falls under the heading of public health sciences. Biostatistics and epidemiology are the foundations of evidence-based medicine and are very high yield. Make sure you can quickly apply biostatistical equations such as sensitivity, specificity, and predictive values in a problem-solving format. Also, know how to set up your own 2 × 2 tables. Quality improvement and patient safety topics were introduced a few years ago on the exam and represent trends in health system science. Medical ethics questions often require application of principles. Typically, you are presented with a patient scenario and then asked how you would respond.

► Epidemiology and Biostatistics 256

▶ Ethics 265

▶ The Well Patient 270

▶ Healthcare Delivery 270

▶ Quality and Safety 273

255

FAS1\_2019\_06-PubHealth.indd 255 11/7/19 4:16 PM

Observational studies STUDY TYPE	DESIGN	MEASURES/EXAMPLE
Cross-sectional study	Frequency of disease and frequency of risk-related factors are assessed in the present. Asks, "What is happening?"	Disease prevalence. Can show risk factor association with disease, bu does not establish causality.
Case-control study	Compares a group of people with disease to a group without disease.  Looks to see if odds of prior exposure or risk factor differ by disease state.  Asks, "What happened?"	Odds ratio (OR). Patients with COPD had higher odds of a smoking history than those without COPD.
Cohort study	Compares a group with a given exposure or risk factor to a group without such exposure.  Looks to see if exposure or risk factor is associated with later development of disease.  Can be prospective or retrospective.	Relative risk (RR).  Smokers had a higher risk of developing COPD than nonsmokers.  Cohort = relative risk.
Crossover study	Compares the effect of a series of ≥2 treatments on a participant.  Order in which participants receive treatments is randomized. Washout period occurs between each treatment.	Allows participants to serve as their own controls.
Twin concordance study	Compares the frequency with which both monozygotic twins vs both dizygotic twins develop the same disease.	Measures heritability and influence of environmental factors ("nature vs nurture").
Adoption study	Compares siblings raised by biological vs adoptive parents.	Measures heritability and influence of environmental factors.
Clinical trial	Experimental study involving humans. Compare treatment and placebo. Study quality improves blinded (ie, neither patient nor doctor knows will group). Triple-blind refers to the additional blin Four phases ("Does the drug SWIM?").	when study is randomized, controlled, and double- hether the patient is in the treatment or control
DRUG TRIALS	TYPICAL STUDY SAMPLE	PURPOSE
Phase I	Small number of either healthy volunteers or patients with disease of interest.	"Is it Safe?" Assesses safety, toxicity, pharmacokinetics, and pharmacodynamics.
Phase II	Moderate number of patients with disease of interest.	"Does it Work?" Assesses treatment efficacy, optimal dosing, and adverse effects.
Phase III	Large number of patients randomly assigned either to the treatment under investigation or to the standard of care (or placebo).	"Is it as good or better?" Compares the new treatment to the current standard of care (any Improvement?).
Phase IV	Postmarketing surveillance of patients after treatment is approved.	"Can it stay?" Detects rare or long-term adverse effects (eg, black box warnings). Can result in treatment being withdrawn from Market.

FAS1\_2019\_06-PubHealth.indd 256 11/7/19 4:16 PM

#### Sensitivity and specificity are fixed properties Disease **Evaluation of (+)** $\Theta$ of a test. PPV and NPV vary depending on diagnostic tests PPV disease prevalence in population being tested. TP FP = TP/(TP + FP) NPV $\Theta$ FN TN = TN/(TN + FN) Prevalence TP + FN (TP + FN + FP + TN) Specificity Sensitivity =TN/(TN + FP Proportion of all people with disease who test = TP / (TP + FN)Sensitivity (truepositive rate) positive, or the probability that when the = 1 - FN rate disease is present, the test is positive. **SN-N-OUT** = highly **SeN**sitive test, when Value approaching 100% is desirable for ruling Negative, rules **OUT** disease out disease and indicates a low false-negative High sensitivity test used for screening rate. Specificity (true-Proportion of all people without disease who = TN / (TN + FP)negative rate) test negative, or the probability that when the = 1 - FP rate disease is absent, the test is negative. **SP-P-IN** = highly **SP**ecific test, when **P**ositive, Value approaching 100% is desirable for ruling rules IN disease in disease and indicates a low false-positive High specificity test used for confirmation after a positive screening test rate Positive predictive Probability that a person who has a positive test PPV = TP / (TP + FP)PPV varies directly with pretest probability result actually has the disease. value (baseline risk, such as prevalence of disease): high pretest probability → high PPV NPV = TN / (TN + FN)**Negative predictive** Probability that a person with a negative test value result actually does not have the disease. NPV varies inversely with prevalence or pretest probability Possible cutoff values for (+) vs (-) test result Disease Disease A = 100% sensitivity cutoff value Number of people absent present **B** = practical compromise between specificity and sensitivity = 100% specificity cutoff value ΤP TN Lowering the cutoff value: ↑ Sensitivity ↑ NPV $\mathbf{B} \rightarrow \mathbf{A} (\uparrow \mathsf{FP} \downarrow \mathsf{FN})$ ↓ Specificity ↓ PPV FN ↑ Specificity ↑ PPV Raising the cutoff value: В $\mathbf{B} \rightarrow \mathbf{C} (\uparrow \mathsf{FN} \downarrow \mathsf{FP})$ ↓ Sensitivity ↓ NPV Test results $LR^{+} = \frac{sensitivity}{1 - specificity}$ Likelihood ratio Likelihood that a given test result would be TP rate expected in a patient with the target disorder compared to the likelihood that the same result would be expected in a patient without the $LR^{-} = \frac{1 - sensitivity}{specificity} = \frac{FN \text{ rate}}{TN \text{ rate}}$ target disorder. LR<sup>+</sup> > 10 indicates a highly specific test, while LR<sup>-</sup> < 0.1 indicates a highly sensitive test. LRs can be multiplied with pretest odds of

FAS1\_2019\_06-PubHealth.indd 257 11/7/19 4:16 PM

disease to estimate posttest odds.

# **Quantifying risk**

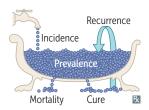
Definitions and formulas are based on the classic  $2 \times 2$  or contingency table.

Ξ.	Disease or	outcome
Exposure intervention (	a	b
or inter	С	d

TERM	DEFINITION	EXAMPLE	FORMULA
Odds ratio	Typically used in case-control studies. Represents the odds of exposure among cases (a/c) vs odds of exposure among controls (b/d).	If in a case-control study, 20/30 lung cancer patients and 5/25 healthy individuals report smoking, the OR is 8; so the lung cancer patients are 8 times more likely to have a history of smoking.	$OR = \frac{a/c}{b/d} = \frac{ad}{bc}$ $\begin{vmatrix} a & b & 5 \\ c & d & 20 \end{vmatrix}$
Relative risk	Typically used in cohort studies.  Risk of developing disease in the exposed group divided by risk in the unexposed group.  RR = 1 → no association between exposure and disease.  RR > 1 → exposure associated with ↑ disease occurrence.  RR < 1 → exposure associated with ↓ disease occurrence.	If 5/10 people exposed to radiation are diagnosed with cancer, and 1/10 people not exposed to radiation are diagnosed with cancer, the RR is 5; so people exposed to radiation have a 5 times greater risk of developing cancer.  For rare diseases (low prevalence), OR approximates RR.	$RR = \frac{a/(a+b)}{c/(c+d)}$ $\begin{bmatrix} a & b & \\ & 5 & & 5 \\ c & & d & \\ & 1 & & 9 \end{bmatrix}$
Relative risk reduction	The proportion of risk reduction attributable to the intervention as compared to a control.	If 2% of patients who receive a flu shot develop the flu, while 8% of unvaccinated patients develop the flu, then RR = 2/8 = 0.25, and RRR = 0.75.	RRR = 1 – RR
Attributable risk	The difference in risk between exposed and unexposed groups.	If risk of lung cancer in smokers is 21% and risk in nonsmokers is 1%, then the attributable risk is 20%.	$AR = \frac{a}{a+b} - \frac{c}{c+d}$ $AR\% = \frac{RR-1}{RR} \times 100$
Absolute risk reduction	The difference in risk (not the proportion) attributable to the intervention as compared to a control.	If 8% of people who receive a placebo vaccine develop the flu vs 2% of people who receive a flu vaccine, then ARR = $8\%-2\% = 6\% = 0.06$ .	$ARR = \frac{c}{c+d} - \frac{a}{a+b}$
Number needed to treat	Number of patients who need to be treated for 1 patient to benefit.  Lower number = better treatment.		NNT = 1/ARR
Number needed to harm	Number of patients who need to be exposed to a risk factor for 1 patient to be harmed. Higher number = safer exposure.		NNH = 1/ <b>AR</b>
Case fatality rate	Percentage of deaths occurring among those with disease.	If 4 patients die among 10 cases of meningitis, case fatality rate is 40%.	$CFR\% = \frac{\text{deaths}}{\text{cases}} \times 100$

FAS1\_2019\_06-PubHealth.indd 258 11/7/19 4:16 PM

## **Incidence vs** prevalence



# of new cases # of people at risk Incidence =

(per unit of time)

# of existing cases
Total # of people (at a point in Prevalence = time) in a population

Prevalence looks at all current cases.

Incidence looks at new cases (incidents).

= Incidence rate × average duration Prevalence 1 – prevalence

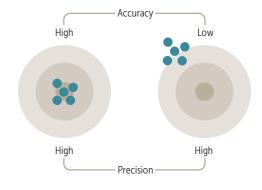
Prevalence ≈ incidence for short duration disease Prevalence ~ pretest probability. ↑ prevalence → ↑ PPV and ↓ NPV. (eg, common cold).

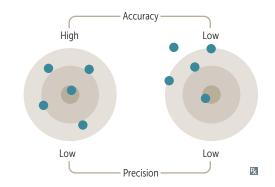
Prevalence > incidence for chronic diseases, due to large # of existing cases (eg, diabetes).

SITUATION	INCIDENCE	PREVALENCE
† survival time	_	†
† mortality	_	ţ
Faster recovery time	_	ţ
Extensive vaccine administration	ţ	ţ
↓ risk factors	ţ	<b>↓</b>

#### **Precision vs accuracy**

, , , , , , , , , , , , , , , , , , , ,		
Precision (reliability)	The consistency and reproducibility of a test.  The absence of random variation in a test.	Random error ↓ precision in a test.  ↑ precision → ↓ standard deviation.  ↑ precision → ↑ statistical power (1 – β).
Accuracy (validity)	The closeness of test results to the true values. The absence of systematic error or bias in a test.	Systematic error ↓ accuracy in a test.



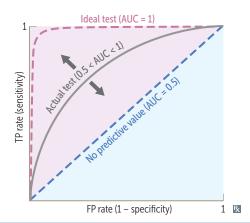


FAS1\_2019\_06-PubHealth.indd 259 11/7/19 4:16 PM

# Receiving operating characteristic curve

ROC curve demonstrates how well a diagnostic test can distinguish between 2 groups (eg, disease vs healthy). Plots the true-positive rate (sensitivity) against the false-positive rate (1 – specificity).

The better performing test will have a higher area under the curve (AUC), with the curve closer to the upper left corner.



## **Bias and study errors**

ТҮРЕ	DEFINITION	EXAMPLES	STRATEGIES TO REDUCE BIAS
Recruiting participants			
Selection bias	Nonrandom sampling or treatment allocation of subjects such that study population is not representative of target population.  Most commonly a sampling bias.	Berkson bias—cases and/ or controls selected from hospitals are less healthy and have different exposures than general population Attrition bias—participants lost to follow up have a different prognosis than those who complete the study	Randomization Ensure the choice of the right comparison/reference group
Performing study			
Recall bias	Awareness of disorder alters recall by subjects; common in retrospective studies	Patients with disease recall exposure after learning of similar cases	Decrease time from exposure to follow-up
Measurement bias	Information is gathered in a systemically distorted manner	Using a faulty automatic sphygmomanometer to measure BP  Hawthorne effect—participants change behavior upon awareness of being observed	Use objective, standardized, and previously tested methods of data collection that are planned ahead of time Use placebo group
Procedure bias	Subjects in different groups are not treated the same	Patients in treatment group spend more time in highly specialized hospital units	Blinding (masking) and use of placebo reduce influence of participants and
Observer-expectancy bias	Researcher's belief in the efficacy of a treatment changes the outcome of that treatment (aka, Pygmalion effect)	An observer expecting treatment group to show signs of recovery is more likely to document positive outcomes	researchers on procedures and interpretation of outcomes as neither are aware of group assignments

FAS1\_2019\_06-PubHealth.indd 260 11/7/19 4:16 PM

# Bias and study errors (continued)

ТҮРЕ	DEFINITION	EXAMPLES	STRATEGY TO REDUCE BIAS
Interpreting results			
Confounding bias	Factor related to both exposure and outcome (but not on causal path) distorts effect of exposure on outcome (vs effect modification, in which the exposure leads to different outcomes in subgroups stratified by the factor)	An uncontrolled study shows an association between drinking coffee and lung cancer. However, coffee drinkers also smoke more, which can account for the association	Multiple/repeated studies Crossover studies (subjects act as their own controls) Matching (patients with similar characteristics in both treatment and control groups)
Lead-time bias	Early detection is confused with † survival	Early detection makes it seem like survival has increased, but the disease's natural history has not changed	Measure "back-end" survival (adjust survival according to the severity of disease at the time of diagnosis)
Length-time bias	Screening test detects diseases with long latency period, while those with shorter latency period become symptomatic earlier	A slowly progressive cancer is more likely detected by a screening test than a rapidly progressive cancer	A randomized controlled trial assigning subjects to the screening program or to no screening

11/7/19 4:16 PM FAS1\_2019\_06-PubHealth.indd 261

Measures of central	Mean = (sum of values)/(total number of values).	Most affected by outliers (extreme values).		
tendency	Median = middle value of a list of data sorted from least to greatest.	If there is an even number of values, the median will be the average of the middle two values.		
	Mode = most common value.	Least affected by outliers.		
Measures of dispersion	Standard deviation = how much variability exists in a set of values, around the mean of these values.  Standard error = an estimate of how much variability exists in a (theoretical) set of sample means around the true population mean.	$\sigma = SD$ ; $n = sample size$ . Variance = $(SD)^2$ . $SE = \sigma/\sqrt{n}$ . $SE \downarrow as n \uparrow$ .		
Normal distribution	Gaussian, also called bell-shaped.  Mean = median = mode.	-3σ -2σ +3σ +3σ +3σ 99.7%		
Nonnormal distribution	ons			
Bimodal	Suggests two different populations (eg, metabolic polymorphism such as fast vs slow acetylators; age at onset of Hodgkin lymphoma; suicide rate by age).			
Positive skew	Typically, mean > median > mode. Asymmetry with longer tail on right.	Mode Median Mean		
Negative skew	Typically, mean < median < mode. Asymmetry with longer tail on left.	Median Mode  Mean		
Statistical hypotheses				
Null (H <sub>0</sub> )	Hypothesis of no difference or relationship (eg, there is no association between the disease and the risk factor in the population).			
Alternative (H <sub>1</sub> )	Hypothesis of some difference or relationship (eg, there is some association between the disease and the risk factor in the population).			

11/7/19 4:16 PM FAS1\_2019\_06-PubHealth.indd 262

## **Outcomes of statistical hypothesis testing**

#### **Correct result**

Stating that there is an effect or difference when one exists (null hypothesis rejected in favor of alternative hypothesis).

Stating that there is no effect or difference when none exists (null hypothesis not rejected).

#### **Incorrect result**

#### Type I error ( $\alpha$ )

Stating that there is an effect or difference when none exists (null hypothesis incorrectly rejected in favor of alternative hypothesis).

 $\alpha$  is the probability of making a type I error. p is judged against a preset  $\alpha$  level of significance (usually 0.05). If p < 0.05 for a study outcome, the probability of obtaining that result purely by chance is < 5%.

Statistical significance ≠ clinical significance.

Also called false-positive error.

 $\alpha$  = you accused an innocent man.

You can never "prove" the alternate hypothesis, but you can reject the null hypothesis as being very unlikely.

#### Type II error (β)

Stating that there is not an effect or difference when one exists (null hypothesis is not rejected when it is in fact false).

 $\beta$  is the probability of making a type II error.  $\beta$  is related to statistical power  $(1-\beta)$ , which is the probability of rejecting the null hypothesis when it is false.

↑ power and  $\downarrow$   $\beta$  by:

- † sample size
- † expected effect size
- † precision of measurement

Also called false-negative error.

β = you blindly let the guilty man go free.
 If you † sample size, you † power. There is power in numbers.

#### **Confidence interval**

Range of values within which the true mean of the population is expected to fall, with a specified probability.

CI for sample mean =  $\bar{x} \pm Z(SE)$ 

The 95% CI (corresponding to  $\alpha = .05$ ) is often used. As sample size increases, CI narrows.

For the 95% CI, Z = 1.96.

For the 99% CI, Z = 2.58.

If the 95% CI for a mean difference between 2 variables includes 0, then there is no significant difference and  $H_0$  is not rejected.

If the 95% CI for odds ratio or relative risk includes 1,  $H_0$  is not rejected.

If the CIs between 2 groups do not overlap

→ statistically significant difference exists.

If the CIs between 2 groups overlap → usually no significant difference exists.

FAS1\_2019\_06-PubHealth.indd 263 11/7/19 4:16 PM

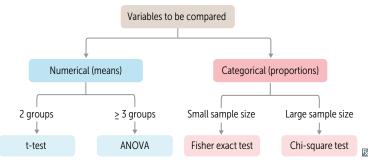
#### **Meta-analysis**

A method of statistical analysis that pools summary data (eg, means, RRs) from multiple studies for a more precise estimate of the size of an effect. Also estimates heterogeneity of effect sizes between studies.

Improves power, strength of evidence, and generalizability of study findings. Limited by quality of individual studies and bias in study selection.

#### **Common statistical tests**

<i>t</i> -test	Checks differences between means of 2 groups.	Tea is meant for 2. Example: comparing the mean blood pressure between men and women.
ANOVA	Checks differences between means of 3 or more groups.	3 words: ANalysis Of VAriance. Example: comparing the mean blood pressure between members of 3 different ethnic groups.
Chi-square (χ²)	Checks differences between 2 or more percentages or proportions of categorical outcomes (not mean values).	Pronounce Chi-tegorical.  Example: comparing the percentage of members of 3 different ethnic groups who have essential hypertension.
Fisher's exact test	Checks differences between 2 percentages or proportions of categorical, nominal outcomes. Use instead of chi-square test with small populations.	Example: comparing the percentage of 20 men and 20 women with hypertension.



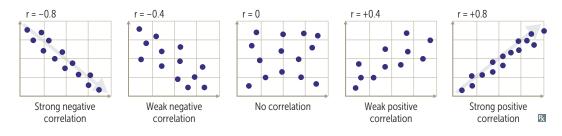
# Pearson correlation coefficient

*r* is always between -1 and +1. The closer the absolute value of *r* is to 1, the stronger the linear correlation between the 2 variables. Variance is how much the measured values differ from the average value in a data set.

Positive *r* value  $\rightarrow$  positive correlation (as one variable  $\uparrow$ ), the other variable  $\uparrow$ ).

Negative *r* value  $\rightarrow$  negative correlation (as one variable †, the other variable ‡).

Coefficient of determination =  $r^2$  (amount of variance in one variable that can be explained by variance in another variable).



FAS1\_2019\_06-PubHealth.indd 264 11/7/19 4:16 PM

#### ▶ PUBLIC HEALTH SCIENCES—ETHICS Core ethical principles **Autonomy** Obligation to respect patients as individuals (truth-telling, confidentiality), to create conditions necessary for autonomous choice (informed consent), and to honor their preference in accepting or not accepting medical care. **Beneficence** Physicians have a special ethical (fiduciary) duty to act in the patient's best interest. May conflict with autonomy (an informed patient has the right to decide) or what is best for society (eg, mandatory TB treatment). Traditionally, patient interest supersedes. Nonmaleficence "Do no harm." Must be balanced against beneficence; if the benefits outweigh the risks, a patient may make an informed decision to proceed (most surgeries and medications fall into this category). **Justice** To treat persons fairly and equitably. This does not always imply equally (eg, triage). **Informed consent** A process (not just a document/signature) that Exceptions to informed consent (WIPE it away): Waiver—patient explicitly waives the right of requires: Disclosure: discussion of pertinent informed consent information (using medical interpreter, if Legally Incompetent—patient lacks decisionmaking capacity (obtain consent from legal needed) Understanding: ability to comprehend surrogate) Capacity: ability to reason and make one's Therapeutic Privilege—withholding own decisions (distinct from competence, a information when disclosure would severely harm the patient or undermine informed legal determination) Voluntariness: freedom from coercion and decision-making capacity manipulation Emergency situation—implied consent may Patients must have an intelligent understanding apply of their diagnosis and the risks/benefits of proposed treatment and alternative options, including no treatment. Patient must be informed that he or she can revoke written consent at any time, even orally. **Consent for minors** A minor is generally any person < 18 years old. Situations in which parental consent is usually Parental consent laws in relation to healthcare not required: vary by state. In general, parental consent Sex (contraception, STIs, pregnancy)

A minor is generally any person < 18 years old. Parental consent laws in relation to healthcare vary by state. In general, parental consent should be obtained, but exceptions exist for emergency treatment (eg, blood transfusions) or if minor is legally emancipated (eg, married, self-supporting, or in the military).

- Drugs (substance abuse)
- Rock and roll (emergency/trauma)

Physicians should always encourage healthy minor-guardian communication.

Physician should seek a minor's assent even if their consent is not required.

FAS1\_2019\_06-PubHealth.indd 265 11/7/19 4:16 PM

# 266

# SECTION II

#### **PUBLIC HEALTH SCIENCES** → PUBLIC HEALTH SCIENCES—ETHICS

# Decision-making capacity

Physician must determine whether the patient is psychologically and legally capable of making a particular healthcare decision. Note that decisions made with capacity cannot be revoked simply if the patient later loses capacity. Intellectual disability alone (eg, Down syndrome, autism) is not an exclusion criterion for informed decision-making.

Capacity is determined by a physician for a specific healthcare-related decision (eg, to refuse medical care). Competency is determined by a judge and usually refers to more global categories of decision making (eg, legally unable to make any healthcare-related decision).

#### Components (think **GIEMSA**):

- Decision is consistent with patient's values and Goals
- Patient is Informed (knows and understands)
- Patient Expresses a choice
- Decision is not a result of altered Mental status (eg, delirium, psychosis, intoxication), Mood disorder
- Decision remains Stable over time
- Patient is ≥ 18 years of Age or otherwise legally emancipated

#### **Advance directives** Instructions given by a patient in anticipation of the need for a medical decision. Details vary per state law. Oral advance directive Incapacitated patient's prior oral statements commonly used as guide. Problems arise from variance in interpretation. If patient was informed, directive was specific, patient made a choice, and decision was repeated over time to multiple people, then the oral directive is more valid. Written advance Specifics specific healthcare interventions that a patient anticipates he or she would accept or reject directive during treatment for a critical or life-threatening illness. A living will is an example. Medical power of Patient designates an agent to make medical decisions in the event that he/she loses decisionmaking capacity. Patient may also specify decisions in clinical situations. Can be revoked by attorney patient if decision-making capacity is intact. More flexible than a living will. DNR order prohibits cardiopulmonary resuscitation (CPR). Other resuscitative measures that may Do not resuscitate follow (eg, feeding tube) are also typically avoided. order Surrogate decision-If a patient loses decision-making capacity and has not prepared an advance directive, individuals maker (surrogates) who know the patient must determine what the patient would have done. Priority of surrogates: spouse → adult Children → Parents → Siblings → other relatives (the spouse ChiPS in).

FAS1\_2019\_06-PubHealth.indd 266 11/7/19 4:16 PM

#### Confidentiality

Confidentiality respects patient privacy and autonomy. If the patient is incapacitated or the situation is emergent, disclosing information to family and friends should be guided by professional judgment of patient's best interest. The patient may voluntarily waive the right to confidentiality (eg, insurance company request).

General principles for exceptions to confidentiality:

- Potential physical harm to others is serious and imminent
- Alternative means to warn or protect those at risk is not possible
- Self-harm is likely
- Steps can be taken to prevent harm

Examples of exceptions to patient confidentiality (many are state specific) include the following ("The physician's good judgment **SAVED** the day"):

- Suicidal/homicidal patients.
- Abuse (children, elderly, and/or prisoners).
- Duty to protect—state-specific laws that sometimes allow physician to inform or somehow protect potential Victim from harm.
- Epileptic patients and other impaired automobile drivers.
- Reportable Diseases (eg, STIs, hepatitis, food poisoning); physicians may have a duty to warn
  public officials, who will then notify people at risk. Dangerous communicable diseases, such as
  TB or Ebola, may require involuntary treatment.

FAS1\_2019\_06-PubHealth.indd 267 11/7/19 4:16 PM

#### **Ethical situations**

SITUATION	APPROPRIATE RESPONSE
Patient is not adherent.	Attempt to identify the reason for nonadherence and determine his/her willingness to change; do not coerce the patient into adhering and do not refer him/her to another physician.
Patient desires an unnecessary procedure.	Attempt to understand why the patient wants the procedure and address underlying concerns. Do not refuse to see the patient and do not refer him/her to another physician. Avoid performing unnecessary procedures.
Patient has difficulty taking medications.	Provide written instructions; attempt to simplify treatment regimens; use teach-back method (ask patient to repeat regimen back to physician) to ensure comprehension.
Family members ask for information about patient's prognosis.	Avoid discussing issues with relatives without the patient's permission.
A patient's family member asks you not to disclose the results of a test if the prognosis is poor because the patient will be "unable to handle it."	Attempt to identify why the family member believes such information would be detrimental to the patient's condition. Explain that as long as the patient has decision-making capacity and does not indicate otherwise, communication of information concerning his/her care will not be withheld. However, if you believe the patient might seriously harm himself/herself or others if informed, then you may invoke therapeutic privilege and withhold the information.
A 17-year-old girl is pregnant and requests an abortion.	Many states require parental notification or consent for minors for an abortion. Unless there are specific medical risks associated with pregnancy, a physician should not sway the patient's decision for, or against, an elective abortion (regardless of maternal age or fetal condition).
A 15-year-old girl is pregnant and wants to keep the child. Her parents want you to tell her to give the child up for adoption.	The patient retains the right to make decisions regarding her child, even if her parents disagree. Provide information to the teenager about the practical issues of caring for a baby. Discuss the options, if requested. Encourage discussion between the teenager and her parents to reach the best decision.
A terminally ill patient requests physician assistance in ending his/her own life.	Overwhelming majority of states refuse involvement in any form of physician-assisted death. Physicians may, however, prescribe medically appropriate analgesics even if they shorten the patient's life.
Patient is suicidal.	Assess the seriousness of the threat. If it is serious, suggest that the patient remain in the hospital voluntarily; patient can be hospitalized involuntarily if he/she refuses.
Patient states that he/she finds you attractive.	Ask direct, closed-ended questions and use a chaperone if necessary. Romantic relationships with patients are never appropriate. It may be necessary to transition care to another physician.
A woman who had a mastectomy says she now feels "ugly."	Find out why the patient feels this way. Do not offer falsely reassuring statements (eg, "You still look good").
Patient is angry about the long time he/she spent in the waiting room.	Acknowledge the patient's anger, but do not take a patient's anger personally. Apologize for any inconvenience. Stay away from efforts to explain the delay.
Patient is upset with the way he/she was treated by another doctor.	Suggest that the patient speak directly to that physician regarding his/her concerns. If the problem is with a member of the office staff, tell the patient you will speak to that person.
An invasive test is performed on the wrong patient.	Regardless of the outcome, a physician is ethically obligated to inform a patient that a mistake has been made.

FAS1\_2019\_06-PubHealth.indd 268 11/7/19 4:16 PM

## **Ethical situations (continued)**

SITUATION	APPROPRIATE RESPONSE
A patient requires a treatment not covered by his/her insurance.	Never limit or deny care because of the expense in time or money. Discuss all treatment options with patients, even if some are not covered by their insurance companies.
A 7-year-old boy loses a sister to cancer and now feels responsible.	At ages 5–7, children begin to understand that death is permanent, that all life functions end completely at death, and that everything that is alive eventually dies. Provide a direct, concrete description of his sister's death. Avoid clichés and euphemisms. Reassure the boy that he is not responsible. Identify and normalize fears and feelings. Encourage play and healthy coping behaviors (eg, remembering her in his own way).
Patient is victim of intimate partner violence.	Ask if patient is safe and has an emergency plan. Do not necessarily pressure patient to leave his or her partner, or disclose the incident to the authorities (unless required by state law).
Patient wants to try alternative or holistic medicine.	Explore any underlying reasons with the patient in a supportive, nonjudgmental manner. Advise the patient of known benefits and risks of treatment, including adverse effects, contraindications, and medication interactions.
Physician colleague presents to work impaired.	If impaired or incompetent, colleague is a threat to patient safety. Report the situation to local supervisory personnel. Should the organization fail to take action, alert the state licensing board.
Patient is officially determined to suffer brain death. Patient's family insists on maintaining life support indefinitely because patient is still moving when touched.	Gently explain to family that there is no chance of recovery, and that brain death is equivalent to death. Movement is due to spinal arc reflex and is not voluntary. Bring case to appropriate ethics board regarding futility of care and withdrawal of life support.
A pharmaceutical company offers you a sponsorship in exchange for advertising its new drug.	Reject this offer. Generally, decline gifts and sponsorships to avoid any appearance of conflict of interest. The AMA Code of Ethics does make exceptions for gifts directly benefitting patients; gifts of minimal value; special funding for medical education of students, residents, fellows; grants whose recipients are chosen by independent institutional criteria; and funds that are distributed without attribution to sponsors.
Patient requests a nonemergent procedure that is against your personal or religious beliefs.	Provide accurate and unbiased information so patients can make an informed decision. Explain to the patient that you do not perform the procedure but offer to refer him/her to another physician.
Mother and 15-year-old daughter are unresponsive following a car accident and are bleeding internally. Father says do not transfuse because they are Jehovah's Witnesses.	Transfuse daughter, but do not transfuse mother. Emergent care can be refused by the healthcare proxy for an adult, particularly when patient preferences are known or reasonably inferred, but not for a minor based solely on faith.
A child presents with injuries inconsistent with parental story.	Contact child protective services and ensure child is in a safe location. Physicians are required by law to report any reasonable suspicion of child abuse or endangerment.

11/7/19 4:16 PM FAS1\_2019\_06-PubHealth.indd 269

# ▶ PUBLIC HEALTH SCIENCES—THE WELL PATIENT

## Changes in the elderly

Sexual changes:

- Men—slower erection/ejaculation, longer refractory period, but unchanged libido.
- Women—vaginal shortening, thinning, and dryness

Sleep patterns: ↓ REM and slow-wave sleep, ↑ sleep latency, ↑ early awakenings

1 suicide rate

- ↓ vision and hearing
- ↓ immune response
- ↓ renal, pulmonary, and GI function
- ↓ muscle mass, † fat

Intelligence does not decrease

# ▶ PUBLIC HEALTH SCIENCES—HEALTHCARE DELIVERY

Disease prevention	
Primary disease prevention	Prevent disease before it occurs (eg, HPV vaccination)
Secondary disease prevention	Screen early for and manage existing but asymptomatic disease (eg, Pap smear for cervical cancer)
Tertiary disease prevention	Treatment to reduce complications from disease that is ongoing or has long-term effects (eg, chemotherapy)
Quaternary disease prevention	Quit (avoid) unnecessary medical interventions to minimize incidental harm (eg, imaging studies, optimizing medications to reduce polypharmacy).

FAS1\_2019\_06-PubHealth.indd 270 11/7/19 4:16 PM

# **Major medical insurance plans**

PLAN	PROVIDERS	PAYMENTS	SPECIALIST CARE
Exclusive provider organization	Restricted to limited panel (except emergencies)		No referral required
Health maintenance organization	Restricted to limited panel (except emergencies)	Denied for any service that does not meet established, evidence-based guidelines	Requires referral from primary care provider
Point of service	Patient can see providers outside network	Higher copays and deductibles for out-of- network services	Requires referral from primary care provider
Preferred provider organization	Patient can see providers outside network	Higher copays and deductibles for all services	No referral required
Accountable care organization	Providers voluntarily enroll	Medicare	Specialists voluntarily enroll

## **Healthcare payment models**

Bundled payment	Healthcare organization receives a set amount per service, regardless of ultimate cost, to be divided among all providers and facilities involved.	
Capitation	Physicians receive a set amount per patient assigned to them per period of time, regardless of how much the patient uses the healthcare system. Used by some HMOs.	
Discounted fee-for- service	Patient pays for each individual service at a discounted rate predetermined by providers and payers (eg, PPOs).	
Fee-for-service	Patient pays for each individual service.	
Global payment	Patient pays for all expenses associated with a single incident of care with a single payment. Most commonly used during elective surgeries, as it covers the cost of surgery as well as the necessary pre- and postoperative visits.	

FAS1\_2019\_06-PubHealth.indd 271 11/7/19 4:16 PM

777

**SECTION II** 

#### **PUBLIC HEALTH SCIENCES** ▶ PUBLIC HEALTH SCIENCES—HEALTHCARE DELIVERY

#### Medicare and Medicaid

Medicare and Medicaid—federal social healthcare programs that originated from amendments to the Social Security Act.

Medicare is available to patients ≥ 65 years old, < 65 with certain disabilities, and those with end-stage renal disease.

Medicaid is joint federal and state health assistance for people with limited income and/ or resources.

Medicar**E** is for **E**lderly. Medicai**D** is for **D**estitute.

The 4 parts of Medicare:

- Part A: HospitAl insurance, home hospice care
- Part B: Basic medical bills (eg, doctor's fees, diagnostic testing)
- Part C: (parts A + B = Combo) delivered by approved private companies
- Part D: Prescription Drugs

#### **Hospice care**

Medical care focused on providing comfort and palliation instead of definitive cure. Available to patients on Medicare or Medicaid and in most private insurance plans whose life expectancy is < 6 months.

During end-of-life care, priority is given to improving the patient's comfort and relieving pain (often includes opioid, sedative, or anxiolytic medications). Facilitating comfort is prioritized over potential side effects (eg, respiratory depression). This prioritization of positive effects over negative effects is called the principle of double effect.

#### Common causes of death (US) by age

	< 1 YR	1–14 YR	15-34 YR	35-44 YR	45-64 YR	65+ YR
#1	Congenital malformations	Unintentional injury	Unintentional injury	Unintentional injury	Cancer	Heart disease
#2	Preterm birth	Cancer	Suicide	Cancer	Heart disease	Cancer
#3	Maternal pregnancy complications	Congenital malformations	Homicide	Heart disease	Unintentional injury	Chronic respiratory disease

# Conditions with frequent hospital readmissions

Readmissions may be reduced by discharge planning and outpatient follow-up appointments. The table below is based on readmission for any reason within 30 days of discharge.

	MEDICARE	MEDICAID	PRIVATE INSURANCE	UNINSURED
#1	Congestive HF	Mood disorders	Maintenance of chemotherapy or radiotherapy	Mood disorders
#2	Septicemia	Schizophrenia/ psychotic disorders	Mood disorders	Alcohol-related disorders
#3	Pneumonia	Diabetes mellitus with complications	Complications of surgical procedures or medical care	Diabetes mellitus with complications

FAS1\_2019\_06-PubHealth.indd 272 11/7/19 4:16 PM

# ▶ PUBLIC HEALTH SCIENCES—QUALITY AND SAFETY

#### Safety culture

Organizational environment in which everyone can freely bring up safety concerns without fear of censure. Facilitates error identification.

Event reporting systems collect data on errors for internal and external monitoring.

#### **Human factors design**

Forcing functions (those that prevent undesirable actions [eg, connecting feeding syringe to IV tubing]) are the most effective.

Standardization improves process reliability (eg, clinical pathways, guidelines, checklists).

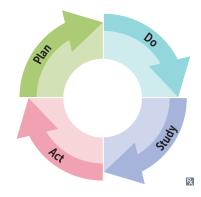
Simplification reduces wasteful activities (eg, consolidating electronic medical records).

Deficient designs hinder workflow and lead to staff workarounds that bypass safety features (eg, patient ID barcodes affixed to computers due to unreadable wristbands).

#### **PDSA cycle**

Process improvement model to test changes in real clinical setting. Impact on patients:

- Plan—define problem and solution
- Do—test new process
- Study—measure and analyze data
- Act—integrate new process into workflow

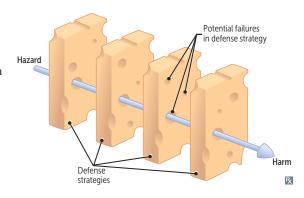


#### **Quality measurements**

	MEASURE	EXAMPLE
Structural	Physical equipment, resources, facilities	Number of diabetes educators
Process	Performance of system as planned	Percentage of diabetic patients whose $HbA_{lc}$ was measured in the past 6 months
Outcome	Impact on patients	Average $\mathrm{HbA}_{\mathrm{lc}}$ of patients with diabetes
Balancing	Impact on other systems/outcomes	Incidence of hypoglycemia among patients who tried an intervention to lower $HbA_{lc}$

#### **Swiss cheese model**

Focuses on systems and conditions rather than an individual's error. The risk of a threat becoming a reality is mitigated by differing layers and types of defenses. Patient harm can occur despite multiple safeguards when "the holes in the cheese line up."



FAS1\_2019\_06-PubHealth.indd 273 11/7/19 4:16 PM

# SECTION II PUBLIC HEALTH SCIENCES → PUBLIC HEALTH SCIENCES—QUALITY AND SAFETY

Types of medical errors	May involve patient identification, diagnosis, monitoring, nosocomial infection, medications, procedures, devices, documentation, handoffs. Medical errors should be disclosed to patients, independent of immediate outcome (harmful or not).	
Active error	Occurs at level of frontline operator (eg, wrong IV pump dose programmed).	Immediate impact.
Latent error	Occurs in processes indirect from operator but impacts patient care (eg, different types of IV pumps used within same hospital).	Accident waiting to happen.
Never event	Adverse event that is identifiable, serious, and usually preventable (eg, scalpel retained in a surgical patient's abdomen).	Major error that should never occur.
Burnout vs fatigue		
Burnout	Prolonged, excessive stress → cynicism, detachment, ↓ motivation and interest, sense of failure and helplessness, ↓ immunity. Medical errors due to lack of concern.	
Fatigue	Sleep deprivation → ↓ energy and motivation, cognitive impairment. Medical errors due to compromised intellectual function.	
Medical error analysis		
	DESIGN	METHODS
Root cause analysis	Retrospective approach. Applied after failure event to prevent recurrence.	Uses records and participant interviews to identify all the underlying problems (eg, process, people, environment, equipment, materials, management) that led to an error.
Failure mode and effects analysis	Forward-looking approach. Applied before process implementation to prevent failure occurrence.	Uses inductive reasoning to identify all the ways a process might fail and prioritizes them by their probability of occurrence and impact on patients.

11/7/19 4:16 PM FAS1\_2019\_06-PubHealth.indd 274

# SECTION III

# **High-Yield Organ Systems**

"Symptoms, then, are in reality nothing but the cry from suffering organs."

—Jean-Martin Charcot

"Man is an intelligence in servitude to his organs."

-Aldous Huxley

"When every part of the machine is correctly adjusted and in perfect harmony, health will hold dominion over the human organism by laws as natural and immutable as the laws of gravity."

-Andrew T. Still

▶ Approaching the	
Organ Systems	276
▶ Cardiovascular	279
▶ Endocrine	325
▶ Gastrointestinal	357
▶ Hematology and	400
Oncology	403
► Musculoskeletal, Skin, and Connective	
Tissue	445
▶ Neurology and	
Special Senses	489
▶ Psychiatry	553
▶ Renal	577
▶ Reproductive	611
▶ Respiratory	659

275

FAS1\_2019\_07-Cardio.indd 275 11/7/19 4:24 PM

#### ▶ APPROACHING THE ORGAN SYSTEMS

In this section, we have divided the High-Yield Facts into the major Organ Systems. Within each Organ System are several subsections, including Embryology, Anatomy, Physiology, Pathology, and Pharmacology. As you progress through each Organ System, refer back to information in the previous subsections to organize these basic science subsections into a "vertically integrated" framework for learning. Below is some general advice for studying the organ systems by these subsections.

#### **Embryology**

Relevant embryology is included in each organ system subsection. Embryology tends to correspond well with the relevant anatomy, especially with regard to congenital malformations.

#### **Anatomy**

Several topics fall under this heading, including gross anatomy, histology, and neuroanatomy. Do not memorize all the small details; however, do not ignore anatomy altogether. Review what you have already learned and what you wish you had learned. Many questions require two or more steps. The first step is to identify a structure on anatomic cross section, electron micrograph, or photomicrograph. The second step may require an understanding of the clinical significance of the structure.

When studying, stress clinically important material. For example, be familiar with gross anatomy and radiologic anatomy related to specific diseases (eg, Pancoast tumor, Horner syndrome), traumatic injuries (eg, fractures, sensory and motor nerve deficits), procedures (eg, lumbar puncture), and common surgeries (eg, cholecystectomy). There are also many questions on the exam involving x-rays, CT scans, and neuro MRI scans. Many students suggest browsing through a general radiology atlas, pathology atlas, and histology atlas. Focus on learning basic anatomy at key levels in the body (eg, sagittal brain MRI; axial CT of the midthorax, abdomen, and pelvis). Basic neuroanatomy (especially pathways, blood supply, and functional anatomy), associated neuropathology, and neurophysiology have good yield. Please note that many of the photographic images in this book are for illustrative purposes and are not necessarily reflective of Step 1 emphasis.

#### **Physiology**

The portion of the examination dealing with physiology is broad and concept oriented and thus does not lend itself as well to fact-based review. Diagrams are often the best study aids, especially given the increasing number of questions requiring the interpretation of diagrams. Learn to apply basic physiologic relationships in a variety of ways (eg, the Fick equation, clearance equations). You are seldom asked to perform complex

FAS1\_2019\_07-Cardio.indd 276 11/7/19 4:24 PM

calculations. Hormones are the focus of many questions, so learn their sites of production and action as well as their regulatory mechanisms.

A large portion of the physiology tested on the USMLE Step 1 is clinically relevant and involves understanding physiologic changes associated with pathologic processes (eg, changes in pulmonary function with COPD). Thus, it is worthwhile to review the physiologic changes that are found with common pathologies of the major organ systems (eg, heart, lungs, kidneys, GI tract) and endocrine glands.

#### **Pathology**

Questions dealing with this discipline are difficult to prepare for because of the sheer volume of material involved. Review the basic principles and hallmark characteristics of the key diseases. Given the clinical orientation of Step 1, it is no longer sufficient to know only the "buzzword" associations of certain diseases (eg. café-au-lait macules and neurofibromatosis); you must also know the clinical descriptions of these findings.

Given the clinical slant of the USMLE Step 1, it is also important to review the classic presenting signs and symptoms of diseases as well as their associated laboratory findings. Delve into the signs, symptoms, and pathophysiology of major diseases that have a high prevalence in the United States (eg, alcoholism, diabetes, hypertension, heart failure, ischemic heart disease, infectious disease). Be prepared to think one step beyond the simple diagnosis to treatment or complications.

The examination includes a number of color photomicrographs and photographs of gross specimens that are presented in the setting of a brief clinical history. However, read the question and the choices carefully before looking at the illustration, because the history will help you identify the pathologic process. Flip through an illustrated pathology textbook, color atlases, and appropriate Web sites in order to look at the pictures in the days before the exam. Pay attention to potential clues such as age, sex, ethnicity, occupation, recent activities and exposures, and specialized lab tests.

#### **Pharmacology**

Preparation for questions on pharmacology is straightforward. Learning all the key drugs and their characteristics (eg, mechanisms, clinical use, and important side effects) is high yield. Focus on understanding the prototype drugs in each class. Avoid memorizing obscure derivatives. Learn the "classic" and distinguishing toxicities of the major drugs. Do not bother with drug dosages or trade names. Reviewing associated biochemistry, physiology, and microbiology can be useful while studying pharmacology. There is a strong emphasis on ANS, CNS, antimicrobial, and cardiovascular agents as well as NSAIDs. Much of the material is clinically relevant. Newer drugs on the market are also fair game.

FAS1 2019 07-Cardio.indd 277 11/7/19 4:24 PM 278

# SECTION III HIGH-YIELD ORGAN SYSTEMS

<b>▶</b> NOTES	

11/7/19 4:24 PM FAS1\_2019\_07-Cardio.indd 278

# HIGH-YIELD SYSTEMS

# Cardiovascular

"As for me, except for an occasional heart attack, I feel as young as I ever did."

—Robert Benchley

"Hearts will never be practical until they are made unbreakable."

—The Wizard of Oz

"As the arteries grow hard, the heart grows soft."

-H. L. Mencken

"Nobody has ever measured, not even poets, how much the heart can hold."

—Zelda Fitzgerald

"Only from the heart can you touch the sky."

—Rumi

"It is not the size of the man but the size of his heart that matters."

—Evander Holyfield

The cardiovascular system is one of the highest yield areas for the boards and, for some students, may be the most challenging. Focusing on understanding the mechanisms instead of memorizing the details can make a big difference, especially for this topic. Pathophysiology of atherosclerosis and heart failure, MOA of drugs (particular physiology interactions) and their adverse effects, ECGs of heart blocks, the cardiac cycle, and the Starling curve are some of the more high-yield topics. Differentiating between systolic and diastolic dysfunction is also very important. Heart murmurs and maneuvers that affect these murmurs have also been high yield and may be asked in a multimedia format.

▶ Embryology 280
▶ Anatomy 283
▶ Physiology 284
▶ Pathology 298
▶ Pharmacology 316

FAS1\_2019\_07-Cardio.indd 279 11/7/19 4:24 PM

#### ► CARDIOVASCULAR—EMBRYOLOGY

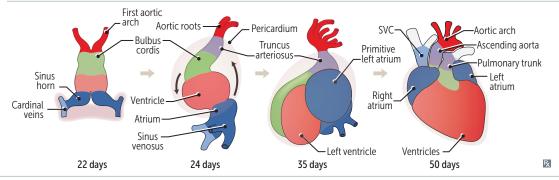
#### **Heart morphogenesis**

First functional organ in vertebrate embryos; beats spontaneously by week 4 of development.

#### **Cardiac looping**

Primary heart tube loops to establish left-right polarity; begins in week 4 of development.

Defect in left-right Dynein (involved in L/R asymmetry) can lead to Dextrocardia, as seen in Kartagener syndrome (1° ciliary Dyskinesia).

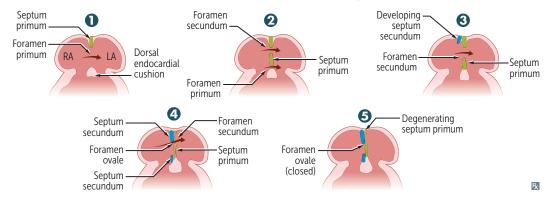


#### Septation of the chambers

Atria

- Septum primum grows toward endocardial cushions, narrowing foramen primum.
- **2** Foramen secundum forms in septum primum (foramen primum regresses).
- Septum secundum develops on the right side of septum primum, as foramen secundum maintains right-to-left shunt.
- Septum secundum expands and covers most of foramen secundum. The residual foramen is the foramen ovale.
- **3** Remaining portion of septum primum forms the one-way valve of the foramen ovale.
- 6. Septum primum closes against septum secundum, sealing the foramen ovale soon after birth because of ↑ LA pressure and ↓ RA pressure.
- Septum secundum and septum primum fuse during infancy/early childhood, forming the atrial septum.

Patent foramen ovale—caused by failure of septum primum and septum secundum to fuse after birth; most are left untreated. Can lead to paradoxical emboli (venous thromboemboli entering the systemic arterial circulation) as can occur in ASD.



FAS1\_2019\_07-Cardio.indd 280 11/7/19 4:24 PM

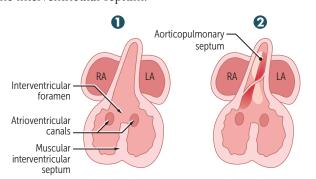
### Heart morphogenesis (continued)

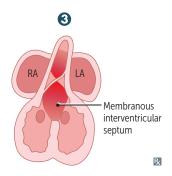
#### Ventricles

- Muscular interventricular septum forms.

  Opening is called interventricular foramen.
- 2 Aorticopulmonary septum rotates and fuses with muscular ventricular septum to form membranous interventricular septum, closing interventricular foramen.
- **3** Growth of endocardial cushions separates atria from ventricles and contributes to both atrial septation and membranous portion of the interventricular septum.

Ventricular septal defect—most common congenital cardiac anomaly, usually occurs in membranous septum.





### Outflow tract formation

Neural crest and endocardial cell migrations

- → truncal and bulbar ridges that spiral and fuse to form aorticopulmonary septum
- → ascending aorta and pulmonary trunk.

Conotruncal abnormalities associated with failure of neural crest cells to migrate:

- Transposition of great vessels.
- Tetralogy of Fallot.
- Persistent truncus arteriosus.

#### Valve development

Aortic/pulmonary: derived from endocardial cushions of outflow tract.

Mitral/tricuspid: derived from fused endocardial cushions of the AV canal.

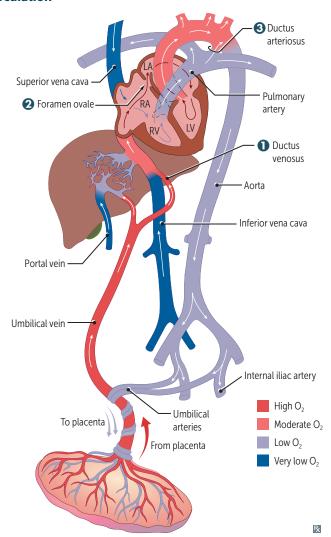
Valvular anomalies may be stenotic, regurgitant, atretic (eg, tricuspid atresia), or displaced (eg, Ebstein anomaly).

### **Heart embryology**

EMBRYONIC STRUCTURE	GIVES RISE TO
Truncus arteriosus	Ascending aorta and pulmonary trunk
Bulbus cordis	Smooth parts (outflow tract) of left and right ventricles
Primitive ventricle	Trabeculated part of left and right ventricles
Primitive atrium	Trabeculated part of left and right atria
Left horn of sinus venosus	Coronary sinus
Right horn of sinus venosus	Smooth part of right atrium (sinus venarum)
Endocardial cushion	Atrial septum, membranous interventricular septum; AV and semilunar valves
Right common cardinal vein and right anterior cardinal vein	Superior vena cava (SVC)
Posterior, subcardinal, and supracardinal veins	Inferior vena cava (IVC)
Primitive pulmonary vein	Smooth part of left atrium

FAS1\_2019\_07-Cardio.indd 281 11/7/19 4:24 PM

### **Fetal circulation**



Blood in umbilical vein has a  $Po_2$  of  $\approx 30$  mm Hg and is  $\approx 80\%$  saturated with  $O_2$ . Umbilical arteries have low  $O_2$  saturation.

### 3 important shunts:

- Blood entering fetus through the umbilical vein is conducted via the ductus venosus into the IVC, bypassing hepatic circulation.
- 2 Most of the highly Oxygenated blood reaching the heart via the IVC is directed through the **foramen Ovale** into the left atrium.
- ② Deoxygenated blood from the SVC passes through the RA → RV → main pulmonary artery → Ductus arteriosus → Descending aorta; shunt is due to high fetal pulmonary artery resistance (due partly to low O₂ tension).

At birth, infant takes a breath → ↓ resistance in pulmonary vasculature → ↑ left atrial pressure vs right atrial pressure → foramen ovale closes (now called fossa ovalis); ↑ in O<sub>2</sub> (from respiration) and ↓ in prostaglandins (from placental separation) → closure of ductus arteriosus.

Indomethacin helps close the patent Ductus arteriosus → ligamentum arteriosum (remnant of ductus arteriosus). Come In and close the

Prostaglandins  $\mathbf{E}_1$  and  $\mathbf{E}_2$  k**EE**p PDA open.

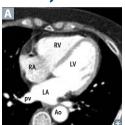
### **Fetal-postnatal derivatives**

FETAL STRUCTURE	POSTNATAL DERIVATIVE	NOTES
Ductus arteriosus	Ligamentum arteriosum	Near the left recurrent laryngeal nerve
Ductus venosus	Ligamentum venosum	
Foramen ovale	Fossa ovalis	
Allantois → urachus	Medi <mark>an</mark> umbilical ligament	Urachus is part of allantoic duct between bladder and umbilicus
Umbilical arteries	Medi <mark>al</mark> umbilical ligaments	
Umbilical vein	Ligamentum teres hepatis (round ligament)	Contained in falciform ligament
Notochord	Nucleus pulposus	

FAS1\_2019\_07-Cardio.indd 282

### ► CARDIOVASCULAR—ANATOMY

#### **Anatomy of the heart**



LA is the most posterior part of the heart A; enlargement of the LA (eg, in mitral stenosis) can lead to compression of the esophagus (dysphagia) and/or the left recurrent laryngeal nerve, a branch of the vagus nerve, causing hoarseness (Ortner syndrome).

RV is the most anterior part of the heart and most commonly injured in trauma.

### Pericardium

Consists of 3 layers (from outer to inner):

- Fibrous pericardium
- Parietal layer of serous pericardium
- Visceral layer of serous pericardium

Pericardial cavity lies between parietal and visceral layers.

Pericardium innervated by phrenic nerve.

Dominance:

### Coronary blood supply

LAD and its branches supply anterior 2/3 of interventricular septum, anterolateral papillary muscle, and anterior surface of LV. Most commonly occluded.

PDA supplies AV node (dependent on dominance), posterior 1/3 of interventricular septum, posterior 2/3 walls of ventricles, and posteromedial papillary muscle.

RCA supplies SA node (blood supply independent of dominance). Infarct may cause nodal dysfunction (bradycardia or heart block). Right (acute) marginal artery supplies RV.

 Right-dominant circulation (85%) = PDA arises from RCA.

Pericarditis can cause referred pain to the neck,

arms, or one or both shoulders (often left).

- Left-dominant circulation (8%) = PDA arises from LCX.
- Codominant circulation (7%) = PDA arises from both LCX and RCA.

Coronary blood flow peaks in early diastole.

LA SVC Aorta SVC RCA RA LAD PT RA LV LV IVC RV RV AMA PDA **Anterior view** Posterior view Ŗ

### Key:

AMA = Acute marginal artery

LAD = Left anterior descending artery

LCA = Left coronary artery LCX = Left circumflex artery

OMA = Obtuse marginal artery

PDA = Posterior descending artery

PT = Pulmonary trunk

PV = Pulmonary vein

RCA = Right coronary artery

FAS1\_2019\_07-Cardio.indd 283 11/7/19 4:24 PM

### ► CARDIOVASCULAR—PHYSIOLOGY

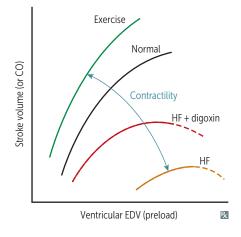
Cardiac output variabl	les	
Stroke volume	Stroke Volume affected by Contractility, Afterload, and Preload.  † SV with:  † Contractility (eg, anxiety, exercise)  † Preload (eg, early pregnancy)  ‡ Afterload	SV CAP. A failing heart has ↓ SV (systolic and/or diastolic dysfunction).
Contractility	<ul> <li>Contractility (and SV) ↑ with:</li> <li>Catecholamine stimulation via β₁ receptor:</li> <li>Activated protein kinase A  → phospholamban phosphorylation  → active Ca²+ ATPase → ↑ Ca²+ storage in sarcoplasmic reticulum</li> <li>Activated protein kinase A → Ca²+ channel phosphorylation → ↑ Ca²+ entry  → ↑ Ca²+-induced Ca²+ release</li> <li>↑ intracellular Ca²+</li> <li>↓ extracellular Na+ (↓ activity of Na+/Ca²+ exchanger)</li> <li>Digitalis (blocks Na+/K+ pump  → ↑ intracellular Na+ → ↓ Na+/Ca²+ exchanger activity → ↑ intracellular Ca²+)</li> </ul>	Contractility (and SV) ↓ with:  ■ β₁-blockade (↓ cAMP)  ■ HF with systolic dysfunction  ■ Acidosis  ■ Hypoxia/hypercapnia (↓ Po₂/↑ Pco₂)  ■ Non-dihydropyridine Ca²+ channel blockers
Preload	Preload approximated by ventricular EDV; depends on venous tone and circulating blood volume.	Vasodilators (eg, nitroglycerin) ↓ preload.
Afterload	Afterload approximated by MAP.  † wall tension per Laplace's law → † pressure  → † afterload.  LV compensates for † afterload by thickening (hypertrophy) in order to ↓ wall stress.	Arterial vasodilators (eg, hydralazine)  ↓ Afterload.  ACE inhibitors and ARBs ↓ both preload and afterload.  Chronic hypertension († MAP) → LV hypertrophy.
Myocardial oxygen demand	Myocardial O₂ demand is ↑ by:  1 Contractility  1 Afterload (proportional to arterial pressure)  1 heart Rate  1 Diameter of ventricle (↑ wall tension)	Wall tension follows Laplace's law:  Wall tension = pressure $\times$ radius  Wall stress = $\frac{\text{pressure} \times \text{radius}}{2 \times \text{wall thickness}}$

FAS1\_2019\_07-Cardio.indd 284 11/7/19 4:24 PM

### **Cardiac output equations**

	EQUATION	NOTES
Stroke volume	SV = EDV - ESV	
Ejection fraction	$EF = \frac{SV}{EDV} = \frac{EDV - ESV}{EDV}$	EF is an index of ventricular contractility (\(\frac{1}{4}\) in systolic HF; usually normal in diastolic HF).
Cardiac output	$CO = SV \times HR$ Fick principle: $CO = \frac{\text{rate of } O_2 \text{ consumption}}{(\text{arterial } O_2 \text{ content} - \text{venous } O_2 \text{ content})}$	In early stages of exercise, CO maintained by  † HR and † SV. In later stages, CO maintained by † HR only (SV plateaus).  Diastole is shortened with †† HR (eg, ventricular tachycardia) → ↓ diastolic filling time → ↓ SV  → ↓ CO.
Pulse pressure	PP = SBP – DBP	PP directly proportional to SV and inversely proportional to arterial compliance.  † PP in hyperthyroidism, aortic regurgitation, aortic stiffening (isolated systolic hypertension in elderly), obstructive sleep apnea († sympathetic tone), anemia, exercise (transient).  † PP in aortic stenosis, cardiogenic shock, cardiac tamponade, advanced HF.
Mean arterial pressure	$MAP = CO \times TPR$	MAP (at resting HR) = $2/3$ DBP + $1/3$ SBP = DBP + $1/3$ PP.

### **Starling curves**



Force of contraction is proportional to enddiastolic length of cardiac muscle fiber (preload).

- † contractility with catecholamines, positive inotropes (eg, digoxin).
- $\downarrow$  contractility with loss of functional myocardium (eg, MI),  $\beta$ -blockers (acutely), non-dihydropyridine  $Ca^{2+}$  channel blockers, dilated cardiomyopathy.

FAS1\_2019\_07-Cardio.indd 285 11/7/19 4:24 PM

### 286

SECTION III

CARDIOVASCULAR ► CARDIOVASCULAR—PHYSIOLOGY

### Resistance, pressure, flow

$$\Delta P = Q \times R$$

Similar to Ohm's law:  $\Delta V = I \times R$ 

Volumetric flow rate (Q) = flow velocity  $(v) \times cross$ -sectional area (A)

Resistance

$$= \frac{\text{driving pressure } (\Delta P)}{Q} = \frac{8\eta \text{ (viscosity)} \times \text{length}}{\pi r^4}$$

Total resistance of vessels in series:

$$R_T = R_1 + R_2 + R_3 ...$$

Total resistance of vessels in parallel:

$$\frac{1}{R_{\rm T}} = \frac{1}{R_1} + \frac{1}{R_2} + \frac{1}{R_3} ...$$

Capillaries have highest total cross-sectional area and lowest flow velocity.

Pressure gradient drives flow from high pressure to low pressure.

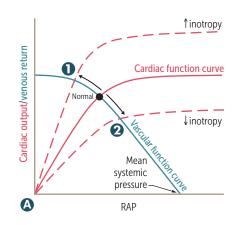
Arterioles account for most of TPR. Veins provide most of blood storage capacity.

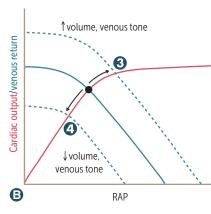
Viscosity depends mostly on hematocrit.

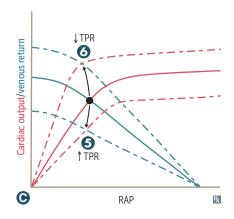
Viscosity † in hyperproteinemic states (eg, multiple myeloma), polycythemia.

Viscosity ↓ in anemia.

### **Cardiac and vascular function curves**







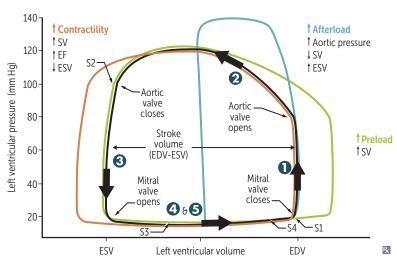
Intersection of curves = operating point of heart (ie, venous return and CO are equal, as circulatory system is a closed system).

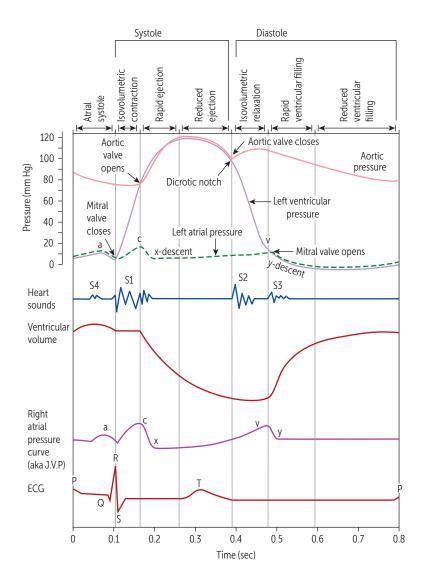
GRAPH	EFFECT	EXAMPLES	
<b>⚠</b> Inotropy	Changes in contractility → altered SV → altered CO/VR and RA pressure (RAP)	<ul><li>Catecholamines, digoxin, exercise ⊕</li><li>HF with reduced EF, narcotic overdose, sympathetic inhibition ⊖</li></ul>	
<b>③ Venous return</b> Changes in circulating volume → altered RAP → altered SV → change in CO		<ul><li>3 Fluid infusion, sympathetic activity ⊕</li><li>4 Acute hemorrhage, spinal anesthesia ⊖</li></ul>	
Total peripheral resistance	Changes in TPR → altered CO Change in RAP unpredictable.	<ul><li>S Vasopressors ⊕</li><li>Exercise, AV shunt ⊖</li></ul>	

Changes often occur in tandem, and may be reinforcing (eg, exercise ↑ inotropy and ↓ TPR to maximize CO) or compensatory (eg, HF ↓ inotropy → fluid retention to ↑ preload to maintain CO).

FAS1\_2019\_07-Cardio.indd 286 11/7/19 4:24 PM

### Pressure-volume loops and cardiac cycle





The black loop represents normal cardiac physiology.

Phases—left ventricle:

- Isovolumetric contraction—period between mitral valve closing and aortic valve opening; period of highest O<sub>2</sub> consumption
- 2 Systolic ejection—period between aortic valve opening and closing
- 3 Isovolumetric relaxation—period between aortic valve closing and mitral valve
- Rapid filling—period just after mitral valve opening
- **3** Reduced filling—period just before mitral valve closing

Heart sounds:

- S1—mitral and tricuspid valve closure. Loudest at mitral area.
- S2—aortic and pulmonary valve closure. Loudest at left upper sternal border.
- S3—in early diastole during rapid ventricular filling phase. Best heard at apex with patient in left lateral decubitus position. Associated with † filling pressures (eg, MR, AR, HF, thyrotoxicosis) and more common in dilated ventricles (but can be normal in children, young adults, athletes, and pregnancy).
- S4—in late diastole ("atrial kick"). Best heard at apex with patient in left lateral decubitus position. High atrial pressure. Associated with ventricular noncompliance (eg, hypertrophy). Left atrium must push against stiff LV wall. Considered abnormal if palpable.

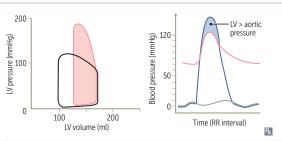
Jugular venous pulse (JVP):

- **a** wave—**a**trial contraction. Absent in atrial fibrillation (AF).
- **c** wave—RV **c**ontraction (closed tricuspid valve bulging into atrium).
- x descent—downward displacement of closed tricuspid valve during rapid ventricular ejection phase. Reduced or absent in tricuspid regurgitation and right HF because pressure gradients are reduced.
- v wave—† right atrial pressure due to filling ("villing") against closed tricuspid valve.
- y descent—RA emptying into RV. Prominent in constrictive pericarditis, absent in cardiac tamponade.

FAS1 2019 07-Cardio.indd 287 11/7/19 4:24 PM

### Pressure-volume loops and valvular disease

### **Aortic stenosis**



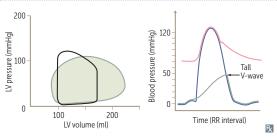
- † LV pressure
- † ESV

No change in EDV

↓ SV

Ventricular hypertrophy → ↓ ventricular compliance → ↑ EDP for given EDV

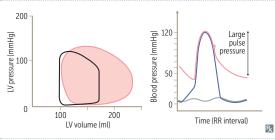
### Mitral regurgitation



No true isovolumetric phase

- ↓ ESV due to ↓ resistance and↑ regurgitation into LA during systole
- ↑ EDV due to ↑ LA volume/pressure from regurgitation → ↑ ventricular filling ↑ SV

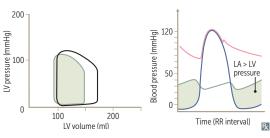
### **Aortic regurgitation**



No true isovolumetric phase

- † EDV
- † SV

### **Mitral stenosis**



- ↑ LA pressure
- ‡ EDV because of impaired ventricular filling
- ↓ ESV
- ↓ SV

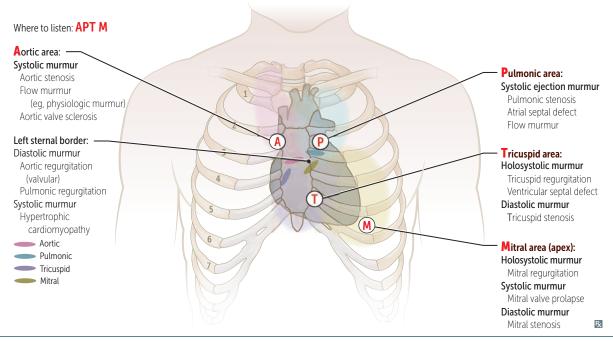
FAS1\_2019\_07-Cardio.indd 288 11/7/19 4:24 PM

### **Splitting of S2**

Physiologic splitting	Inspiration → drop in intrathoracic pressure  → ↑ venous return → ↑ RV filling → ↑ RV  stroke volume → ↑ RV ejection time  → delayed closure of pulmonic valve.  ↓ pulmonary impedance (↑ capacity of the pulmonary circulation) also occurs during inspiration, which contributes to delayed closure of pulmonic valve.	E S1 A2 P2 Normal delay  ■ E = Expiration ■ Inspiration
Wide splitting	Seen in conditions that delay RV emptying (eg, pulmonic stenosis, right bundle branch block). Causes delayed pulmonic sound (especially on inspiration). An exaggeration of normal splitting.	S1 A2 P2 Abnormal delay
Fixed splitting	Heard in ASD. ASD → left-to-right shunt → ↑ RA and RV volumes → ↑ flow through pulmonic valve → delayed pulmonic valve closure (independent of respiration).	E
Paradoxical splitting	Heard in conditions that delay aortic valve closure (eg, aortic stenosis, left bundle branch block). Normal order of semilunar valve closure is reversed so that P2 sound occurs before delayed A2 sound. On inspiration, P2 closes later and moves closer to A2, "paradoxically" eliminating the split. On expiration, the split can be heard (opposite to physiologic splitting).	E

FAS1\_2019\_07-Cardio.indd 289 11/7/19 4:24 PM

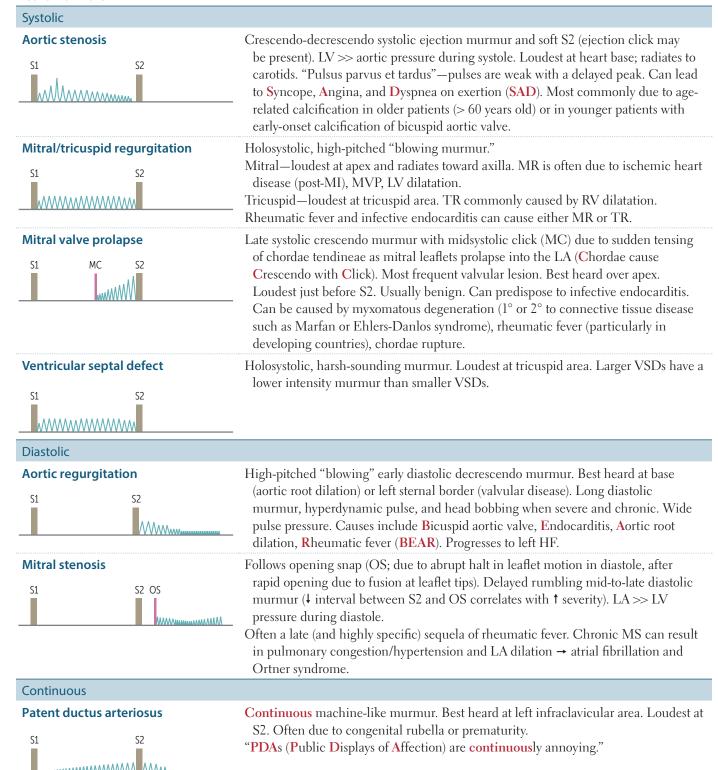
### **Auscultation of the heart**



MANEUVER	CARDIOVASCULAR CHANGES	MURMURS THAT INCREASE WITH MANEUVER	MURMURS THAT DECREASE WITH MANEUVER
Standing Valsalva (strain phase)	↓ preload (↓ LV volume)	MVP (↓ LV volume) HCM (↓ LV volume)	Most murmurs (‡ flow through stenotic or regurgitant valve)
Passive leg raise	† preload († LV volume)	Mark	MX/D (* 137 l)
Squatting	† preload, † afterload († LV volume)	Most murmurs († flow through stenotic or regurgitant valve)	MVP († LV volume) HCM († LV volume)
Hand grip	↑↑ afterload → ↑ reverse flow across aortic valve (↑ LV volume)	Most other left-sided murmurs (AR, MR, VSD)	AS (\$\frac{1}{4}\$ transaortic valve pressure gradient)  HCM (\$\frac{1}{4}\$ LV volume)
Inspiration	↑ venous return to right heart, ↓ venous return to left heart	Most right-sided murmurs	Most left-sided murmurs

FAS1\_2019\_07-Cardio.indd 290 11/7/19 4:24 PM

#### **Heart murmurs**



FAS1\_2019\_07-Cardio.indd 291 11/7/19 4:24 PM

Ŗ

### Myocardial action potential

**Phase 0** = rapid upstroke and depolarization—voltage-gated Na<sup>+</sup> channels open.

**Phase 1** = initial repolarization—inactivation of voltage-gated Na<sup>+</sup> channels. Voltage-gated K<sup>+</sup> channels begin to open.

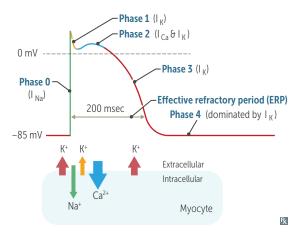
**Phase 2** = plateau—Ca<sup>2+</sup> influx through voltagegated Ca<sup>2+</sup> channels balances K<sup>+</sup> efflux. Ca<sup>2+</sup> influx triggers Ca<sup>2+</sup> release from sarcoplasmic reticulum and myocyte contraction.

**Phase 3** = rapid repolarization—massive K<sup>+</sup> efflux due to opening of voltage-gated slow delayed-rectifier K<sup>+</sup> channels and closure of voltage-gated Ca<sup>2+</sup> channels.

**Phase 4** = resting potential—high  $K^+$  permeability through  $K^+$  channels.

In contrast to skeletal muscle:

- Cardiac muscle action potential has a plateau due to Ca<sup>2+</sup> influx and K<sup>+</sup> efflux.
- Cardiac muscle contraction requires Ca<sup>2+</sup> influx from ECF to induce Ca<sup>2+</sup> release from sarcoplasmic reticulum (Ca<sup>2+</sup>-induced Ca<sup>2+</sup> release).
- Cardiac myocytes are electrically coupled to each other by gap junctions.



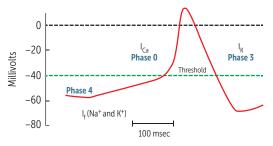
Occurs in all cardiac myocytes except for those in the SA and AV nodes.

### Pacemaker action potential

Occurs in the SA and AV nodes. Key differences from the ventricular action potential include: **Phase 0** = upstroke—opening of voltage-gated  $Ca^{2+}$  channels. Fast voltage-gated  $Na^{+}$  channels are permanently inactivated because of the less negative resting potential of these cells. Results in a slow conduction velocity that is used by the AV node to prolong transmission from the atria to ventricles. Phases 1 and 2 are absent.

**Phase 3** = repolarization—inactivation of the Ca<sup>2+</sup> channels and  $\uparrow$  activation of K<sup>+</sup> channels  $\rightarrow \uparrow$  K<sup>+</sup> efflux.

**Phase 4** = slow spontaneous diastolic depolarization due to  $I_f$  ("funny current").  $I_f$  channels responsible for a slow, mixed  $Na^+/K^+$  inward current; different from  $I_{Na}$  in phase 0 of ventricular action potential. Accounts for automaticity of SA and AV nodes. The slope of phase 4 in the SA node determines HR. ACh/adenosine  $\downarrow$  the rate of diastolic depolarization and  $\downarrow$  HR, while catecholamines  $\uparrow$  depolarization and  $\uparrow$  HR. Sympathetic stimulation  $\uparrow$  the chance that  $I_f$  channels are open and thus  $\uparrow$  HR.



FAS1\_2019\_07-Cardio.indd 292 11/7/19 4:24 PM

#### **Electrocardiogram**

Conduction pathway: SA node → atria → AV node → bundle of His → right and left bundle branches → Purkinje fibers → ventricles; left bundle branch divides into left anterior and posterior fascicles.

SA node—located at junction of RA and SVC; "pacemaker" inherent dominance with slow phase of upstroke.

AV node—located in posteroinferior part of interatrial septum. Blood supply usually from RCA. 100-msec delay allows time for ventricular filling.

Pacemaker rates: SA > AV > bundle of His/ Purkinje/ventricles.

Speed of conduction: His-Purkinje > Atria > Ventricles > AV node. He Parks At Ventura Avenue.

P wave—atrial depolarization.

PR interval—time from start of atrial depolarization to start of ventricular depolarization (normally 120-200 msec).

QRS complex—ventricular depolarization (normally < 100 msec).

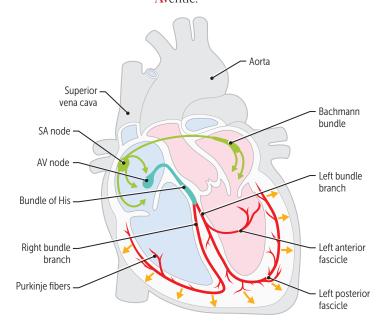
QT interval—ventricular depolarization, mechanical contraction of the ventricles, ventricular repolarization.

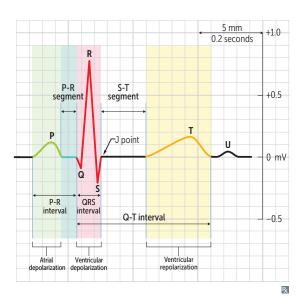
T wave—ventricular repolarization. T-wave inversion may indicate ischemia or recent MI.

J point—junction between end of QRS complex and start of ST segment.

ST segment—isoelectric, ventricles depolarized.

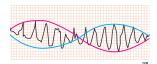
**U** wave—prominent in hypokalemia (think hyp"**U**"kalemia), bradycardia.





FAS1\_2019\_07-Cardio.indd 293 11/7/19 4:24 PM

#### **Torsades de pointes**



Polymorphic ventricular tachycardia, characterized by shifting sinusoidal waveforms on ECG; can progress to ventricular fibrillation (VF). Long QT interval predisposes to torsades de pointes. Caused by drugs, \(\psi \) K<sup>+</sup>, \(\psi \) Mg<sup>2+</sup>, \(\psi \) Ca<sup>2+</sup>, congenital abnormalities. Treatment includes magnesium sulfate.

Drug-induced long QT (ABCDE):

AntiArrhythmics (class IA, III)

AntiBiotics (eg, macrolides)

Anti"C"ychotics (eg, haloperidol)

AntiDepressants (eg, TCAs)

AntiEmetics (eg, ondansetron)

Torsades de pointes = twisting of the points

### Congenital long QT syndrome

Inherited disorder of myocardial repolarization, typically due to ion channel defects (most commonly loss-of-function mutations affecting K<sup>+</sup> channels); † risk of sudden cardiac death (SCD) due to torsades de pointes. Includes:

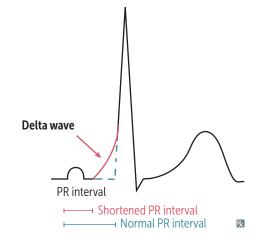
- Romano-Ward syndrome—autosomal dominant, pure cardiac phenotype (no deafness).
- Jervell and Lange-Nielsen syndrome autosomal recessive, sensorineural deafness.

### Brugada syndrome

Autosomal dominant disorder most common in Asian males. ECG pattern of pseudo-right bundle branch block and ST elevations in  $V_1$ - $V_3$ . † risk of ventricular tachyarrhythmias and SCD. Prevent SCD with implantable cardioverter-defibrillator (ICD).

### Wolff-Parkinson-White syndrome

Most common type of ventricular preexcitation syndrome. Abnormal fast accessory conduction pathway from atria to ventricle (bundle of Kent) bypasses the rate-slowing AV node → ventricles begin to partially depolarize earlier → characteristic delta wave with widened QRS complex and shortened PR interval on ECG. May result in reentry circuit → supraventricular tachycardia.



FAS1\_2019\_07-Cardio.indd 294 11/7/19 4:24 PM

### **ECG** tracings

RHYTHM	DESCRIPTION	EXAMPLE
Atrial fibrillation	Chaotic and erratic baseline with no discrete P waves in between irregularly spaced QRS complexes. Irregularly irregular heartbeat. Most common risk factors include hypertension and coronary artery disease (CAD). Occasionally seen after binge drinking ("holiday heart syndrome"). Can lead to thromboembolic events, particularly stroke.  Treatment: anticoagulation, rate and rhythm control and/or cardioversion.	$RR_{1} \neq RR_{2} \neq RR_{3} \neq RR_{4}$ $Irregular baseline (absent P waves)$
Atrial flutter	A rapid succession of identical, back-to-back atrial depolarization waves. The identical appearance accounts for the "sawtooth" appearance of the flutter waves.  Treat like atrial fibrillation +/- catheter ablation.	$RR_1 = RR_2 = RR_3$ $4:1 \text{ sawtooth pattern}$
Ventricular fibrillation	A completely erratic rhythm with no identifiable waves. Fatal arrhythmia without immediate CPR and defibrillation.	No discernible rhythm
AV block		
First-degree AV block	The PR interval is prolonged (> 200 msec). Benign and asymptomatic. No treatment required.	$PR_1 = PR_2 = PR_3 = PR_4$
Second-degree AV block		
Mobitz type I (Wenckebach)	Progressive lengthening of PR interval until a beat is "dropped" (a P wave not followed by a QRS complex). Usually asymptomatic. Variable RR interval with a pattern (regularly irregular).	PR <sub>1</sub> < PR <sub>2</sub> < PR <sub>3</sub> P wave, absent QRS
Mobitz type II	Dropped beats that are not preceded by a change in the length of the PR interval (as in type I).  May progress to 3rd-degree block. Often treated with pacemaker	1 1
Third-degree (complete) AV block	The atria and ventricles beat independently of each other. P wave and QRS complexes not rhythmically associated. Atrial rate > ventricular rate. Usually treated with pacemaker. Can be cause by Lym3 disease.	
	PP <sub>1</sub> = PP <sub>2</sub> = PP <sub>3</sub> = PF	= RR <sub>2</sub> P wave on QRS complex On T wave

FAS1\_2019\_07-Cardio.indd 295 11/7/19 4:24 PM

#### CARDIOVASCULAR ► CARDIOVASCULAR—PHYSIOLOGY

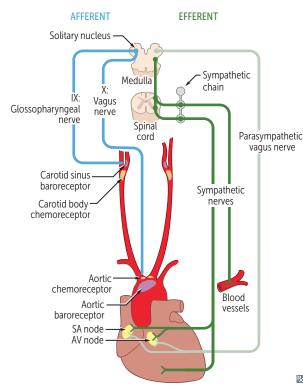
### **Atrial natriuretic** peptide

Released from atrial myocytes in response to † blood volume and atrial pressure. Acts via cGMP. Causes vasodilation and ↓ Na<sup>+</sup> reabsorption at the renal collecting tubule. Dilates afferent renal arterioles and constricts efferent arterioles, promoting diuresis and contributing to "aldosterone escape" mechanism.

### **B-type** (brain) natriuretic peptide

Released from ventricular myocytes in response to † tension. Similar physiologic action to ANP, with longer half-life. BNP blood test used for diagnosing HF (very good negative predictive value). Available in recombinant form (nesiritide) for treatment of HF.

### **Baroreceptors and chemoreceptors**



### **Receptors:**

- Aortic arch transmits via vagus nerve to solitary nucleus of medulla (responds to changes in BP).
- Carotid sinus (dilated region at carotid bifurcation) transmits via glossopharyngeal nerve to solitary nucleus of medulla (responds to changes in BP).

#### **Baroreceptors:**

- Hypotension → ↓ arterial pressure → ↓ stretch → ↓ afferent baroreceptor firing → ↑ efferent sympathetic firing and ↓ efferent parasympathetic stimulation → vasoconstriction, † HR, † contractility, † BP. Important in the response to severe hemorrhage.
- Carotid massage—↑ pressure on carotid sinus → ↑ stretch → ↑ afferent baroreceptor firing → ↑ AV node refractory period → ↓ HR.
- Component of Cushing reflex (triad of hypertension, bradycardia, and respiratory depression)—↑ intracranial pressure constricts arterioles → cerebral ischemia → ↑ pCO<sub>2</sub> and  $\downarrow$  pH  $\rightarrow$  central reflex sympathetic  $\uparrow$  in perfusion pressure (hypertension) → ↑ stretch → peripheral reflex baroreceptor induced bradycardia.

### **Chemoreceptors:**

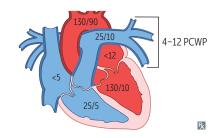
Ŗ

- Peripheral—carotid and aortic bodies are stimulated by † Pco<sub>2</sub>,  $\downarrow$  pH of blood, and  $\downarrow$  Po<sub>2</sub> (< 60 mm Hg).
- Central—are stimulated by changes in pH and Pco<sub>2</sub> of brain interstitial fluid, which in turn are influenced by arterial CO2 as H<sup>+</sup> cannot cross the blood-brain barrier. Do not directly respond to Po<sub>2</sub>. Central chemoreceptors become less responsive with chronically ↑ Pco<sub>2</sub> (eg, COPD) → ↑ dependence on peripheral chemoreceptors to detect  $\downarrow$  O<sub>2</sub> to drive respiration.

FAS1 2019 07-Cardio.indd 296 11/7/19 4:24 PM

### Normal cardiac pressures

Pulmonary capillary wedge pressure (PCWP; in mm Hg) is a good approximation of left atrial pressure. In mitral stenosis, PCWP > LV end diastolic pressure. PCWP is measured with pulmonary artery catheter (Swan-Ganz catheter).



Autoregulation	How blood flow to an organ remains constant over a wide range of perfusion pressures.		
ORGAN	FACTORS DETERMINING AUTOREGULATION		
Heart	Local metabolites (vasodilatory): adenosine, NO, CO₂, ↓ O₂	The pulmonary vasculature is unique in that alveolar hypoxia causes vasoconstriction so	
Brain	Local metabolites (vasodilatory): CO <sub>2</sub> (pH)	that only well-ventilated areas are perfused. In	
Kidneys	Myogenic and tubuloglomerular feedback	other organs, hypoxia causes vasodilation.	
Lungs	Hypoxia causes vasoconstriction		
CO <sub>2</sub> , H <sup>+</sup> , Adenosine, Lactate, K <sup>+</sup> At rest: sympathetic tone in arteries		CHALK	
Skin	Sympathetic vasoconstriction most important mechanism for temperature control		

### Capillary fluid exchange

Starling forces determine fluid movement through capillary membranes:

- P<sub>c</sub> = capillary hydrostatic pressure—pushes fluid out of capillary
- P<sub>i</sub> = interstitial hydrostatic pressure—pushes fluid into capillary
- $\pi_c$  = plasma colloid osmotic (oncotic) pressure—pulls fluid into capillary
- $\pi_i$  = interstitial fluid colloid osmotic pressure—pulls fluid out of capillary

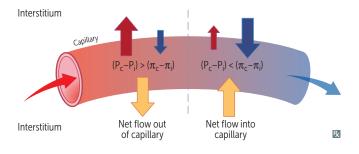
 $J_v = \text{net fluid flow} = K_f \left[ (P_c - P_i) - \sigma(\pi_c - \pi_i) \right]$ 

 $K_f$  = capillary permeability to fluid

 $\sigma$  = reflection coefficient (measure of capillary permeability to protein)

Edema—excess fluid outflow into interstitium commonly caused by:

- † capillary pressure († P<sub>c</sub>; eg, HF)
- † capillary permeability († K<sub>f</sub>; eg, toxins, infections, burns)
- † interstitial fluid colloid osmotic pressure (†  $\pi_i$ ; eg, lymphatic blockage)
- $\downarrow$  plasma proteins ( $\downarrow \pi_c$ ; eg, nephrotic syndrome, liver failure, protein malnutrition)



FAS1\_2019\_07-Cardio.indd 297 11/7/19 4:24 PM

### ► CARDIOVASCULAR—PATHOLOGY

### **Congenital heart diseases**

### RIGHT-TO-LEFT SHUNTS

Early cyanosis—"blue babies." Often diagnosed prenatally or become evident immediately after birth. Usually require urgent surgical treatment and/or maintenance of a PDA.

#### The **5 T**'s:

- 1. Truncus arteriosus (1 vessel)
- 2. Transposition (2 switched vessels)
- 3. Tricuspid atresia (3 = Tri)
- **4.** Tetralogy of Fallot (**4 = Tetra**)
- **5.** TAPVR (**5** letters in the name)

### Persistent truncus arteriosus

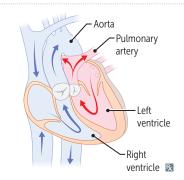
Truncus arteriosus fails to divide into pulmonary trunk and aorta due to failure of aorticopulmonary septum formation; most patients have accompanying VSD.

### 4. Tetralegy of Fallet (4 – Tetra)

### D-transposition of great vessels

Aorta leaves RV (anterior) and pulmonary trunk leaves LV (posterior) → separation of systemic and pulmonary circulations. Not compatible with life unless a shunt is present to allow mixing of blood (eg, VSD, PDA, or patent foramen ovale).

Due to failure of the aorticopulmonary septum to spiral ("egg on a string" appearance on CXR). Without surgical intervention, most infants die within the first few months of life.



#### **Tricuspid atresia**

Absence of tricuspid valve and hypoplastic RV; requires both ASD and VSD for viability.

### **Tetralogy of Fallot** Caused by ante

# A P.Z.

Caused by anterosuperior displacement of the infundibular septum. Most common cause of early childhood cyanosis.

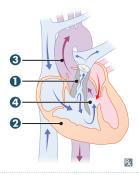
- Pulmonary infundibular stenosis (most important determinant for prognosis)
- **2** Right ventricular hypertrophy (RVH)—boot-shaped heart on CXR A
- **3** Overriding aorta
- 4 VSD

Pulmonary stenosis forces right-to-left flow across VSD → RVH, "tet spells" (often caused by crying, fever, and exercise due to exacerbation of RV outflow obstruction).

#### PROVe.

Squatting: ↑ SVR, ↓ right-to-left shunt, improves cyanosis.

Associated with 22q11 syndromes.



## Total anomalous pulmonary venous return

Pulmonary veins drain into right heart circulation (SVC, coronary sinus, etc); associated with ASD and sometimes PDA to allow for right-to-left shunting to maintain CO.

### **Ebstein anomaly**

Displacement of tricuspid valve leaflets downward into RV, artificially "atrializing" the ventricle. Associated with tricuspid regurgitation, accessory conduction pathways, right-sided HF. Can be caused by lithium exposure in utero.

FAS1\_2019\_07-Cardio.indd 298 11/7/19 4:24 PM

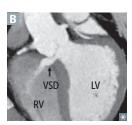
### **Congenital heart diseases (continued)**

#### **LEFT-TO-RIGHT SHUNTS**

### Acyanotic at presentation; cyanosis may occur years later. Frequency: VSD > ASD > PDA.

### Right-to-Left shunts: eaRLy cyanosis. Left-to-Right shunts: "LateR" cyanosis.

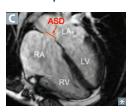
### Ventricular septal defect



Asymptomatic at birth, may manifest weeks later or remain asymptomatic throughout life. Most self resolve; larger lesions **B** may lead to LV overload and HF.

 $O_2$  saturation  $\uparrow$  in RV and pulmonary artery.

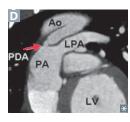
### **Atrial septal defect**



Defect in interatrial septum **C**; wide, fixed split S2. Ostium secundum defects most common and usually an isolated finding; ostium primum defects rarer and usually occur with other cardiac anomalies. Symptoms range from none to HF. Distinct from patent foramen ovale in that septa are missing tissue rather than unfused.

O<sub>2</sub> saturation † in RA, RV, and pulmonary artery. May lead to paradoxical emboli (systemic venous emboli use ASD to bypass lungs and become systemic arterial emboli). Associated with Down syndrome.

### Patent ductus arteriosus



In fetal period, shunt is right to left (normal). In neonatal period, ↓ pulmonary vascular resistance → shunt becomes left to right → progressive RVH and/or LVH and HF.

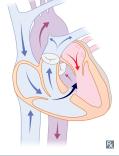
Associated with a continuous, "machine-like" murmur. Patency is maintained by PGE synthesis and low O₂ tension. Uncorrected PDA □ can eventually result in late cyanosis in the lower extremities (differential cyanosis).

PDA is normal in utero and normally closes only after birth.

### Eisenmenger syndrome

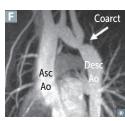


Uncorrected left-to-right shunt (VSD, ASD, PDA) → ↑ pulmonary blood flow → pathologic remodeling of vasculature → pulmonary arterial hypertension. RVH occurs to compensate → shunt becomes right to left. Causes late cyanosis, clubbing **E**, and polycythemia. Age of onset varies.



#### OTHER ANOMALIES

### Coarctation of the aorta



Aortic narrowing **F** near insertion of ductus arteriosus ("juxtaductal"). Associated with bicuspid aortic valve, other heart defects, and Turner syndrome. Hypertension in upper extremities and weak, delayed pulse in lower extremities (brachial-femoral delay). With age, intercostal arteries enlarge due to collateral circulation; arteries erode ribs → notched appearance on CXR.

Complications include HF, † risk of cerebral hemorrhage (berry aneurysms), aortic rupture, and possible endocarditis.

FAS1\_2019\_07-Cardio.indd 299 11/7/19 4:24 PM

### **CARDIOVASCULAR** → CARDIOVASCULAR—PATHOLOGY

### Congenital cardiac defect associations

DISORDER	DEFECT
Alcohol exposure in utero (fetal alcohol syndrome)	VSD, PDA, ASD, tetralogy of Fallot
Congenital rubella	PDA, pulmonary artery stenosis, septal defects
Down syndrome	AV septal defect (endocardial cushion defect), VSD, ASD
Infant of diabetic mother	Transposition of great vessels, VSD
Marfan syndrome	MVP, thoracic aortic aneurysm and dissection, aortic regurgitation
Prenatal lithium exposure	Ebstein anomaly
Turner syndrome	Bicuspid aortic valve, coarctation of aorta
Williams syndrome	Supravalvular aortic stenosis
22q11 syndromes	Truncus arteriosus, tetralogy of Fallot

### **Hypertension**

Persistent systolic BP  $\geq$  130 mm Hg and/or diastolic BP  $\geq$  80 mm Hg.

RISK FACTORS

† age, obesity, diabetes, physical inactivity, excess salt intake, excess alcohol intake, cigarette smoking, family history; African American > Caucasian > Asian.

#### **FEATURES**

A

PREDISPOSES TO

90% of hypertension is 1° (essential) and related to † CO or † TPR. Remaining 10% mostly 2° to renal/renovascular diseases such as fibromuscular dysplasia (characteristic "string of beads" appearance of renal artery A, usually seen in women of child-bearing age) and atherosclerotic renal artery stenosis or to 1° hyperaldosteronism.

**Hypertensive urgency**—severe (≥ 180/≥ 120 mm Hg) hypertension without acute end-organ damage.

**Hypertensive emergency**—severe hypertension with evidence of acute end-organ damage (eg, encephalopathy, stroke, retinal hemorrhages and exudates, papilledema, MI, HF, aortic dissection, kidney injury, microangiopathic hemolytic anemia, eclampsia).

CAD, LVH, HF, atrial fibrillation; aortic dissection, aortic aneurysm; stroke; CKD (hypertensive nephropathy); retinopathy.

FAS1\_2019\_07-Cardio.indd 300 11/7/19 4:24 PM

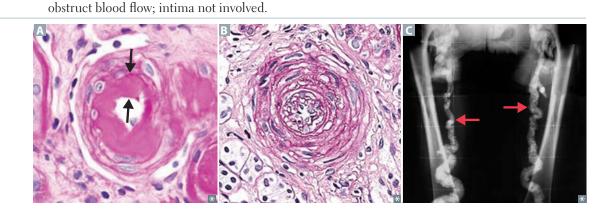
### Hyperlipidemia signs

sclerosis)

Xanthomas	Plaques or nodules composed of lipid-laden histiocytes in skin A, especially the eyelids (xanthelasma B).
Tendinous xanthoma	Lipid deposit in tendon 🕻, especially Achilles.
Corneal arcus	Lipid deposit in cornea. Common in elderly (arcus senilis <b>D</b> ), but appears earlier in life with hypercholesterolemia.



#### **Arteriosclerosis** Hardening of arteries, with arterial wall thickening and loss of elasticity. **Arteriolosclerosis** Common. Affects small arteries and arterioles. Two types: hyaline (thickening of vessel walls 2° to plasma protein leak into endothelium in essential hypertension or diabetes mellitus A) and hyperplastic ("onion skinning" in severe hypertension B with proliferation of smooth muscle Mönckeberg sclerosis Uncommon. Affects Medium-sized arteries. Calcification of internal elastic lamina and media of (Medial calcific arteries → vascular stiffening without obstruction. "Pipestem" appearance on x-ray C. Does not



FAS1\_2019\_07-Cardio.indd 301 11/7/19 4:24 PM

### 302

### **SECTION III**

### CARDIOVASCULAR → CARDIOVASCULAR—PATHOLOGY

### **Atherosclerosis**

Very common. Disease of elastic arteries and large- and medium-sized muscular arteries; a form of arteriosclerosis caused by buildup of cholesterol plaques in intima.

LOCATION

Abdominal aorta > Coronary artery > Popliteal artery > Carotid artery > circle of Willis. A CoPy Cat named Willis.

RISK FACTORS

Modifiable: smoking, hypertension, dyslipidemia († LDL, ↓ HDL), diabetes.

Non-modifiable: age, sex († in men and postmenopausal women), family history.

**SYMPTOMS** 

Angina, claudication, but can be asymptomatic.

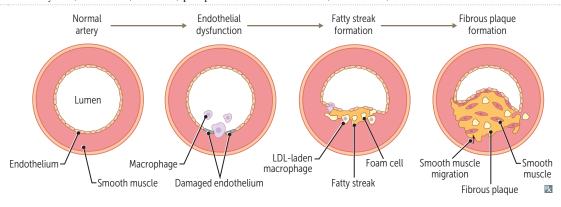
PROGRESSION



Inflammation important in pathogenesis: endothelial cell dysfunction → macrophage and LDL accumulation → foam cell formation → fatty streaks → smooth muscle cell migration (involves PDGF and FGF), proliferation, and extracellular matrix deposition → fibrous plaque → complex atheromas A → calcification (calcium content correlates with risk of complications).

#### COMPLICATIONS

Aneurysms, ischemia, infarcts, peripheral vascular disease, thrombus, emboli.



#### **Aortic aneurysm**

Localized pathologic dilation of the aorta. May cause abdominal and/or back pain, which is a sign of leaking, dissection, or imminent rupture.

### Abdominal aortic aneurysm



Usually associated with atherosclerosis. Risk factors include history of tobacco use, † age, male sex, family history. May present as palpable pulsatile abdominal mass (arrows in A point to outer dilated calcified aortic wall, with partial crescent-shaped non-opacification of aorta due to flap/clot). Most often infrarenal (distal to origin of renal arteries).

### Thoracic aortic aneurysm

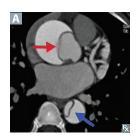
Associated with cystic medial degeneration. Risk factors include hypertension, bicuspid aortic valve, connective tissue disease (eg, Marfan syndrome). Also associated with 3° syphilis (obliterative endarteritis of the vasa vasorum). Aortic root dilatation may lead to aortic valve regurgitation.

FAS1\_2019\_07-Cardio.indd 302

### Traumatic aortic rupture

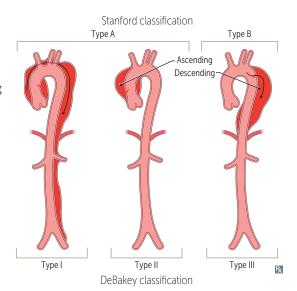
Due to trauma and/or deceleration injury, most commonly at aortic isthmus (proximal descending aorta just distal to origin of left subclavian artery). X-ray may reveal widened mediastinum.

#### **Aortic dissection**



Longitudinal intimal tear forming a false lumen. Associated with hypertension, bicuspid aortic valve, inherited connective tissue disorders (eg, Marfan syndrome). Can present with tearing, sudden-onset chest pain radiating to the back +/— markedly unequal BP in arms. CXR can show mediastinal widening. Can result in organ ischemia, aortic rupture, death. Two types:

- Stanford type A (proximal): involves
   Ascending aorta (red arrow in A). May
   extend to aortic arch or descending aorta
   (blue arrow in A). May result in acute
   aortic regurgitation or cardiac tamponade.
   Treatment: surgery.
- Stanford type **B** (distal): involves only descending aorta (**B**elow left subclavian artery). Treatment: β-blockers, then vasodilators.



FAS1\_2019\_07-Cardio.indd 303 11/7/19 4:24 PM

### **Ischemic heart disease manifestations** Chest pain due to ischemic myocardium 2° to coronary artery narrowing or spasm; no myocyte **Angina** necrosis. ■ Stable—usually 2° to atherosclerosis (≥ 70% occlusion); exertional chest pain in classic distribution (usually with ST depression on ECG), resolving with rest or nitroglycerin. Vasospastic (also called Prinzmetal or Variant)—occurs at rest 2° to coronary artery spasm; transient ST elevation on ECG. Smoking is a risk factor; hypertension and hypercholesterolemia are not. Triggers include cocaine, alcohol, and triptans. Treat with Ca<sup>2+</sup> channel blockers, nitrates, and smoking cessation (if applicable). Unstable—thrombosis with incomplete coronary artery occlusion; +/- ST depression and/or T-wave inversion on ECG but no cardiac biomarker elevation (unlike NSTEMI); † in frequency or intensity of chest pain or any chest pain at rest. Distal to coronary stenosis, vessels are maximally dilated at baseline. Administration of vasodilators **Coronary steal** (eg, dipyridamole, regadenoson) dilates normal vessels → blood is shunted toward well-perfused syndrome areas → ischemia in myocardium perfused by stenosed vessels. Principle behind pharmacologic stress tests with coronary vasodilators. Sudden cardiac death Death from cardiac causes within 1 hour of onset of symptoms, most commonly due to a lethal arrhythmia (eg, VF). Associated with CAD (up to 70% of cases), cardiomyopathy (hypertrophic, dilated), and hereditary ion channelopathies (eg, long QT syndrome, Brugada syndrome). Prevent with ICD. **Chronic ischemic**

### heart disease

Progressive onset of HF over many years due to chronic ischemic myocardial damage.

### **Myocardial infarction**

Most often due to rupture of coronary artery atherosclerotic plaque → acute thrombosis. ↑ cardiac biomarkers (CK-MB, troponins) are diagnostic.

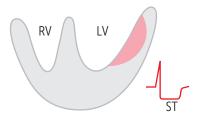
### Non-ST-segment elevation MI (NSTEMI)

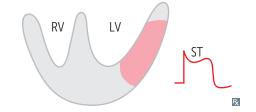
Subendocardial infarcts Subendocardium (inner 1/3) especially vulnerable to ischemia ST depression on ECG

### ST-segment elevation MI (STEMI)

Transmural infarcts Full thickness of myocardial wall involved

ST elevation, pathologic Q waves on ECG





FAS1 2019 07-Cardio.indd 304 11/7/19 4:24 PM

### **Evolution of** myocardial infarction

Commonly occluded coronary arteries: LAD > RCA > circumflex. Symptoms: diaphoresis, nausea, vomiting, severe retrosternal pain, pain in left arm and/or jaw, shortness of breath, fatigue.

TIME	GROSS	LIGHT MICROSCOPE	COMPLICATIONS
0–24 hr	Dark mottling  Occluded artery  Infarct Dark mottling; pale with tetrazolium stain	Early coagulative necrosis  → cell content released into blood; edema, hemorrhage, wavy fibers  Reperfusion injury → free radicals and ↑ Ca <sup>2+</sup> influx  → hypercontraction of myofibrils (dark eosinophilic stripes)	Ventricular arrhythmia, HF, cardiogenic shock
1–3 days	Hyperemia	Extensive coagulative necrosis Tissue surrounding infarct shows acute inflammation with neutrophils	Postinfarction fibrinous pericarditis
3–14 days	Hyperemic border; central yellow-brown softening	Macrophages, then granulation tissue at margins	Free wall rupture → tamponade; papillary muscle rupture → mitral regurgitation; interventricular septal rupture due to macrophage-mediated structural degradation → left- to-right shunt LV pseudoaneurysm (risk of rupture)
2 weeks to several months	Recanalized artery Gray-white scar	Contracted scar complete	Dressler syndrome, HF, arrhythmias, true ventricular aneurysm (risk of mural thrombus)

FAS1\_2019\_07-Cardio.indd 305 11/7/19 4:24 PM

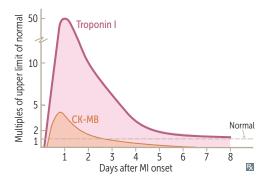
### Diagnosis of myocardial infarction

In the first 6 hours, ECG is the gold standard. Cardiac troponin I rises after 4 hours (peaks at 24 hr) and is † for 7–10 days; more specific than other protein markers.

CK-MB rises after 6–12 hours (peaks at 16–24 hr) and is predominantly found in myocardium but can also be released from skeletal muscle. Useful in diagnosing reinfarction following acute MI because levels return to normal after 48 hours.

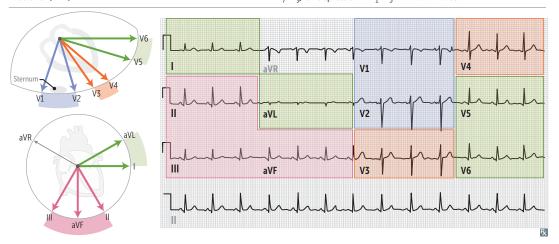
Large MIs lead to greater elevations in troponin I and CK-MB. Exact curves vary with testing procedure.

ECG changes can include ST elevation (STEMI, transmural infarct), ST depression (NSTEMI, subendocardial infarct), hyperacute (peaked) T waves, T-wave inversion, new left bundle branch block, and pathologic Q waves or poor R wave progression (evolving or old transmural infarct).



### **ECG localization of STEMI**

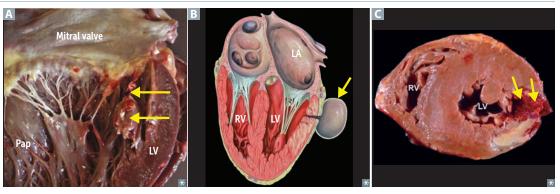
INFARCT LOCATION	LEADS WITH ST-SEGMENT ELEVATIONS OR Q WAVES
Anteroseptal (LAD)	$V_1$ – $V_2$
Anteroapical (distal LAD)	$V_3$ – $V_4$
Anterolateral (LAD or LCX)	V <sub>5</sub> -V <sub>6</sub>
Lateral (LCX)	I, aV <mark>L</mark>
InFerior (RCA)	II, III, aVF
Posterior (PDA)	$V_7 - V_0$ , ST depression in $V_1 - V_3$ with tall R waves



FAS1\_2019\_07-Cardio.indd 306 11/7/19 4:24 PM

### **Myocardial infarction complications**

Cardiac arrhythmia	Occurs within the first few days after MI. Important cause of death before reaching the hospital and within the first 24 hours post-MI.
Postinfarction fibrinous pericarditis	1–3 days: friction rub.
Papillary muscle rupture	2–7 days: posteromedial papillary muscle rupture A † risk due to single blood supply from posterior descending artery. Can result in severe mitral regurgitation.
Interventricular septal rupture	3–5 days: macrophage-mediated degradation $\rightarrow$ VSD $\rightarrow$ † $O_2$ saturation and pressure in RV.
Ventricular pseudoaneurysm formation	3–14 days: free wall rupture contained by adherent pericardium or scar tissue <b>□</b> ; ↓ CO, risk of arrhythmia, embolus from mural thrombus.
Ventricular free wall rupture	5–14 days: free wall rupture C → cardiac tamponade. LV hypertrophy and previous MI protect against free wall rupture. Acute form usually leads to sudden death.
True ventricular aneurysm	2 weeks to several months: outward bulge with contraction ("dyskinesia"), associated with fibrosis.
Dressler syndrome	Several weeks: autoimmune phenomenon resulting in fibrinous pericarditis.
LV failure and pulmonary edema	Can occur 2° to LV infarction, VSD, free wall rupture, papillary muscle rupture with mitral regurgitation.



### **Acute coronary** syndrome treatments

**Unstable angina/NSTEMI**—Anticoagulation (eg, heparin), antiplatelet therapy (eg, aspirin)

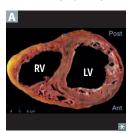
+ ADP receptor inhibitors (eg, clopidogrel), β-blockers, ACE inhibitors, statins. Symptom control with nitroglycerin and morphine.

**STEMI**—In addition to above, reperfusion therapy most important (percutaneous coronary intervention preferred over fibrinolysis).

FAS1\_2019\_07-Cardio.indd 307 11/7/19 4:24 PM

### **Cardiomyopathies**

### Dilated cardiomyopathy



Most common cardiomyopathy (90% of cases). Often idiopathic or familial (eg, due to mutation of *TTN* gene encoding the sarcomeric protein titin).

Other etiologies include drugs (eg, alcohol, cocaine, doxorubicin), infection (eg, coxsackie B virus, Chagas disease), ischemia (eg, CAD), systemic conditions (eg, hemochromatosis, sarcoidosis, thyrotoxicosis, wet beriberi), peripartum cardiomyopathy.

Findings: HF, S3, systolic regurgitant murmur, dilated heart on echocardiogram, balloon appearance of heart on CXR.

Treatment: Na<sup>+</sup> restriction, ACE inhibitors, β-blockers, diuretics, mineralocorticoid receptor blockers (eg, spironolactone), digoxin, ICD, heart transplant. Leads to systolic dysfunction.

Dilated cardiomyopathy A displays eccentric hypertrophy (sarcomeres added in series).

Takotsubo cardiomyopathy: broken heart syndrome—ventricular apical ballooning likely due to increased sympathetic stimulation (eg, stressful situations).

# Hypertrophic obstructive cardiomyopathy



60–70% of cases are familial, autosomal dominant (most commonly due to mutations in genes encoding sarcomeric proteins, such as myosin binding protein C and β-myosin heavy chain). Causes syncope during exercise and may lead to sudden death (eg, in young athletes) due to ventricular arrhythmia.

Findings: S4, systolic murmur. May see mitral regurgitation due to impaired mitral valve closure.

Treatment: cessation of high-intensity athletics, use of  $\beta$ -blocker or non-dihydropyridine Ca<sup>2+</sup> channel blockers (eg, verapamil). ICD if syncope occurs.

Diastolic dysfunction ensues.

Marked ventricular concentric hypertrophy (sarcomeres added in parallel) **B**, often septal predominance. Myofibrillar disarray and fibrosis.

Physiology of HOCM—asymmetric septal hypertrophy and systolic anterior motion of mitral valve → outflow obstruction → dyspnea, possible syncope.

Other causes of concentric LV hypertrophy: chronic HTN, Friedreich ataxia.

### Restrictive/infiltrative cardiomyopathy

Postradiation fibrosis, Löffler endocarditis, Endocardial fibroelastosis (thick fibroelastic tissue in endocardium of young children), Amyloidosis, Sarcoidosis, Hemochromatosis (although dilated cardiomyopathy is more common) (Puppy LEASH). Diastolic dysfunction ensues. Can have low-voltage ECG despite thick myocardium (especially in amyloidosis).

Löffler endocarditis—associated with hypereosinophilic syndrome; histology shows eosinophilic infiltrates in myocardium.

FAS1 2019 07-Cardio.indd 308 11/7/19 4:24 PM

#### **Heart failure**



Clinical syndrome of cardiac pump dysfunction → congestion and low perfusion. Symptoms include dyspnea, orthopnea, fatigue; signs include S3 heart sound, rales, jugular venous distention (JVD), pitting edema A.

Systolic dysfunction—reduced EF, ↑ EDV; ↓ contractility often 2° to ischemia/MI or dilated cardiomyopathy.

Diastolic dysfunction—preserved EF, normal EDV; ↓ compliance († EDP) often 2° to myocardial hypertrophy.

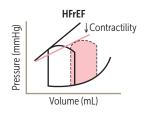
Right HF most often results from left HF. Cor pulmonale refers to isolated right HF due to pulmonary cause.

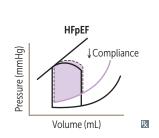
ACE inhibitors or angiotensin II receptor blockers, β-blockers (except in acute decompensated HF), and spironolactone ↓ mortality. Loop and thiazide diuretics are used mainly for symptomatic relief. Hydralazine with nitrate therapy improves both symptoms and mortality in select patients.

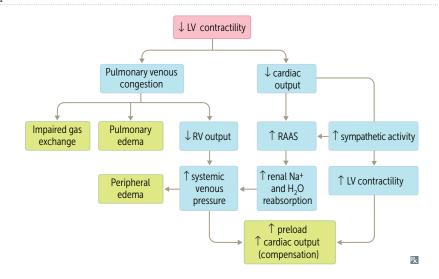
### Left heart failure Orthopnea Shortness of breath when supine: 1 venous return from redistribution of blood (immediate gravity effect) exacerbates pulmonary vascular congestion. **Paroxysmal** Breathless awakening from sleep: † venous return from redistribution of blood, reabsorption of nocturnal dyspnea peripheral edema, etc. **Pulmonary edema** ↑ pulmonary venous pressure → pulmonary venous distention and transudation of fluid. Presence of hemosiderin-laden macrophages ("HF" cells) in lungs. Right heart failure Hepatomegaly ↑ central venous pressure → ↑ resistance to portal flow. Rarely, leads to "cardiac cirrhosis." (nutmeg liver) Jugular venous † venous pressure.

distention
Peripheral edema

† venous pressure → fluid transudation.







FAS1\_2019\_07-Cardio.indd 309 11/7/19 4:24 PM

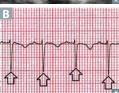
### **Shock**

Inadequate organ perfusion and delivery of nutrients necessary for normal tissue and cellular function. Initially may be reversible but life threatening if not treated promptly.

	CAUSED BY	SKIN	PCWP (PRELOAD)	СО	SVR (AFTERLOAD)	TREATMENT
Hypovolemic shock	Hemorrhage, dehydration, burns	Cold, clammy	++	ţ	†	IV fluids
Cardiogenic shock	Acute MI, HF, valvular dysfunction, arrhythmia	Cold,	<b>A</b> 1		•	Inotropes, diuresis
Obstructive shock	Cardiac tamponade, pulmonary embolism, tension pneumothorax	clammy	↑ or ↓	11	I	Relieve obstruction
Distributive shock	Sepsis, anaphylaxis CNS injury	Warm Dry	†	<b>†</b>	†† ††	IV fluids, pressors, epinephrine (anaphylaxis)

### **Cardiac tamponade**





Compression of the heart by fluid (eg, blood, effusions [arrows in  $\blacksquare$ ] in pericardial space)  $\rightarrow \downarrow$  CO. Equilibration of diastolic pressures in all 4 chambers.

Findings: Beck triad (hypotension, distended neck veins, distant heart sounds), † HR, pulsus paradoxus. ECG shows low-voltage QRS and electrical alternans 

(due to "swinging" movement of heart in large effusion).

Pulsus paradoxus—↓ in amplitude of systolic BP by > 10 mm Hg during inspiration. Seen in constrictive Pericarditis, obstructive pulmonary disease (eg, Croup, OSA, Asthma, COPD), cardiac Tamponade (Pea COAT).

FAS1\_2019\_07-Cardio.indd 310 11/7/19 4:24 PM

#### **Bacterial endocarditis**

Acute—*S aureus* (high virulence). Large vegetations on previously normal valves A. Rapid onset.

Subacute—viridans streptococci (low virulence). Smaller vegetations on congenitally abnormal or diseased valves. Sequela of dental procedures. Gradual onset.

Symptoms: fever (most common), new murmur, Roth spots (round white spots on retina surrounded by hemorrhage B), Osler nodes (Ouchy raised lesions on finger or toe pads due to immune complex deposition), Janeway lesions (small, painless, erythematous lesions on palm or sole) D, splinter hemorrhages E on nail bed.

Associated with glomerulonephritis, septic arterial or pulmonary emboli.

May be nonbacterial (marantic/thrombotic) 2° to malignancy, hypercoagulable state, or lupus.

**FROM JANE** with **♥**:

Fever

Roth spots

Osler nodes

Murmur

Janeway lesions

**A**nemia

Nail-bed hemorrhage

**E**mboli

Requires multiple blood cultures for diagnosis. If culture ⊖, most likely *Coxiella burnetii*, *Bartonella* spp.

Mitral valve is most frequently involved.

Tricuspid valve endocarditis is associated with IV drug abuse (don't "tri" drugs). Associated with *S aureus*, *Pseudomonas*, and *Candida*.

*S bovis (gallolyticus)* is present in colon cancer, *S epidermidis* on prosthetic valves.

Native valve endocarditis may be due to **HACEK** organisms (*Haemophilus*, *Aggregatibacter* [formerly *Actinobacillus*], *Cardiobacterium*, *Eikenella*, *Kingella*).





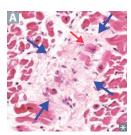






FAS1\_2019\_07-Cardio.indd 311 11/7/19 4:24 PM

#### **Rheumatic fever**



A consequence of pharyngeal infection with group A β-hemolytic streptococci. Late sequelae include rheumatic heart disease, which affects heart valves—mitral > aortic >> tricuspid (high-pressure valves affected most). Early lesion is mitral valve regurgitation; late lesion is mitral stenosis.

Associated with Aschoff bodies (granuloma with giant cells [blue arrows in A]), Anitschkow cells (enlarged macrophages with ovoid, wavy, rod-like nucleus [red arrow in A]), † anti-streptolysin O (ASO) and † anti-DNase B titers.

Immune mediated (type II hypersensitivity); not a direct effect of bacteria. Antibodies to M protein cross-react with self antigens, often myosin (molecular mimicry).

Treatment/prophylaxis: penicillin.

JVNES (major criteria):

Joint (migratory polyarthritis)

♥ (carditis)

Nodules in skin (subcutaneous)

Erythema marginatum (evanescent rash with ring margin)

Sydenham chorea

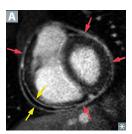
### Syphilitic heart disease

3° syphilis disrupts the vasa vasorum of the aorta with consequent atrophy of vessel wall and dilation of aorta and valve ring. May see calcification of aortic root, ascending aortic arch, and thoracic aorta. Leads to "tree bark" appearance of aorta.

Can result in aneurysm of ascending aorta or aortic arch, aortic insufficiency.

FAS1\_2019\_07-Cardio.indd 312 11/7/19 4:24 PM

### **Acute pericarditis**



Inflammation of the pericardium [A, red arrows]. Commonly presents with sharp pain, aggravated by inspiration, and relieved by sitting up and leaning forward. Often complicated by pericardial effusion [between yellow arrows in A]. Presents with friction rub. ECG changes include widespread ST-segment elevation and/or PR depression.

Causes include idiopathic (most common; presumed viral), confirmed infection (eg, coxsackievirus B), neoplasia, autoimmune (eg, SLE, rheumatoid arthritis), uremia, cardiovascular (acute STEMI or Dressler syndrome), radiation therapy.

Treatment: NSAIDs, colchicine, glucocorticoids, dialysis (uremia).

### **Myocarditis**

Inflammation of myocardium → global enlargement of heart and dilation of all chambers. Major cause of SCD in adults < 40 years old.

Presentation highly variable, can include dyspnea, chest pain, fever, arrhythmias (persistent tachycardia out of proportion to fever is characteristic).

Multiple causes:

- Viral (eg, adenovirus, coxsackie B, parvovirus Bl9, HIV, HHV-6); lymphocytic infiltrate with focal necrosis highly indicative of viral myocarditis.
- Parasitic (eg, Trypanosoma cruzi, Toxoplasma gondii)
- Bacterial (eg, Borrelia burgdorferi, Mycoplasma pneumoniae, Corynebacterium diphtheriae)
- Toxins (eg, carbon monoxide, black widow venom)
- Rheumatic fever
- Drugs (eg, doxorubicin, cocaine)
- Autoimmune (eg, Kawasaki disease, sarcoidosis, SLE, polymyositis/dermatomyositis)

Complications include sudden death, arrhythmias, heart block, dilated cardiomyopathy, HF, mural thrombus with systemic emboli.

FAS1\_2019\_07-Cardio.indd 313 11/7/19 4:24 PM

### **Vasculitides**

	EPIDEMIOLOGY/PRESENTATION	NOTES
Large-vessel vasculitis		
Giant cell (temporal) arteritis	Usually elderly females. Unilateral headache, possible temporal artery tenderness, jaw claudication. May lead to irreversible blindness due to ophthalmic artery occlusion. Associated with polymyalgia rheumatica.	Most commonly affects branches of carotid artery.  Focal granulomatous inflammation A.  † ESR.  Treat with high-dose corticosteroids prior to temporal artery biopsy to prevent blindness.
Takayasu arteritis	Usually Asian females < 40 years old.  "Pulseless disease" (weak upper extremity pulses), fever, night sweats, arthritis, myalgias, skin nodules, ocular disturbances.	Granulomatous thickening and narrowing of aortic arch and proximal great vessels <b>B</b> . † ESR. Treatment: corticosteroids.
Medium-vessel vasculiti	s	
Buerger disease (thromboangiitis obliterans)	Heavy smokers, males < 40 years old. Intermittent claudication. May lead to gangrene , autoamputation of digits, superficial nodular phlebitis. Raynaud phenomenon is often present.	Segmental thrombosing vasculitis with vein and nerve involvement.  Treatment: smoking cessation.
Kawasaki disease (mucocutaneous lymph node syndrome)	Asian children < 4 years old.  Conjunctival injection, Rash (polymorphous  → desquamating), Adenopathy (cervical),  Strawberry tongue (oral mucositis) D, Hand- foot changes (edema, erythema), fever.	CRASH and burn on a Kawasaki.  May develop coronary artery aneurysms <b>E</b> ; thrombosis or rupture can cause death.  Treatment: IV immunoglobulin and aspirin.
Polyarteritis nodosa	Usually middle-aged men. Hepatitis B seropositivity in 30% of patients. Fever, weight loss, malaise, headache. GI: abdominal pain, melena. Hypertension, neurologic dysfunction, cutaneous eruptions, renal damage.	Typically involves renal and visceral vessels, not pulmonary arteries.  Different stages of transmural inflammation with fibrinoid necrosis.  Innumerable renal microaneurysms  and spasms on arteriogram (string of pearls appearance).  Treatment: corticosteroids, cyclophosphamide.
Small-vessel vasculitis		
Behçet syndrome	High incidence in people of Turkish and eastern Mediterranean descent.  Recurrent aphthous ulcers, genital ulcerations, uveitis, erythema nodosum. Can be precipitated by HSV or parvovirus. Flares last 1–4 weeks.	Immune complex vasculitis. Associated with HLA-B51.
Cutaneous small- vessel vasculitis	Occurs 7-10 days after certain medications (penicillin, cephalosporins, phenytoin, allopurinol) or infections (eg, HCV, HIV). Palpable purpura, no visceral involvement.	Immune complex-mediated leukocytoclastic vasculitis; late involvement indicates systemic vasculitis.

FAS1\_2019\_07-Cardio.indd 314 11/7/19 4:24 PM

### **Vasculitides** (continued)

	EPIDEMIOLOGY/PRESENTATION	NOTES
Small-vessel vasculitis (c	ontinued)	
Eosinophilic granulomatosis with polyangiitis (Churg- Strauss)	Asthma, sinusitis, skin nodules or purpura, peripheral neuropathy (eg, wrist/foot drop). Can also involve heart, GI, kidneys (pauci-immune glomerulonephritis).	Granulomatous, necrotizing vasculitis with eosinophilia <b>G</b> . MPO-ANCA/p-ANCA, † IgE level.
Granulomatosis with polyangiitis (Wegener)	Upper respiratory tract: perforation of nasal septum, chronic sinusitis, otitis media, mastoiditis.  Lower respiratory tract: hemoptysis, cough, dyspnea.  Renal: hematuria, red cell casts.	<ul> <li>Triad:</li> <li>Focal necrotizing vasculitis</li> <li>Necrotizing granulomas in lung and upper airway</li> <li>Necrotizing glomerulonephritis</li> <li>PR3-ANCA/c-ANCA ☐ (anti-proteinase 3).</li> <li>CXR: large nodular densities.</li> <li>Treatment: cyclophosphamide, corticosteroids.</li> </ul>
Immunoglobulin A vasculitis	Also called Henoch-Schönlein purpura.  Most common childhood systemic vasculitis.  Often follows URI.  Classic triad:  Skin: palpable purpura on buttocks/legs  Arthralgias  GI: abdominal pain (associated with intussusception)	Vasculitis 2° to IgA immune complex deposition.  Associated with IgA nephropathy (Berger disease).  Treatment: supportive care, possibly corticosteroids.
Microscopic polyangiitis	Necrotizing vasculitis commonly involving lung, kidneys, and skin with pauci-immune glomerulonephritis and palpable purpura. Presentation similar to granulomatosis with polyangiitis but without nasopharyngeal involvement.	No granulomas.  MPO-ANCA/p-ANCA (antimyeloperoxidase).  Treatment: cyclophosphamide, corticosteroids.
Mixed cryoglobulinemia	Often due to viral infections, especially HCV. Triad of palpable purpura, weakness, arthralgias. May also have peripheral neuropathy and renal disease (eg, glomerulonephritis).	Cryoglobulins are immunoglobulins that precipitate in the Cold.  Vasculitis due to mixed IgG and IgM immune complex deposition.
	RSC AAo **	LAD LAD

FAS1\_2019\_07-Cardio.indd 315

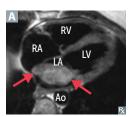
316 SECTION III

### **CARDIOVASCULAR** ► CARDIOVASCULAR—PHARMACOLOGY

#### **Cardiac tumors**

Most common heart tumor is a metastasis (eg, melanoma).

### **Myxomas**



Most common 1° cardiac tumor in adults (arrows in A). 90% occur in the atria (mostly left atrium). Myxomas are usually described as a "ball valve" obstruction in the left atrium (associated with multiple syncopal episodes). IL-6 production by tumor → constitutional symptoms (eg, fever, weight loss). May auscultate early diastolic "tumor plop" sound. Histology: gelatinous material, myxoma cells immersed in glycosaminoglycans.

Adults make myxed drinks.

### Rhabdomyomas

Most frequent 1° cardiac tumor in children (associated with tuberous sclerosis). Histology: hamartomatous growths.

### **Kussmaul sign**

† in JVP on inspiration instead of a normal ↓.

Inspiration → negative intrathoracic pressure not transmitted to heart → impaired filling of right ventricle → blood backs up into vena cava → JVD. May be seen with constrictive pericarditis, restrictive cardiomyopathies, right heart failure, massive pulmonary embolism, right atrial or ventricular tumors.

### Hereditary hemorrhagic telangiectasia

Also called Osler-Weber-Rendu syndrome. Autosomal dominant disorder of blood vessels. Findings: blanching lesions (telangiectasias) on skin and mucous membranes, recurrent epistaxis, skin discolorations, arteriovenous malformations (AVMs), GI bleeding, hematuria.

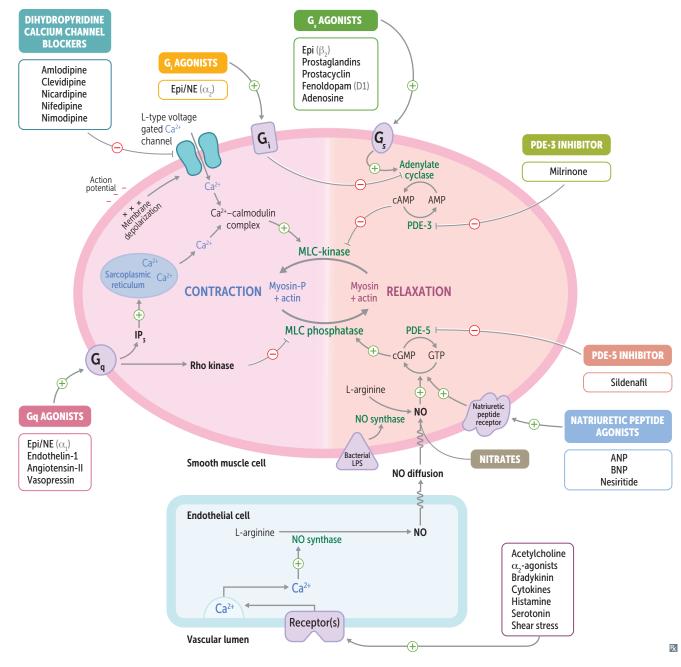
### ► CARDIOVASCULAR—PHARMACOLOGY

#### **Hypertension treatment**

Primary (essential) hypertension	Thiazide diuretics, ACE inhibitors, angiotensin II receptor blockers (ARBs), dihydropyridine Ca <sup>2+</sup> channel blockers.	
Hypertension with heart failure	Diuretics, ACE inhibitors/ARBs, β-blockers (compensated HF), aldosterone antagonists.	β-blockers must be used cautiously in decompensated HF and are contraindicated in cardiogenic shock.  In HF, ARBs may be combined with the neprilysin inhibitor sacubitril.
Hypertension with diabetes mellitus	ACE inhibitors/ARBs, $Ca^{2+}$ channel blockers, thiazide diuretics, $\beta$ -blockers.	ACE inhibitors/ARBs are protective against diabetic nephropathy. β-blockers can mask hypoglycemia symptoms.
Hypertension in asthma	ARBs, $Ca^{2+}$ channel blockers, thiazide diuretics, cardioselective $\beta$ -blockers.	Avoid nonselective β-blockers to prevent β <sub>2</sub> -receptor–induced bronchoconstriction. Avoid ACE inhibitors to prevent confusion between drug or asthma-related cough.
Hypertension in pregnancy	Hydralazine, labetalol, methyldopa, nifedipine.	"He likes my neonate."

FAS1\_2019\_07-Cardio.indd 316 11/7/19 4:24 PM

#### **Cardiac therapy**



FAS1\_2019\_07-Cardio.indd 317 11/7/19 4:24 PM

### CARDIOVASCULAR → CARDIOVASCULAR—PHARMACOLOGY

Calcium channel blockers	Amlodipine, clevidipine, nicardipine, nifedipine, nimodipine (dihydropyridines, act on vascular smooth muscle); diltiazem, verapamil (non-dihydropyridines, act on heart).		
MECHANISM	Block voltage-dependent L-type calcium channels of cardiac and smooth muscle → ↓ muscle contractility.		
	Vascular smooth muscle—amlodipine = nifedipine > diltiazem > verapamil. Heart—verapamil > diltiazem > amlodipine = nifedipine (verapamil = ventricle).		
CLINICAL USE	Dihydropyridines (except nimodipine): hypertension, angina (including vasospastic type), Raynauc phenomenon.  Nimodipine: subarachnoid hemorrhage (prevents cerebral vasospasm).		
	Nicardipine, clevidipine: hypertensive urgency or emergency.  Non-dihydropyridines: hypertension, angina, atrial fibrillation/flutter.		
ADVERSE EFFECTS	Gingival hyperplasia. Dihydropyridine: peripheral edema, flushing, dizziness.		
	Non-dihydropyridine: cardiac depression, AV block, hyperprolactinemia (verapamil), constipation.		
Hydralazine			
MECHANISM	↑ cGMP → smooth muscle relaxation. Vasodilates arterioles > veins; afterload reduction.		
CLINICAL USE	Severe hypertension (particularly acute), HF (with organic nitrate). Safe to use during pregnancy. Frequently coadministered with a β-blocker to prevent reflex tachycardia.		
ADVERSE EFFECTS	Compensatory tachycardia (contraindicated in angina/CAD), fluid retention, headache, angina, drug-induced lupus.		
Hypertensive emergency	Treat with labetalol, clevidipine, fenoldopam, nicardipine, nitroprusside.		
Nitroprusside	Short acting vasodilator (arteries = veins); † cGMP via direct release of NO. Can cause cyanide toxicity (releases cyanide).		
Fenoldopam	Dopamine D₁ receptor agonist—coronary, peripheral, renal, and splanchnic vasodilation. ↓ BP, ↑ natriuresis. Also used postoperatively as an antihypertensive. Can cause hypotension and tachycardia.		
Nitrates	Nitroglycerin, isosorbide dinitrate, isosorbide mononitrate.		
MECHANISM	Vasodilate by ↑ NO in vascular smooth muscle → ↑ in cGMP and smooth muscle relaxation. Dilate veins >>> arteries. ↓ preload.		
CLINICAL USE	Angina, acute coronary syndrome, pulmonary edema.		
ADVERSE EFFECTS	Reflex tachycardia (treat with β-blockers), hypotension, flushing, headache, "Monday disease" in industrial exposure: development of tolerance for the vasodilating action during the work week and loss of tolerance over the weekend → tachycardia, dizziness, headache upon reexposure. Contraindicated in right ventricular infarction, hypertrophic cardiomyopathy, and with concurrent PDE-5 inhibitor use.		

FAS1\_2019\_07-Cardio.indd 318

#### **Antianginal therapy**

Goal is reduction of myocardial  $O_2$  consumption (MVO<sub>2</sub>) by  $\downarrow$  1 or more of the determinants of MVO<sub>2</sub>: end-diastolic volume, BP, HR, contractility.

COMPONENT	NITRATES	β-BLOCKERS	NITRATES + β-BLOCKERS
End-diastolic volume	<b>↓</b>	No effect or †	No effect or ↓
Blood pressure	ţ	ţ	<b>↓</b>
Contractility	↑ (reflex response)	<b>†</b>	Little/no effect
Heart rate	↑ (reflex response)	<b>↓</b>	No effect or ↓
Ejection time	ţ	†	Little/no effect
MVO <sub>2</sub>	ţ	ţ	11

Verapamil is similar to  $\beta$ -blockers in effect.

Pindolol and acebutolol are partial  $\beta$ -agonists that should be used with caution in angina.

#### Ranolazine

MECHANISM	Inhibits the late phase of inward sodium current thereby reducing diastolic wall tension and oxygen consumption. Does not affect heart rate or blood pressure.
CLINICAL USE	Angina refractory to other medical therapies.
ADVERSE EFFECTS	Constipation, dizziness, headache, nausea.

#### **Sacubitril**

Sacabitiii	
MECHANISM	A neprilysin inhibitor; prevents degradation of natriuretic peptides, angiotensin II, and substance P  → ↑ vasodilation, ↓ ECF volume.
CLINICAL USE	Used in combination with valsartan (an ARB) to treat HFrEF.
ADVERSE EFFECTS	Hypotension, hyperkalemia, cough, dizziness; contraindicated with ACE inhibitors due to angioedema.

FAS1\_2019\_07-Cardio.indd 319 11/7/19 4:24 PM

320 SECTION III

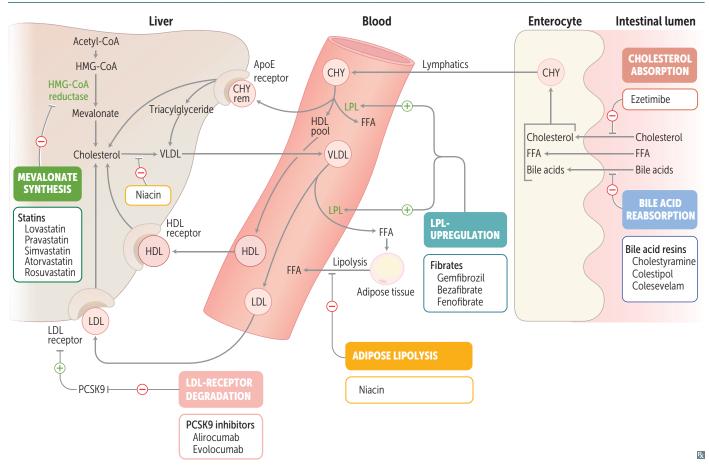
**CARDIOVASCULAR** ► CARDIOVASCULAR—PHARMACOLOGY

#### **Lipid-lowering agents**

DRUG	LDL	HDL	TRIGLYCERIDES	MECHANISMS OF ACTION	ADVERSE EFFECTS/PROBLEMS
HMG-CoA reductase inhibitors (eg, atorvastatin, simvastatin)	111	<b>†</b>	1	Inhibit conversion of HMG-CoA to mevalonate, a cholesterol precursor;  ↑ LDL recycling;  ↓ mortality in CAD patients	Hepatotoxicity († LFTs), myopathy (esp when used with fibrates or niacin)
Bile acid resins Cholestyramine, colestipol, colesevelam	<b>‡</b> ‡	† slightly	† slightly	Prevent intestinal reabsorption of bile acids; liver must use cholesterol to make more	GI upset, \(\psi\) absorption of other drugs and fatsoluble vitamins
Ezetimibe	<b>†</b> †	1/—	<b>\</b> /_	Prevents cholesterol absorption at small intestine brush border	Rare † LFTs, diarrhea
Fibrates Gemfibrozil, bezafibrate, fenofibrate	1	<b>†</b>	111	Upregulate LPL → ↑ TG clearance Activates PPAR-α to induce HDL synthesis	Myopathy († risk with statins), cholesterol gallstones (via inhibition of cholesterol 7α-hydroxylase)
Niacin	11	††	1	Inhibits lipolysis (hormone- sensitive lipase) in adipose tissue; reduces hepatic VLDL synthesis	Flushed face (\$\ddagger\$ by NSAIDs or long-term use) Hyperglycemia Hyperuricemia
PCSK9 inhibitors Alirocumab, evolocumab	111	†	1	Inactivation of LDL-receptor degradation → ↑ removal of LDL from bloodstream	Myalgias, delirium, dementia, other neurocognitive effects
Fish oil and marine omega-3 fatty acids	† slightly	† slightly	↓ at high doses	Believed to decrease FFA delivery to liver and decrease activity of TG-synthesizing enzymes	Nausea, fish-like taste

FAS1\_2019\_07-Cardio.indd 320 11/7/19 4:24 PM

#### **Lipid-lowering agents (continued)**



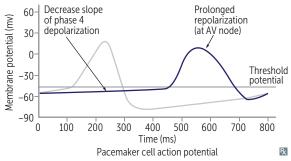
Cardiac glycosides	Digoxin.		
MECHANISM	Direct inhibition of Na <sup>+</sup> /K <sup>+</sup> ATPase  → indirect inhibition of Na <sup>+</sup> /Ca <sup>2+</sup> exchanger.  † [Ca <sup>2+</sup> ] <sub>i</sub> → positive inotropy. Stimulates vagus nerve → ↓ HR.	Na <sup>+</sup> /Ca <sup>2+</sup> Na <sup>+</sup> /K <sup>+</sup> exchanger  Na <sup>+</sup> / $ATPase$ $R^+$ $ATPase$ $R^+$ $ATPase$ $R^+$	
CLINICAL USE	HF († contractility); atrial fibrillation (↓ conduction at	AV node and depression of SA node).	
ADVERSE EFFECTS	Cholinergic effects (nausea, vomiting, diarrhea), blurry yellow vision (think van Glow), arrhythmias, AV block.  Can lead to hyperkalemia, which indicates poor prognosis.  Factors predisposing to toxicity: renal failure (\$\dagger\$ excretion), hypokalemia (permissive for digoxin binding at K*-binding site on Na*/K* ATPase), drugs that displace digoxin from tissue-binding sites, and \$\dagger\$ clearance (eg, verapamil, amiodarone, quinidine).		
ANTIDOTE	Slowly normalize K <sup>+</sup> , cardiac pacer, anti-digoxin Fab fragments, Mg <sup>2+</sup> .		

FAS1\_2019\_07-Cardio.indd 321 11/7/19 4:24 PM

Antiarrhythmics— sodium channel blockers (class I)	Slow or block (4) conduction (especially in depola state dependent (selectively depress tissue that is	
Class IA	Quinidine, Procainamide, Disopyramide. "The Queen Proclaims Diso's pyramid."	0 mV
MECHANISM	Moderate Na <sup>+</sup> channel blockade.  † AP duration, † effective refractory period (ERP) in ventricular action potential, † QT interval, some potassium channel blocking effects.	Slope of phase 0
CLINICAL USE	Both atrial and ventricular arrhythmias, especially re-entrant and ectopic SVT and VT.	
ADVERSE EFFECTS	Cinchonism (headache, tinnitus with quinidine), reversible SLE-like syndrome (procainamide), HF (disopyramide), thrombocytopenia, torsades de pointes due to † QT interval.	
Class IB	Lidocaine, MexileTine. "I'd Buy Liddy's Mexican Tacos."	0 mV Slope of
MECHANISM	Weak Na <sup>+</sup> channel blockade.  ↓ AP duration. Preferentially affect ischemic or depolarized Purkinje and ventricular tissue.  Phenytoin can also fall into the IB category.	phase 0
CLINICAL USE	Acute ventricular arrhythmias (especially post-MI), digitalis-induced arrhythmias.  IB is Best post-MI.	№
ADVERSE EFFECTS	CNS stimulation/depression, cardiovascular depression.	
Class IC	Flecainide, Propafenone. "Can I have Fries, Please."	0 mV
MECHANISM	Strong Na <sup>+</sup> channel blockade. Significantly prolongs ERP in AV node and accessory bypass tracts. No effect on ERP in Purkinje and ventricular tissue. Minimal effect on AP duration.	Slope of phase 0
CLINICAL USE	SVTs, including atrial fibrillation. Only as a last resort in refractory VT.	
ADVERSE EFFECTS	Proarrhythmic, especially post-MI (contraindicated). IC is Contraindicated in structural and ischemic heart disease.	

11/7/19 4:24 PM FAS1\_2019\_07-Cardio.indd 322

Antiarrhythmics— β-blockers (class II)	Metoprolol, propranolol, esmolol, atenolol, timolol, carvedilol.
MECHANISM	Decrease SA and AV nodal activity by ↓ cAMP, ↓ Ca <sup>2+</sup> currents. Suppress abnormal pacemakers by ↓ slope of phase 4.  AV node particularly sensitive—↑ PR interval. Esmolol very short acting.
CLINICAL USE	SVT, ventricular rate control for atrial fibrillation and atrial flutter.
ADVERSE EFFECTS	Impotence, exacerbation of COPD and asthma, cardiovascular effects (bradycardia, AV block, HF), CNS effects (sedation, sleep alterations). May mask the signs of hypoglycemia. Metoprolol can cause dyslipidemia. Propranolol can exacerbate vasospasm in vasospastic angina. $\beta$ -blockers (except the nonselective $\alpha$ - and $\beta$ -antagonists carvedilol and labetalol) cause unopposed $\alpha_l$ -agonism if given alone for pheochromocytoma or for cocaine toxicity (unsubstantiated). Treat $\beta$ -blocker overdose with saline, atropine, glucagon.



# Antiarrhythmics—

Amiodarone, Ibutilide, Dofetilide, Sotalol.

AIDS.

Cell action potential

Ŗ

MECHANISM	↑ AP duration, ↑ ERP, ↑ QT interval.	
CLINICAL USE	Atrial fibrillation, atrial flutter; ventricular tachycardia (amiodarone, sotalol).	
ADVERSE EFFECTS	Sotalol—torsades de pointes, excessive β blockade.  Ibutilide—torsades de pointes.  Amiodarone—pulmonary fibrosis, hepatotoxicity, hypothyroidism or hyperthyroidism (amiodarone is 40% iodine by weight), acts as hapten (corneal deposits, blue/gray skin deposits resulting in photodermatitis), neurologic effects, constipation, cardiovascular effects (bradycardia, heart block, HF).	Remember to check PFTs, LFTs, and TFTs when using amiodarone.  Amiodarone is lipophilic and has class I, II, III, and IV effects.
	0 mV	Markedly prolonged repolarization (I <sub>K</sub> )

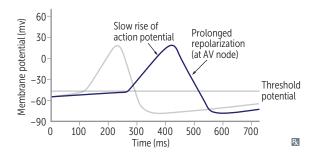
FAS1\_2019\_07-Cardio.indd 323 11/7/19 4:24 PM

-85 mV =

# Antiarrhythmics—calcium channel blockers (class IV)

#### Diltiazem, Verapamil

MECHANISM	Decrease conduction Velocity, † ERP, † PR interval.
CLINICAL USE	Prevention of nodal arrhythmias (eg, SVT), rate control in atrial fibrillation.
ADVERSE EFFECTS	Constipation, flushing, edema, cardiovascular effects (HF, AV block, sinus node depression).



#### Other antiarrhythmics

Adenosine	↑ $K^+$ out of cells → hyperpolarizing the cell and ↓ $I_{Ca}$ , decreasing AV node conduction. Drug of
	choice in diagnosing/terminating certain forms of SVT. Very short acting (~ 15 sec). Effects
	blunted by theophylline and caffeine (both are adenosine receptor antagonists). Adverse effects
	include flushing, hypotension, chest pain, sense of impending doom, bronchospasm.
Magnesium	Effective in torsades de pointes and digoxin toxicity.

### Ivabradine

MECHANISM	<b>IV</b> abradine prolongs slow depolarization (phase " <b>IV</b> ") by selectively inhibiting "funny" sodium channels (I <sub>f</sub> ).
CLINICAL USE	Chronic stable angina in patients who cannot take β-blockers. Chronic HFrEF.
ADVERSE EFFECTS	Luminous phenomena/visual brightness, hypertension, bradycardia.

FAS1\_2019\_07-Cardio.indd 324 11/7/19 4:24 PM

### HIGH-YIELD SYSTEMS

### **Endocrine**

"If you skew the endocrine system, you lose the pathways to self."

—Hilary Mantel

"We have learned that there is an endocrinology of elation and despair, a chemistry of mystical insight, and, in relation to the autonomic nervous system, a meteorology and even . . . an astro-physics of changing moods."

—Aldous Huxley

"Chocolate causes certain endocrine glands to secrete hormones that affect your feelings and behavior by making you happy."

-Elaine Sherman, Book of Divine Indulgences

The endocrine system comprises widely distributed organs that work in a highly integrated manner to orchestrate a state of hormonal equilibrium within the body. Generally speaking, endocrine diseases can be classified either as diseases of underproduction or overproduction, or as conditions involving the development of mass lesions—which themselves may be associated with underproduction or overproduction of hormones. Therefore, study the endocrine system first by learning the glands, their hormones, and their regulation, and then by integrating disease manifestations with diagnosis and management. Take time to learn the multisystem connections.

<b>▶</b> Embryology	326
▶ Anatomy	327
▶ Physiology	328
▶ Pathology	338
▶ Pharmacology	352

FAS1\_2019\_08-Endocrine.indd 325 11/7/19 4:30 PM

#### ► ENDOCRINE—EMBRYOLOGY

#### **Thyroid development**

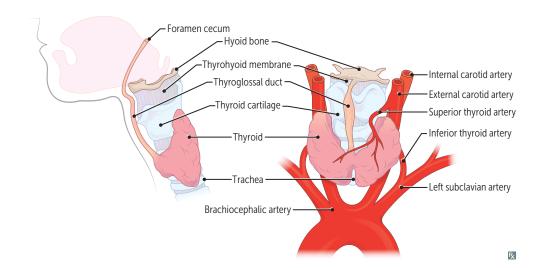


Thyroid diverticulum arises from floor of primitive pharynx and descends into neck. Connected to tongue by thyroglossal duct, which normally disappears but may persist as cysts or the pyramidal lobe of thyroid. Foramen cecum is normal remnant of thyroglossal duct.

Most common ectopic thyroid tissue site is the tongue (lingual thyroid). Removal may result in hypothyroidism if it is the only thyroid tissue present.

Thyroglossal duct cyst A presents as an anterior midline neck mass that moves with swallowing or protrusion of the tongue (vs persistent cervical sinus leading to pharyngeal cleft cyst in lateral neck).

Thyroid follicular cells derived from endoderm.



FAS1\_2019\_08-Endocrine.indd 326 11/7/19 4:30 PM

#### ► ENDOCRINE—ANATOMY

#### **Pituitary gland**

## Anterior pituitary (adenohypophysis)

Secretes FSH, LH, ACTH, TSH, prolactin, GH, and  $\beta$ -endorphin. Melanotropin (MSH) secreted from intermediate lobe of pituitary. Derived from oral ectoderm (Rathke pouch).

- α subunit—hormone subunit common to TSH, LH, FSH, and hCG.
- β subunit—determines hormone specificity.

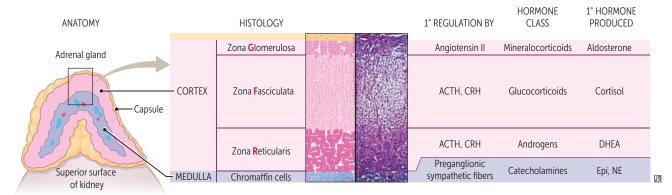
### Posterior pituitary (neurohypophysis)

Stores and releases vasopressin (antidiuretic hormone, or ADH) and oxytocin, both made in the hypothalamus (supraoptic and paraventricular nuclei) and transported to posterior pituitary via neurophysins (carrier proteins). Derived from neuroectoderm.

Proopiomelanocortin derivatives—β-endorphin, ACTH, and MSH. Go pro with a BAM! FLAT PiG: FSH, LH, ACTH, TSH, PRL, GH. B-FLAT: Basophils—FSH, LH, ACTH, TSH. Acid PiG: Acidophils — PRL, GH.

### Adrenal cortex and medulla

Adrenal cortex (derived from mesoderm) and medulla (derived from neural crest).



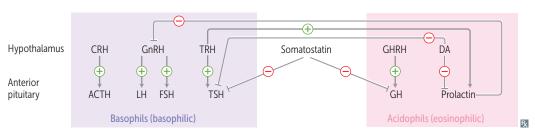
**GFR** corresponds with **S**alt (mineralocorticoids), **S**ugar (glucocorticoids), and **S**ex (androgens). "The deeper you go, the sweeter it gets."

FAS1\_2019\_08-Endocrine.indd 327 11/7/19 4:30 PM

### ► ENDOCRINE—PHYSIOLOGY

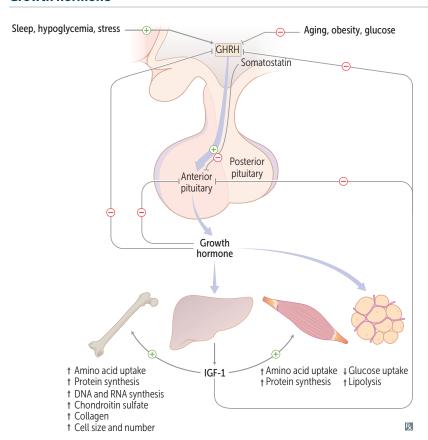
#### **Hypothalamic-pituitary hormones**

HORMONE	FUNCTION	CLINICAL NOTES
ADH	↑ water permeability of distal convoluted tubule and collecting duct cells in kidney to ↑ water reabsorption	Stimulus for secretion is ↑ plasma osmolality, except in SIADH, in which ADH is elevated despite ↓ plasma osmolality
CRH	† ACTH, MSH, β-endorphin	↓ in chronic exogenous steroid use
Dopamine	↓ prolactin, TSH	Also called prolactin-inhibiting factor Dopamine antagonists (eg, antipsychotics) can cause galactorrhea due to hyperprolactinemia
GHRH	↑ GH	Analog (tesamorelin) used to treat HIV-associated lipodystrophy
GnRH	↑ FSH, LH	Suppressed by hyperprolactinemia Tonic GnRH analog (eg, leuprolide) suppresses hypothalamic-pituitary-gonadal axis. Pulsatile GnRH leads to puberty, fertility
MSH	↑ melanogenesis by melanocytes	Causes hyperpigmentation in Cushing disease, as MSH and ACTH share the same precursor molecule, proopiomelanocortin
Oxytocin	Causes uterine contractions during labor. Responsible for milk letdown reflex in response to suckling.	Modulates fear, anxiety, social bonding, mood, and depression
Prolactin	↓ GnRH Stimulates lactogenesis.	Pituitary prolactinoma → amenorrhea, osteoporosis, hypogonadism, galactorrhea Breastfeeding → ↑ prolactin → ↓ GnRH → delayed postpartum ovulation (natural contraception)
Somatostatin	↓ GH, TSH	Also called growth hormone inhibiting hormone (GHIH) Analogs used to treat acromegaly
TRH	† TSH, prolactin	† TRH (eg, in 1°/2° hypothyroidism) may increase prolactin secretion → galactorrhea



FAS1\_2019\_08-Endocrine.indd 328 11/7/19 4:30 PM

#### **Growth hormone**



Also called somatotropin. Secreted by anterior pituitary.

Stimulates linear growth and muscle mass through IGF-1 (somatomedin C) secretion by liver. † insulin resistance (diabetogenic).

Released in pulses in response to growth hormone–releasing hormone (GHRH).

Secretion † during exercise, deep sleep, puberty, hypoglycemia, CKD.

Secretion ↓ by glucose, somatostatin, somatomedin (regulatory molecule secreted by liver in response to GH acting on target tissues).

Excess secretion of GH (eg, pituitary adenoma) may cause acromegaly (adults) or gigantism (children). Treatment: somatostatin analogs (eg, octreotide) or surgery.

Antidiuretic hormone	Also called vasopressin.	
SOURCE	Synthesized in hypothalamus (supraoptic and paraventricular nuclei), stored and secreted by posterior pituitary.	
FUNCTION	Regulates blood pressure (V <sub>1</sub> -receptors) and serum osmolality (V <sub>2</sub> -receptors). Primary function is serum osmolality regulation (ADH ↓ serum osmolality, † urine osmolality) via regulation of aquaporin channel insertion in principal cells of renal collecting duct.	ADH level is ↓ in central diabetes insipidus (DI), normal or † in nephrogenic DI.  Nephrogenic DI can be caused by mutation in V₂-receptor.  Desmopressin (ADH analog) is a treatment for central DI and nocturnal enuresis.
REGULATION	Plasma osmolality (1°); hypovolemia.	

FAS1\_2019\_08-Endocrine.indd 329 11/7/19 4:30 PM

#### Prolactin

SOURCE	Secreted mainly by anterior pituitary. Structurally homologous to growth hormone.
FUNCTION	Stimulates milk production in breast; inhibits ovulation in females and spermatogenesis in males by inhibiting GnRH synthesis and release.  Excessive amounts of prolactin associated with \$\displaystyle{1}\$ libido.
REGULATION	Prolactin secretion from anterior pituitary is tonically inhibited by dopamine from tuberoinfundibular pathway of hypothalamus. Prolactin in turn inhibits its own secretion by † dopamine synthesis and secretion from hypothalamus. TRH † prolactin secretion (eg, in 1° or 2° hypothyroidism).  Dopamine agonists (eg, bromocriptine) inhibit prolactin secretion and can be used in treatment of prolactinoma. Dopamine antagonists (eg, most antipsychotics metoclopramide) and estrogens (eg, OCPs, pregnancy) stimulate prolactin secretion.
	Sight/cry of baby ——————————————————————————————————
	Hypothalamus
	Medications Chest wall injury (via ANS) Nipple stimulation  TRH  1° hypothyroidism
	Anterior pituitary Posterior
	Estrogen + Pregnancy
	Reduced prolactin elimination  Renal failure  Prolactin  GnRH  Ovulation  Spermatogenesis
	⊕ Milk production

FAS1\_2019\_08-Endocrine.indd 330 11/7/19 4:30 PM

#### Thyroid produces triiodothyronine $(T_3)$ and thyroxine $(T_4)$ , iodine-containing hormones that **Thyroid hormones** control the body's metabolic rate. Follicles of thyroid. 5'-deiodinase converts T<sub>4</sub> (the major thyroid product) to T<sub>3</sub> in peripheral tissue **SOURCE** (5, 4, 3). Peripheral conversion is inhibited by glucocorticoids, $\beta$ -blockers, and propylthiouracil (PTU). Reverse T<sub>3</sub> (rT<sub>3</sub>) is a metabolically inactive byproduct of the peripheral conversion of T<sub>4</sub> and its production is increased by growth hormone and glucocorticoids. Functions of thyroid peroxidase include oxidation, organification of iodine, and coupling of monoiodotyrosine (MIT) and diiodotyrosine (DIT). Inhibited by PTU and methimazole. DIT + DIT = $T_4$ . DIT + MIT = $T_3$ . Wolff-Chaikoff effect—excess iodine temporarily turns off thyroid peroxidase $\rightarrow \ \ T_3/T_4$ production (protective autoregulatory effect). **FUNCTION** Only free hormone is active. T<sub>3</sub> binds nuclear receptor with greater affinity than T<sub>4</sub>. T<sub>3</sub> functions **−7 B**'s: Brain maturation Bone growth (synergism with GH) ■ β-adrenergic effects. ↑ $β_1$ receptors in heart → ↑ CO, HR, SV, contractility; β-blockers alleviate adrenergic symptoms in thyrotoxicosis ■ Basal metabolic rate $\uparrow$ (via Na<sup>+</sup>/K<sup>+</sup>-ATPase activity $\rightarrow \uparrow$ O<sub>2</sub> consumption, RR, body temperature) Blood sugar († glycogenolysis, gluconeogenesis) Break down lipids († lipolysis) Stimulates surfactant synthesis in Babies REGULATION

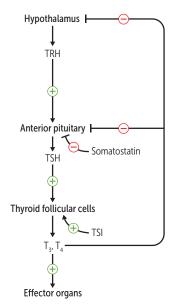
TRH ⊕ TSH release → ⊕ follicular cells. Thyroid-stimulating immunoglobulin (TSI) may ⊕ follicular cells in Graves disease.

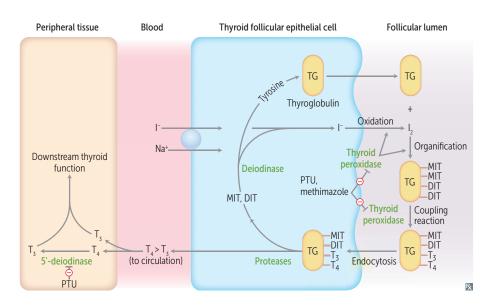
Negative feedback primarily by free  $T_3/T_4$ :

- Anterior pituitary → ↓ sensitivity to TRH
- Hypothalamus → ↓ TRH secretion

Thyroxine-binding globulin (TBG) binds most  $T_3/T_4$  in blood. Bound  $T_3/T_4$  = inactive.

- † TBG in pregnancy, OCP use (estrogen  $\rightarrow$  † TBG)  $\rightarrow$  † total  $T_3/T_4$
- ↓ TBG in steroid use, nephrotic syndrome





FAS1 2019 08-Endocrine.indd 331 11/7/19 4:30 PM

### **ENDOCRINE** ► ENDOCRINE—PHYSIOLOGY

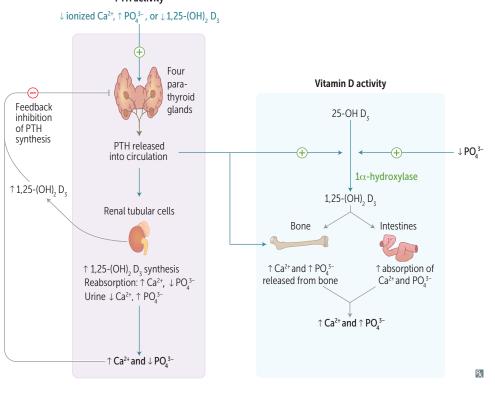
#### **Parathyroid hormone**

SOURCE	Chief cells of parathyroid	
FUNCTION	† free Ca <sup>2+</sup> in the blood (1° function) † Ca <sup>2+</sup> and PO <sub>4</sub> <sup>3-</sup> absorption in GI system † Ca <sup>2+</sup> and PO <sub>4</sub> <sup>3-</sup> from bone resorption † Ca <sup>2+</sup> reabsorption from DCT † PO <sub>4</sub> <sup>3-</sup> reabsorption in PCT † 1,25-(OH) <sub>2</sub> D <sub>3</sub> (calcitriol) production by activating 1α-hydroxylase in PCT Tri to make D <sub>3</sub> in the PCT	PTH ↑ serum Ca <sup>2+</sup> , ↓ serum PO <sub>4</sub> <sup>3-</sup> , ↑ urine PO <sub>4</sub> <sup>3-</sup> , ↑ urine cAMP ↑ RANK-L (receptor activator of NF-κB ligand) secreted by osteoblasts and osteocytes; binds RANK (receptor) on osteoclasts and their precursors to stimulate osteoclasts and ↑ Ca <sup>2+</sup> → bone resorption (intermittent PTH release can also stimulate bone formation)  PTH = Phosphate-Trashing Hormone  PTH-related peptide (PTHrP) functions like PTH and is commonly increased in malignancies (eg, squamous cell carcinoma of the lung, renal cell carcinoma)

REGULATION

↓ serum Ca<sup>2+</sup> → ↑ PTH secretion
↑ serum PO<sub>4</sub><sup>3-</sup> → ↑ PTH secretion
↓ serum Mg<sup>2+</sup> → ↑ PTH secretion
↓↓ serum Mg<sup>2+</sup> → ↓ PTH secretion
Common causes of ↓ Mg<sup>2+</sup> include diarrhea, aminoglycosides, diuretics, alcohol abuse

#### PTH activity



FAS1\_2019\_08-Endocrine.indd 332 11/7/19 4:30 PM

Cal	cium	homeostasi	c
Cal	Clulli	HUHIEUStasi	ы

Plasma Ca<sup>2+</sup> exists in three forms:

- Ionized/free (~ 45%, active form)
- Bound to albumin (~ 40%)
- Bound to anions (~ 15%)

 $\uparrow$  pH (less H<sup>+</sup>) → albumin binds more  $Ca^{2+} \rightarrow \downarrow$  ionized  $Ca^{2+}$  (eg, cramps, pain, paresthesias, carpopedal spasm) → † PTH  $\downarrow$  pH (more H<sup>+</sup>) → albumin binds less Ca<sup>2+</sup> → † ionized  $Ca^{2+}$  → ‡ PTH Ionized/free Ca<sup>2+</sup> is 1° regulator of PTH; changes in pH alter PTH secretion, whereas

changes in albumin concentration do not

**SECTION III** 

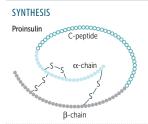
#### **Calcitonin**

SOURCE	Parafollicular cells (C cells) of thyroid.	Calcitonin opposes actions of PTH. Not
FUNCTION	↓ bone resorption of Ca <sup>2+</sup> .	important in normal Ca <sup>2+</sup> homeostasis
REGULATION	↑ serum $Ca^{2+} \rightarrow \uparrow$ calcitonin secretion.	Calcitonin tones down serum Ca <sup>2+</sup> levels and keeps it in bones

Giucagon	
SOURCE	Made by $\alpha$ cells of pancreas.
FUNCTION	Promotes glycogenolysis, gluconeogenesis, lipolysis, ketogenesis. Elevates blood sugar levels to maintain homeostasis when bloodstream glucose levels fall too low (ie, fasting state).
REGULATION	Secreted in response to hypoglycemia. Inhibited by insulin, hyperglycemia, somatostatin.

FAS1\_2019\_08-Endocrine.indd 333 11/7/19 4:30 PM

#### Insulin



Preproinsulin (synthesized in RER of pancreatic  $\beta$  cells)  $\rightarrow$  cleavage of "presignal"  $\rightarrow$  proinsulin (stored in secretory granules)  $\rightarrow$  cleavage of proinsulin  $\rightarrow$  exocytosis of insulin and C-peptide equally. Insulin and C-peptide are  $\uparrow$  in insulinoma and sulfonylurea use, whereas exogenous insulin lacks C-peptide.

**FUNCTION** 

Binds insulin receptors (tyrosine kinase activity ①), inducing glucose uptake (carrier-mediated transport) into insulin-dependent tissue ② and gene transcription.

Anabolic effects of insulin:

- † glucose transport in skeletal muscle and adipose tissue
- † glycogen synthesis and storage
- † triglyceride synthesis
- Na<sup>+</sup> retention (kidneys)
- † protein synthesis (muscles)
- ↑ cellular uptake of K<sup>+</sup> and amino acids
- ↓ glucagon release
- ↓ lipolysis in adipose tissue

Unlike glucose, insulin does not cross placenta.

Insulin-dependent glucose transporters:

 GLUT4: adipose tissue, striated muscle (exercise can also † GLUT4 expression)

Insulin-independent transporters:

- GLUT1: RBCs, brain, cornea, placenta
- GLUT2 (bidirectional): β islet cells, liver, kidney, GI tract (think 2-way street)
- GLUT3: brain, placenta
- GLUT5 (Fructose): spermatocytes, GI tract
- SGLT1/SGLT2 (Na<sup>+</sup>-glucose cotransporters): kidney, small intestine

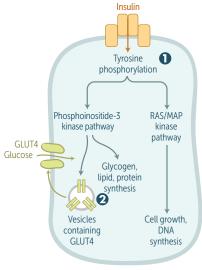
Brain prefers glucose, but may use ketone bodies during starvation. RBCs utilize glucose, as they lack mitochondria for aerobic metabolism.

BRICK LIPS (insulin-independent glucose uptake): Brain, RBCs, Intestine, Cornea, Kidney, Liver, Islet (β) cells, Placenta, Spermatocytes.

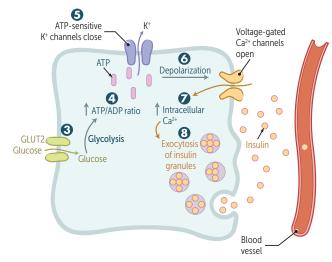
REGULATION

Glucose is the major regulator of insulin release.  $\uparrow$  insulin response with oral vs IV glucose due to incretins (eg, glucagon-like peptide 1 [GLP-1], glucose-dependent insulinotropic polypeptide [GIP]), which are released after meals and  $\uparrow$   $\beta$  cell sensitivity to glucose. Release  $\downarrow$  by  $\alpha_2$ ,  $\uparrow$  by  $\beta_2$  stimulation (2 = regulates insulin)

Glucose enters  $\beta$  cells  $\mathfrak{S} \to \uparrow$  ATP generated from glucose metabolism  $\mathfrak{S}$  closes  $K^+$  channels (target of sulfonylureas)  $\mathfrak{S}$  and depolarizes  $\beta$  cell membrane  $\mathfrak{S}$ . Voltage-gated  $Ca^{2+}$  channels open  $\to Ca^{2+}$  influx  $\mathfrak{S}$  and stimulation of insulin exocytosis  $\mathfrak{S}$ .



Insulin-dependent glucose uptake

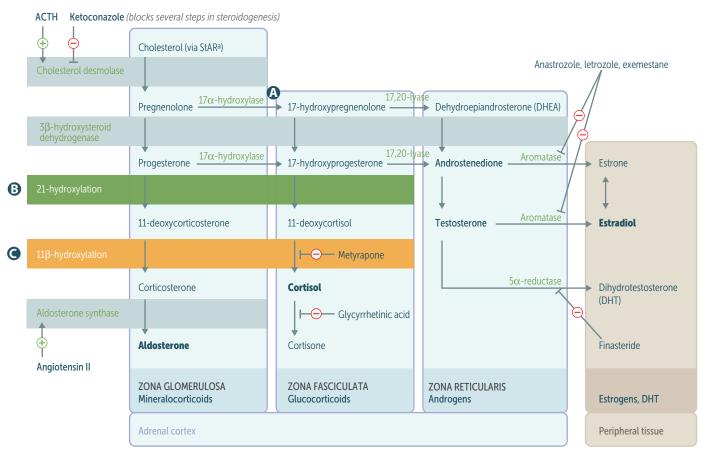


Insulin secretion by pancreatic  $\beta$  cells

Ŗ

FAS1\_2019\_08-Endocrine.indd 334 11/7/19 4:30 PM

#### Adrenal steroids and congenital adrenal hyperplasias



<sup>a</sup>Rate-limiting step.

ENZYME DEFICIENCY	MINERALOCORTICOIDS	[K <sup>+</sup> ]	ВР	CORTISOL	SEX HORMONES	LABS	PRESENTATION
<b>A</b> 17α-hydroxylase <sup>a</sup>	1	1	<b>†</b>	ţ	1	↓ androstenedione	XY: ambiguous genitalia, undescended testes XX: lacks 2° sexual development
<b>(B)</b> 21-hydroxylase <sup>a</sup>	1	1	ţ	ţ	t	† renin activity † 17-hydroxy- progesterone	Most common Presents in infancy (salt wasting) or childhood (precocious puberty) XX: virilization
<b>( )</b> 11β-hydroxylase <sup>a</sup>	↓ aldosterone ↑ 11-deoxycorti- costerone (results in ↑ BP)	1	<b>†</b>	ţ	t	↓ renin activity	Presents in infancy (severe hypertension) or childhood (precocious puberty) XX: virilization

<sup>&</sup>lt;sup>a</sup>All congenital adrenal enzyme deficiencies are autosomal recessive disorders and most are characterized by skin hyperpigmentation (due to † MSH production, which is coproduced and secreted with ACTH) and bilateral adrenal gland enlargement (due to † ACTH stimulation).

If deficient enzyme starts with 1, it causes hypertension; if deficient enzyme ends with 1, it causes virilization in females.

FAS1\_2019\_08-Endocrine.indd 335 11/7/19 4:30 PM

#### Cortisol

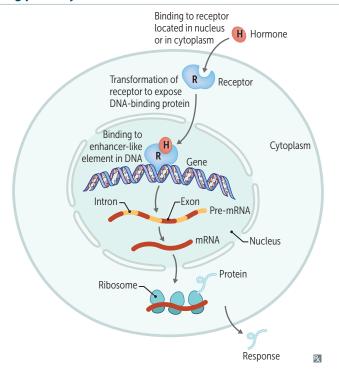
SOURCE	Adrenal zona fasciculata.	Bound to corticosteroid-binding globulin.		
UNCTION	<ul> <li>↑ Appetite</li> <li>↑ Blood pressure:</li> <li>■ Upregulates α₁-receptors on arterioles</li> <li>→ ↑ sensitivity to norepinephrine and epinephrine (permissive action)</li> <li>■ At high concentrations, can bind to mineralocorticoid (aldosterone) receptors</li> <li>↑ Insulin resistance (diabetogenic)</li> <li>↑ Gluconeogenesis, lipolysis, and proteolysis (↓ glucose utilization)</li> <li>↓ Fibroblast activity (poor wound healing, ↓ collagen synthesis, ↑ striae)</li> <li>↓ Inflammatory and Immune responses:</li> <li>■ Inhibits production of leukotrienes and prostaglandins</li> <li>■ Inhibits WBC adhesion → neutrophilia</li> <li>■ Blocks histamine release from mast cells</li> <li>■ Eosinopenia, lymphopenia</li> <li>■ Blocks IL-2 production</li> <li>↓ Bone formation (↓ osteoblast activity)</li> </ul>	Cortisol is A BIG FIB.  Exogenous corticosteroids can cause reactivation of TB and candidiasis (blocks IL-production).  Stress Circadian rhythm  Anterior Proopiomelanocortin  ACTH  Cortisol		
REGULATION	CRH (hypothalamus) stimulates ACTH release (pituitary) → cortisol production in adrenal zona fasciculata. Excess cortisol ↓ CRH, ACTH, and cortisol secretion.	Chronic stress may induce prolonged cortisol secretion, cortisol resistance, impaired immunocompetency, and dysregulation of HPA axis.		
ppetite regulation				
Ghrelin	Stimulates hunger (orexigenic effect) and GH release (via GH secretagog receptor). Produced by stomach. Sleep deprivation, fasting, or Prader-Willi syndrome → ↑ ghrelin production.  Ghrelin makes you hunghre and ghrow. Acts on lateral area of hypothalamus (hunger center) to ↑ appetite.			
Leptin	Satiety hormone. Produced by adipose tissue. Mutation of leptin gene → central obesity. (Obese people have ↑ leptin due to ↑ adipose tissue but also appear resistant to leptin's anorexigenic effect.) Sleep deprivation or starvation → ↓ leptin production.  Leptin keeps you thin. Acts on ventromedial area of hypothalamus (satiety center) to ↓ appetite.			
Endocannabinoids	Act at cannabinoid receptors in hypothalamus and nucleus accumbens, two key brain areas for the homeostatic and hedonic control of food intake → ↑ appetite.  Exogenous cannabinoids cause "the munchies."			

FAS1\_2019\_08-Endocrine.indd 336 11/7/19 4:30 PM

#### Signaling pathways of endocrine hormones

orginaling patients or c	indoctific floriflorics	
cAMP FSH, LH, ACTH, TSH, CRH, hCG, ADH (V <sub>2</sub> -receptor), MSH, PTH, Calcitonin, Histamine (H <sub>2</sub> -receptor), Glucagon, GHRH		FLAT ChAMPs CHuGG
cGMP	BNP, ANP, EDRF (NO)	BAD GraMPa Think vasodilation and diuresis
IP <sub>3</sub>	GnRH, Oxytocin, ADH (V <sub>1</sub> -receptor), TRH, Histamine (H <sub>1</sub> -receptor), Angiotensin II, Gastrin	GOAT HAG
Intracellular receptor	Progesterone, Estrogen, Testosterone, Cortisol, Aldosterone, T <sub>3</sub> /T <sub>4</sub> , Vitamin D	PET CAT on TV
Receptor tyrosine kinase	IGF-1, FGF, PDGF, EGF, TGF-β, Insulin	MAP kinase pathway Get Found In the MAP
Nonreceptor tyrosine kinase	Prolactin, Immunomodulators (eg, cytokines IL-2, IL-6, IFN), GH, G-CSF, Erythropoietin, Thrombopoietin	JAK/STAT pathway Think acidophils and cytokines PIGGLET

#### Signaling pathways of steroid hormones



Steroid hormones are lipophilic and therefore must circulate bound to specific binding globulins, which † their solubility.

In men, ↑ sex hormone–binding globulin (SHBG) lowers free testosterone

→ gynecomastia.

In women, ↓ SHBG raises free testosterone → hirsutism.

↑ estrogen (eg, OCPs, pregnancy) → ↑ SHBG.

FAS1\_2019\_08-Endocrine.indd 337 11/7/19 4:30 PM

#### ▶ ENDOCRINE—PATHOLOGY

#### Syndrome of inappropriate antidiuretic hormone secretion

Characterized by:

- Excessive free water retention
- Euvolemic hyponatremia with continued urinary Na<sup>+</sup> excretion
- Urine osmolality > serum osmolality

Body responds to water retention with

- ↓ aldosterone and ↑ ANP and BNP
- → † urinary Na<sup>+</sup> secretion → normalization of extracellular fluid volume → euvolemic hyponatremia. Very low serum Na<sup>+</sup> levels can lead to cerebral edema, seizures. Correct slowly to prevent osmotic demyelination syndrome (formerly called central pontine myelinolysis).

SIADH causes include:

- Ectopic ADH (eg, small cell lung cancer)
- CNS disorders/head trauma
- Pulmonary disease
- Drugs (eg, SSRIs, carbamazepine, cyclophosphamide)

Treatment: fluid restriction (first line), salt tablets, IV hypertonic saline, diuretics, ADH antagonists (eg, conivaptan, tolvaptan, demeclocycline).

#### **Diabetes insipidus**

Characterized by intense thirst and polyuria with inability to concentrate urine due to lack of ADH (central) or failure of response to circulating ADH (nephrogenic).

	(central) or failure of response to circulating	ADH (nephrogenic).
	Central DI	Nephrogenic DI
ETIOLOGY	Pituitary tumor, autoimmune, trauma, surgery ischemic encephalopathy, idiopathic	to hypercalcemia, hypokalemia, lithium, demeclocycline (ADH antagonist)
FINDINGS	↓ ADH	Normal or † ADH levels
	Urine osmolal Serum osmola	gravity < 1.006 lity < 300 mOsm/kg ality > 290 mOsm/kg volume contraction
WATER DEPRIVATION TEST <sup>a</sup>	> 50% † in urine osmolality only after administration of ADH analog	Minimal change in urine osmolality, even after administration of ADH analog
TREATMENT	Desmopressin Hydration	HCTZ, indomethacin, amiloride Hydration, dietary salt restriction, avoidance of offending agent

aNo water intake for 2–3 hr followed by hourly measurements of urine volume and osmolality as well as plasma Na<sup>+</sup> concentration and osmolality. ADH analog (desmopressin) is administered if serum osmolality > 295–300 mOsm/kg, plasma Na<sup>+</sup> ≥ 145 mEq/L, or urine osmolality does not rise despite a rising plasma osmolality.

FAS1\_2019\_08-Endocrine.indd 338 11/7/19 4:30 PM

**SECTION III** 

#### Hypopituitarism

Undersecretion of pituitary hormones due to:

- Nonsecreting pituitary adenoma, craniopharyngioma
- Sheehan syndrome—ischemic infarct of pituitary following postpartum bleeding; pregnancyinduced pituitary growth → ↑ susceptibility to hypoperfusion. Usually presents with failure to lactate, absent menstruation, cold intolerance
- Empty sella syndrome—atrophy or compression of pituitary (which lies in the sella turcica), often idiopathic, common in obese women; associated with idiopathic intracranial hypertension
- Pituitary apoplexy—sudden hemorrhage of pituitary gland, often in the presence of an existing pituitary adenoma. Usually presents with sudden onset severe headache, visual impairment (eg, bitemporal hemianopia, diplopia due to CN III palsy), and features of hypopituitarism
- Brain injury
- Radiation

Treatment: hormone replacement therapy (corticosteroids, thyroxine, sex steroids, human growth hormone)

Acromegaly	Excess GH in adults. Typically caused by pituitary adenoma.	
FINDINGS	Large tongue with deep furrows, deep voice, large hands and feet, coarsening of facial features with aging A, frontal bossing, diaphoresis (excessive sweating), impaired glucose tolerance (insulin resistance), hypertension. † risk of colorectal polyps and cancer.	† GH in children → gigantism († linea growth). HF most common cause of c
DIAGNOSIS	† serum IGF-1; failure to suppress serum GH following oral glucose tolerance test; pituitary mass seen on brain MRI.	Baseline
TREATMENT	Pituitary adenoma resection. If not cured, treat with octreotide (somatostatin analog), pegvisomant (GH receptor antagonist), or dopamine agonists (eg, cabergoline).	•

ar bone death.



FAS1\_2019\_08-Endocrine.indd 339 11/7/19 4:30 PM

#### Hypothyroidism vs hyperthyroidism

FINDINGS	Hypothyroidism	Hyperthyroidism
METABOLIC	Cold intolerance, ↓ sweating, weight gain (↓ basal metabolic rate → ↓ calorigenesis), hyponatremia (↓ free water clearance)	Heat intolerance, ↑ sweating, weight loss (↑ synthesis of Na+-K+ ATPase → ↑ basal metabolic rate → ↑ calorigenesis)
SKIN/HAIR  A  R  R	Dry, cool skin (due to ↓ blood flow); coarse, brittle hair; diffuse alopecia; brittle nails; puffy facies and generalized nonpitting edema (myxedema) due to † GAGs in interstitial spaces → † osmotic pressure → water retention	Warm, moist skin (due to vasodilation); fine hair; onycholysis (A); pretibial myxedema in Graves disease
OCULAR	Periorbital edema	Ophthalmopathy in Graves disease (including periorbital edema, exophthalmos), lid lag/retraction († sympathetic stimulation of levator palpebrae superioris and superior tarsal muscle)
GASTROINTESTINAL	Constipation (↓ GI motility), ↓ appetite	Hyperdefecation/diarrhea († GI motility), † appetite
MUSCULOSKELETAL	Hypothyroid myopathy (proximal weakness,  † CK), carpal tunnel syndrome, myoedema (small lump rising on the surface of a muscle when struck with a hammer)	Thyrotoxic myopathy (proximal weakness, normal CK), osteoporosis/† fracture rate (T <sub>3</sub> directly stimulates bone resorption)
REPRODUCTIVE	Abnormal uterine bleeding, ↓ libido, infertility	Abnormal uterine bleeding, gynecomastia, ↓ libido, infertility
NEUROPSYCHIATRIC	Hypoactivity, lethargy, fatigue, weakness, depressed mood, ↓ reflexes (delayed/slow relaxing)	Hyperactivity, restlessness, anxiety, insomnia, fine tremors (due to † β-adrenergic activity), † reflexes (brisk)
CARDIOVASCULAR	Bradycardia, dyspnea on exertion (‡ cardiac output)	Tachycardia, palpitations, dyspnea, arrhythmias (eg, atrial fibrillation), chest pain and systolic HTN due to ↑ number and sensitivity of β-adrenergic receptors, ↑ expression of cardiac sarcolemmal ATPase and ↓ expression of phospholamban
LABS	↑ TSH (if 1°) ↓ free T <sub>3</sub> and T <sub>4</sub> Hypercholesterolemia (due to ↓ LDL receptor expression)	↓ TSH (if 1°) ↑ free T₃ and T₄ ↓ LDL, HDL, and total cholesterol

FAS1\_2019\_08-Endocrine.indd 340 11/7/19 4:30 PM

#### Hypothyroidism

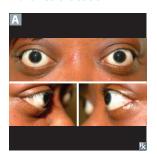
Hashimoto thyroiditis	Most common cause of hypothyroidism in iodine-sufficient regions; an autoimmune disorder with antithyroid peroxidase (antimicrosomal) and antithyroglobulin antibodies. Associated with HLA-DR3, HLA-DR5, † risk of non-Hodgkin lymphoma (typically of B-cell origin). May be hyperthyroid early in course due to thyrotoxicosis during follicular rupture. Histology: Hürthle cells A, lymphoid aggregates with germinal centers. Findings: moderately enlarged, nontender thyroid.
Postpartum thyroiditis	Self-limited thyroiditis arising up to 1 year after delivery. Presents as transient hyperthyroidism, hypothyroidism, or hyperthyroidism followed by hypothyroidism. Majority of women are euthyroid following resolution. Thyroid usually painless and normal in size. Histology: lymphocytic infiltrate with occasional germinal center formation.
Congenital hypothyroidism (cretinism)	Severe fetal hypothyroidism due to antibody-mediated maternal hypothyroidism, thyroid dysgenesis (most common cause in US; eg, agenesis, ectopy, hypoplasia), iodine deficiency, dyshormonogenetic goiter (commonly due to mutations in thyroid peroxidase).  Findings (6 P's): Pot-bellied, Pale, Puffy-faced child  with Protruding umbilicus, Protuberant tongue  and Poor brain development.
Subacute granulomatous thyroiditis (de Quervain)	Self-limited disease often following a flu-like illness (eg, viral infection).  May be hyperthyroid early in course, followed by hypothyroidism (permanent in ~15% of cases).  Histology: granulomatous inflammation.  Findings: † ESR, jaw pain, very tender thyroid. (de Quervain is associated with pain.)
Riedel thyroiditis	Thyroid replaced by fibrous tissue and inflammatory infiltrate . Fibrosis may extend to local structures (eg, trachea, esophagus), mimicking anaplastic carcinoma. It of patients are hypothyroid. Considered a manifestation of IgG4-related systemic disease (eg, autoimmune pancreatitis, retroperitoneal fibrosis, noninfectious aortitis). Findings: fixed, hard (rock-like), painless goiter.
Other causes	Iodine deficiency (with goiter 🔳), goitrogens (eg, amiodarone, lithium), Wolff-Chaikoff effect (thyroid gland downregulation in response to † iodide).



FAS1\_2019\_08-Endocrine.indd 341 11/7/19 4:30 PM

#### Hyperthyroidism

#### **Graves disease**



Most common cause of hyperthyroidism. Thyroid-stimulating immunoglobulin (IgG, can cause transient neonatal hyperthyroidism; type II hypersensitivity) stimulates TSH receptors on thyroid (hyperthyroidism, diffuse goiter), dermal fibroblasts (pretibial myxedema), and orbital fibroblasts (Graves orbitopathy). Activation of T-cells  $\rightarrow$  lymphocytic infiltration of retroorbital space  $\rightarrow$  † cytokines (eg, TNF- $\alpha$ , IFN- $\gamma$ )  $\rightarrow$  † fibroblast secretion of hydrophilic GAGs  $\rightarrow$  † osmotic muscle swelling, muscle inflammation, and adipocyte count  $\rightarrow$  exophthalmos  $\blacksquare$ . Often presents during stress (eg, pregnancy). Associated with HLA-DR3 and HLA-B8. Histology: tall, crowded follicular epithelial cells; scalloped colloid.

### Toxic multinodular goiter

Focal patches of hyperfunctioning follicular cells distended with colloid working independently of TSH (due to TSH receptor mutations in 60% of cases). † release of T<sub>3</sub> and T<sub>4</sub>. Hot nodules are rarely malignant.

#### **Thyroid storm**

Uncommon but serious complication that occurs when hyperthyroidism is incompletely treated/ untreated and then significantly worsens in the setting of acute stress such as infection, trauma, surgery. Presents with agitation, delirium, fever, diarrhea, coma, and tachyarrhythmia (cause of death). May see † LFTs. Treat with the 4 P's:  $\beta$ -blockers (eg, Propranolol), Propylthiouracil, corticosteroids (eg, Prednisolone), Potassium iodide (Lugol iodine). Iodide load  $\rightarrow \downarrow T_4$  synthesis  $\rightarrow$  Wolff-Chaikoff effect.

### Jod-Basedow phenomenon

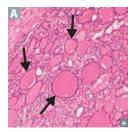
Iodine-induced hyperthyroidism. Occurs when a patient with iodine deficiency and partially autonomous thyroid tissue (eg, autonomous nodule) is made iodine replete. Can happen after iodine IV contrast or amiodarone use. Opposite to Wolff-Chaikoff effect.

#### **Causes of goiter**

Smooth/diffuse: Graves disease, Hashimoto thyroiditis, iodine deficiency, TSH-secreting pituitary adenoma.

Nodular: toxic multinodular goiter, thyroid adenoma, thyroid cancer, thyroid cyst.

#### Thyroid adenoma



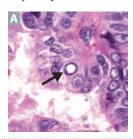
Benign solitary growth of the thyroid. Most are nonfunctional ("cold"), can rarely cause hyperthyroidism via autonomous thyroid hormone production ("hot" or "toxic"). Most common histology is follicular (arrows in A); absence of capsular or vascular invasion (unlike follicular carcinoma).

FAS1 2019 08-Endocrine.indd 342 11/7/19 4:30 PM

#### **Thyroid cancer**

Typically diagnosed with fine needle aspiration; treated with thyroidectomy. Complications of surgery include hypocalcemia (due to removal of parathyroid glands), transection of recurrent laryngeal nerve during ligation of inferior thyroid artery (leads to dysphagia and dysphonia [hoarseness]), and injury to the external branch of the superior laryngeal nerve during ligation of superior thyroid vascular pedicle (may lead to loss of tenor usually noticeable in professional voice users).

#### **Papillary carcinoma**

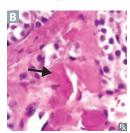


Most common, excellent prognosis. Empty-appearing nuclei with central clearing ("Orphan Annie" eyes) A, psamMoma bodies, nuclear grooves (Papi and Moma adopted Orphan Annie). † risk with RET/PTC rearrangements and BRAF mutations, childhood irradiation. Papillary carcinoma: most Prevalent, Palpable lymph nodes. Good prognosis.

#### Follicular carcinoma

Good prognosis. Invades thyroid capsule and vasculature (unlike follicular adenoma), uniform follicles; hematogenous spread is common. Associated with RAS mutation and PAX8-PPAR-γ translocations.

#### Medullary carcinoma

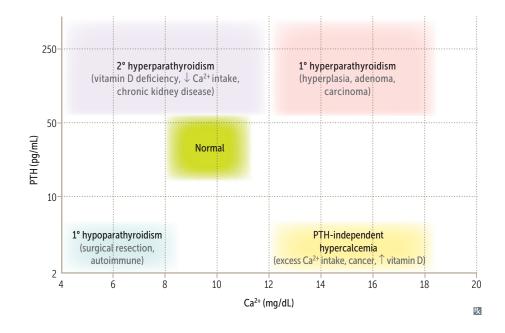


From parafollicular "C cells"; produces calcitonin, sheets of polygonal cells in an amyloid stroma **B** (stains with Congo red). Associated with MEN 2A and 2B (RET mutations).

#### Undifferentiated/ anaplastic carcinoma

Older patients; presents with rapidly enlarging neck mass → compressive symptoms (eg, dyspnea, dysphagia, hoarseness); very poor prognosis. Associated with TP53 mutation.

#### Diagnosing parathyroid disease



FAS1 2019 08-Endocrine.indd 343 11/7/19 4:30 PM

#### Hypoparathyroidism



Due to injury to parathyroid glands or their blood supply (usually during surgery), autoimmune destruction, or DiGeorge syndrome. Findings: tetany, hypocalcemia, hyperphosphatemia. Chvostek sign—tapping of facial nerve (tap the Cheek) → contraction of facial muscles. Trousseau sign—occlusion of brachial artery with BP cuff (cuff the Triceps) → carpal spasm.

Pseudohypoparathyroidism type 1A—autosomal dominant, maternally transmitted mutations (imprinted GNAS gene). GNAS1-inactivating mutation (coupled to PTH receptor) that encodes the  $G_s$  protein  $\alpha$  subunit  $\rightarrow$  inactivation of adenylate cyclase when PTH binds to its receptor  $\rightarrow$  end-organ resistance (kidney and bone) to PTH.

Physical findings: Albright hereditary osteodystrophy (shortened 4th/5th digits A, short stature, round face, subcutaneous calcifications, developmental delay).

Labs: ↑ PTH, ↓ Ca<sup>2+</sup>, ↑ PO<sub>4</sub><sup>3-</sup>.

**Pseudopseudohypoparathyroidism**—autosomal dominant, paternally transmitted mutations (imprinted GNAS gene) but without end-organ resistance to PTH due to normal maternal allele maintaining renal responsiveness to PTH.

Physical findings: same as Albright hereditary osteodystrophy.

Labs: normal PTH, Ca<sup>2+</sup>, PO<sub>4</sub><sup>3-</sup>.

### Lab values in hypocalcemia

DISORDER	Ca <sup>2+</sup>	PO <sub>4</sub> <sup>3-</sup>	PTH
Vitamin D deficiency	ţ	ţ	<b>†</b>
Hypoparathyroidism	ţ	1	ţ
2° hyperparathyroidism (CKD)	ţ	<b>†</b>	<b>†</b>
Pseudohypoparathyroidism	ţ	1	<b>†</b>
Hyperphosphatemia	ţ	<b>†</b>	<b>†</b>

FAS1\_2019\_08-Endocrine.indd 344 11/7/19 4:30 PM

#### Hyperparathyroidism

#### Primary hyperparathyroidism



Usually due to parathyroid adenoma or hyperplasia. Hypercalcemia, hypercalciuria (renal stones), polyuria (thrones), hypophosphatemia, † PTH, † ALP, † urinary cAMP. Most often asymptomatic. May present with bone pain, weakness, constipation ("groans"), abdominal/flank pain (kidney stones, acute pancreatitis), neuropsychiatric disturbances ("psychiatric overtones").

Osteitis fibrosa cystica—cystic bone spaces filled with brown fibrous tissue A ("brown tumor" consisting of osteoclasts and deposited hemosiderin from hemorrhages; causes bone pain). Due to † PTH, classically associated with 1° (but also seen with 2°) hyperparathyroidism.

"Stones, thrones, bones, groans, and psychiatric overtones."

Secondary hyperparathyroidism 2° hyperplasia due to ↓ Ca<sup>2+</sup> absorption and/or ↑ PO<sub>4</sub><sup>3-</sup>, most often in chronic kidney disease (causes hypovitaminosis D and hyperphosphatemia → ↓ Ca<sup>2+</sup>). **Hypocalcemia**, hyperphosphatemia in chronic kidney disease (vs hypophosphatemia with most other causes), ↑ ALP, ↑ PTH.

**Renal osteodystrophy**—renal disease → 2° and 3° hyperparathyroidism → bone lesions.

Tertiary hyperparathyroidism

Refractory (autonomous) hyperparathyroidism resulting from chronic kidney disease.

11 PTH, 1 Ca<sup>2+</sup>.

# Familial hypocalciuric hypercalcemia

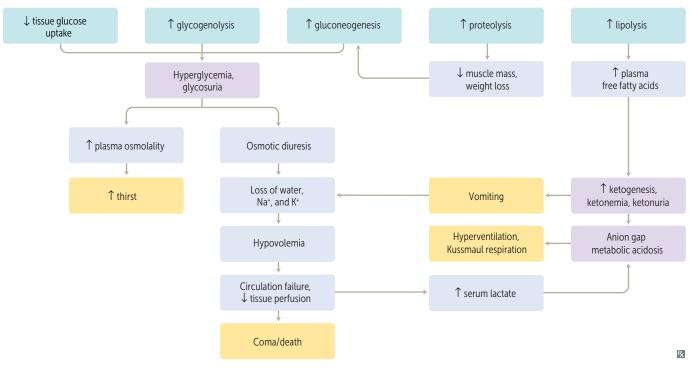
Defective G-coupled  $Ca^{2+}$ -sensing receptors in multiple tissues (eg, parathyroids, kidneys). Higher than normal  $Ca^{2+}$  levels required to suppress PTH. Excessive renal  $Ca^{2+}$  reabsorption  $\rightarrow$  mild hypercalcemia and hypocalciuria with normal to  $\uparrow$  PTH levels.

FAS1\_2019\_08-Endocrine.indd 345 11/7/19 4:30 PM

#### **Diabetes mellitus**

ACUTE MANIFESTATIONS	Polydipsia, polyuria, polyphagia, we (type 2).	ight loss, DKA (type 1)	), hyperosmolar hyperglycemic state
	Rarely, can be caused by unopposed glucocorticoid therapy (steroid dial		epinephrine. Also seen in patients on
CHRONIC COMPLICATIONS	<ul> <li>glucocorticoid therapy (steroid diabetes).</li> <li>Nonenzymatic glycation:         <ul> <li>Small vessel disease (diffuse thickening of basement membrane) → retinopathy (hemorrh: exudates, microaneurysms, vessel proliferation), glaucoma, nephropathy. Nodular glomerulosclerosis → progressive proteinuria (initially microalbuminuria; ACE inhibitors and ARBs are renoprotective) and arteriolosclerosis (causing hypertension) → chronic kidr disease.</li> <li>Large vessel atherosclerosis, CAD, peripheral vascular occlusive disease, gangrene → limb cerebrovascular disease. MI most common cause of death.</li> </ul> </li> <li>Osmotic damage (sorbitol accumulation in organs with aldose reductase and ↓ or absent sorbi dehydrogenase):         <ul> <li>Neuropathy (motor, sensory [glove and stocking distribution], and autonomic degeneration</li> <li>Cataracts.</li> </ul> </li> </ul>		oma, nephropathy. Nodular microalbuminuria; ACE inhibitors using hypertension) → chronic kidney occlusive disease, gangrene → limb loss, eath.  dose reductase and ↓ or absent sorbitol
DIAGNOSIS	TEST	DIAGNOSTIC CUTOFF	NOTES
	$\mathrm{HbA}_{\mathrm{lc}}$	≥ 6.5%	Reflects average blood glucose over prior 3 months
	Fasting plasma glucose	≥ 126 mg/dL	Fasting for $> 8$ hours
	2-hour oral glucose tolerance test	≥ 200 mg/dL	2 hours after consumption of 75 g of glucose in water

#### Insulin deficiency or severe insulin insensitivity



FAS1\_2019\_08-Endocrine.indd 346 11/7/19 4:30 PM

#### Type 1 vs type 2 diabetes mellitus

	Type 1	Type 2
1° DEFECT	Autoimmune T-cell–mediated destruction of β cells (eg, due to presence of glutamic acid decarboxylase antibodies)	† resistance to insulin, progressive pancreatic β-cell failure
INSULIN NECESSARY IN TREATMENT	Always	Sometimes
AGE (EXCEPTIONS COMMON)	< 30 yr	> 40 yr
ASSOCIATION WITH OBESITY	No	Yes
GENETIC PREDISPOSITION	Relatively weak (50% concordance in identical twins), polygenic	Relatively strong (90% concordance in identica twins), polygenic
ASSOCIATION WITH HLA SYSTEM	Yes, HLA-DR4 and -DR3 $(4 - 3 = \text{type } 1)$	No
GLUCOSE INTOLERANCE	Severe	Mild to moderate
INSULIN SENSITIVITY	High	Low
KETOACIDOSIS	Common	Rare
β-CELL NUMBERS IN THE ISLETS	<b>↓</b>	Variable (with amyloid deposits)
SERUM INSULIN LEVEL	<b>↓</b>	↑ initially, but ↓ in advanced disease
CLASSIC SYMPTOMS OF POLYURIA, POLYDIPSIA, POLYPHAGIA, WEIGHT LOSS	Common	Sometimes
Diabetic ketoacidosis	Islet leukocytic infiltrate  Insulin absent, ketones present (→ complication Insulin noncompliance or ↑ requirements from ↑	
	Insulin absent, ketones present (→ complication Insulin noncompliance or ↑ requirements from ↑ tetogenesis from ↑ free fatty acids → ketone both DKA is Deadly: Delirium/psychosis, Kussmaul results of the complex of	ns).  The stress (eg, infection) → excess fat breakdown and odies (β-hydroxybutyrate > acetoacetate).  The stress (eg, infection) → excess fat breakdown and odies (β-hydroxybutyrate).
Diabetic ketoacidosis	Insulin absent, ketones present (→ complication Insulin noncompliance or ↑ requirements from ↑ ketogenesis from ↑ free fatty acids → ketone border DKA is Deadly: Delirium/psychosis, Kussmaul repain/nausea/vomiting, Dehydration. Fruity breadth	ns).  stress (eg, infection) → excess fat breakdown and odies (β-hydroxybutyrate > acetoacetate).  espirations (rapid, deep breathing), Abdominal ath odor (due to exhaled acetone).
Diabetic ketoacidosis SIGNS/SYMPTOMS	Insulin absent, ketones present (→ complication Insulin noncompliance or ↑ requirements from ↑ tetogenesis from ↑ free fatty acids → ketone both DKA is Deadly: Delirium/psychosis, Kussmaul results of the complex of	ns).  I stress (eg, infection) → excess fat breakdown and odies (β-hydroxybutyrate > acetoacetate).  Respirations (rapid, deep breathing), Abdominal ath odor (due to exhaled acetone).  Read abolic acidosis), ↑ urine and blood ketone levels, intracellular K⁺ due to transcellular shift from
Diabetic ketoacidosis SIGNS/SYMPTOMS	Insulin absent, ketones present (→ complication Insulin noncompliance or ↑ requirements from ↑ ketogenesis from ↑ free fatty acids → ketone b  DKA is Deadly: Delirium/psychosis, Kussmaul r pain/nausea/vomiting, Dehydration. Fruity bree  Hyperglycemia, ↑ H+, ↓ HCO <sub>3</sub> - (↑ anion gap met leukocytosis. Normal/↑ serum K+, but depleted	ns).  If stress (eg, infection) → excess fat breakdown and odies (β-hydroxybutyrate > acetoacetate).  Respirations (rapid, deep breathing), Abdominal ath odor (due to exhaled acetone).  Rebolic acidosis), ↑ urine and blood ketone levels, intracellular K⁺ due to transcellular shift from loss in urine → total body K⁺ depletion.
Diabetic ketoacidosis  SIGNS/SYMPTOMS  LABS	Insulin absent, ketones present (→ complication Insulin noncompliance or ↑ requirements from ↑ ketogenesis from ↑ free fatty acids → ketone be DKA is Deadly: Delirium/psychosis, Kussmaul repain/nausea/vomiting, Dehydration. Fruity breathyperglycemia, ↑ H+, ↓ HCO <sub>3</sub> - (↑ anion gap methology leukocytosis. Normal/↑ serum K+, but depleted ↓ insulin and acidosis. Osmotic diuresis → ↑ K+	ns).  stress (eg, infection) → excess fat breakdown and odies (β-hydroxybutyrate > acetoacetate).  espirations (rapid, deep breathing), Abdominal ath odor (due to exhaled acetone).  abolic acidosis), ↑ urine and blood ketone levels, intracellular K⁺ due to transcellular shift from loss in urine → total body K⁺ depletion.  cardiac arrhythmias, HF.
Diabetic ketoacidosis  SIGNS/SYMPTOMS  LABS  COMPLICATIONS	Insulin absent, ketones present (→ complication Insulin noncompliance or ↑ requirements from ↑ ketogenesis from ↑ free fatty acids → ketone be DKA is Deadly: Delirium/psychosis, Kussmaul repain/nausea/vomiting, Dehydration. Fruity breathyperglycemia, ↑ H+, ↓ HCO <sub>3</sub> - (↑ anion gap metheukocytosis. Normal/↑ serum K+, but depleted ↓ insulin and acidosis. Osmotic diuresis → ↑ K+ Life-threatening mucormycosis, cerebral edema, IV fluids, IV insulin, K+ (to replete intracellular service) Insulin present, ketones absent.  Profound hyperglycemia → excessive osmotic diagrams.	ns).  If stress (eg, infection) → excess fat breakdown and odies (β-hydroxybutyrate > acetoacetate).  Respirations (rapid, deep breathing), Abdominal ath odor (due to exhaled acetone).  Rabolic acidosis), ↑ urine and blood ketone levels, intracellular K⁺ due to transcellular shift from loss in urine → total body K⁺ depletion.  Rardiac arrhythmias, HF.  Retores) +/- glucose to prevent hypoglycemia.
Diabetic ketoacidosis  SIGNS/SYMPTOMS  LABS  COMPLICATIONS  TREATMENT  Hyperosmolar	Insulin absent, ketones present (→ complication Insulin noncompliance or ↑ requirements from ↑ ketogenesis from ↑ free fatty acids → ketone be DKA is Deadly: Delirium/psychosis, Kussmaul repain/nausea/vomiting, Dehydration. Fruity breathyperglycemia, ↑ H+, ↓ HCO <sub>3</sub> - (↑ anion gap methology leukocytosis. Normal/↑ serum K+, but depleted ↓ insulin and acidosis. Osmotic diuresis → ↑ K+ Life-threatening mucormycosis, cerebral edema, IV fluids, IV insulin, K+ (to replete intracellular service). Insulin present, ketones absent.	ns).  If stress (eg, infection) → excess fat breakdown and odies (β-hydroxybutyrate > acetoacetate).  Respirations (rapid, deep breathing), Abdominal ath odor (due to exhaled acetone).  Rabolic acidosis), ↑ urine and blood ketone levels, intracellular K⁺ due to transcellular shift from loss in urine → total body K⁺ depletion.  Reardiac arrhythmias, HF.  Retores) +/- glucose to prevent hypoglycemia.
Diabetic ketoacidosis  SIGNS/SYMPTOMS  LABS  COMPLICATIONS  TREATMENT  Hyperosmolar hyperglycemic state	Insulin absent, ketones present (→ complication Insulin noncompliance or ↑ requirements from ↑ ketogenesis from ↑ free fatty acids → ketone b  DKA is Deadly: Delirium/psychosis, Kussmaul r pain/nausea/vomiting, Dehydration. Fruity bree  Hyperglycemia, ↑ H⁺, ↓ HCO₃⁻ (↑ anion gap met leukocytosis. Normal/↑ serum K⁺, but depleted ↓ insulin and acidosis. Osmotic diuresis → ↑ K⁺  Life-threatening mucormycosis, cerebral edema,  IV fluids, IV insulin, K⁺ (to replete intracellular s  Insulin present, ketones absent.  Profound hyperglycemia → excessive osmotic diu → HHS. Classically seen in elderly type 2 diabeter.	ns).  If stress (eg, infection) → excess fat breakdown and odies (β-hydroxybutyrate > acetoacetate).  Respirations (rapid, deep breathing), Abdominal ath odor (due to exhaled acetone).  Rabolic acidosis), ↑ urine and blood ketone levels, intracellular K⁺ due to transcellular shift from loss in urine → total body K⁺ depletion.  Reardiac arrhythmias, HF.  Retores) +/- glucose to prevent hypoglycemia.  Retoresis → dehydration and ↑ serum osmolality etics with limited ability to drink.  Rets, seizures.  Rolality (> 320 mOsm/kg), normal pH (no
Diabetic ketoacidosis  SIGNS/SYMPTOMS  LABS  COMPLICATIONS  TREATMENT  Hyperosmolar hyperglycemic state  SIGNS/SYMPTOMS	Insulin absent, ketones present (→ complication Insulin noncompliance or ↑ requirements from ↑ ketogenesis from ↑ free fatty acids → ketone be DKA is Deadly: Delirium/psychosis, Kussmaul repain/nausea/vomiting, Dehydration. Fruity breathyperglycemia, ↑ H+, ↓ HCO3- (↑ anion gap metheukocytosis. Normal/↑ serum K+, but depleted ↓ insulin and acidosis. Osmotic diuresis → ↑ K+ Life-threatening mucormycosis, cerebral edema, IV fluids, IV insulin, K+ (to replete intracellular service in the service of	ns).  If stress (eg, infection) → excess fat breakdown and odies (β-hydroxybutyrate > acetoacetate).  Respirations (rapid, deep breathing), Abdominal ath odor (due to exhaled acetone).  Rabolic acidosis), ↑ urine and blood ketone levels, intracellular K⁺ due to transcellular shift from loss in urine → total body K⁺ depletion.  Reardiac arrhythmias, HF.  Retores) +/- glucose to prevent hypoglycemia.  Retoresis → dehydration and ↑ serum osmolality etics with limited ability to drink.  Rets, seizures.  Rolality (> 320 mOsm/kg), normal pH (no

FAS1\_2019\_08-Endocrine.indd 347 11/7/19 4:30 PM

#### **Cushing syndrome**

#### ETIOLOGY

† cortisol due to a variety of causes:

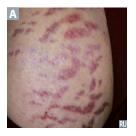
- Exogenous corticosteroids → ↓ ACTH → bilateral adrenal atrophy. Most common cause.
- Primary adrenal adenoma, hyperplasia, or carcinoma → ↓ ACTH → atrophy of uninvolved adrenal gland.
- ACTH-secreting pituitary adenoma (Cushing disease); paraneoplastic ACTH secretion (eg, small cell lung cancer, bronchial carcinoids) → bilateral adrenal hyperplasia. Cushing disease is responsible for the majority of endogenous cases of Cushing syndrome.

FINDINGS

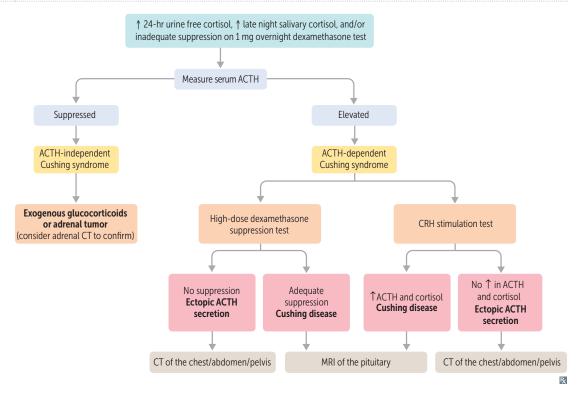
CUSHING Syndrome: † Cholesterol, † Urinary free cortisol, Skin changes (thinning, striae A), Hypertension, Immunosuppression, Neoplasm (a cause, not a finding), Growth retardation (in children), † Sugar (hyperglycemia, insulin resistance). Also, amenorrhea, moon facies B, buffalo hump, osteoporosis, † weight (truncal obesity), hirsutism.

DIAGNOSIS

Screening tests include: † free cortisol on 24-hr urinalysis, † late night salivary cortisol, and no suppression with overnight low-dose dexamethasone test.







#### **Nelson syndrome**

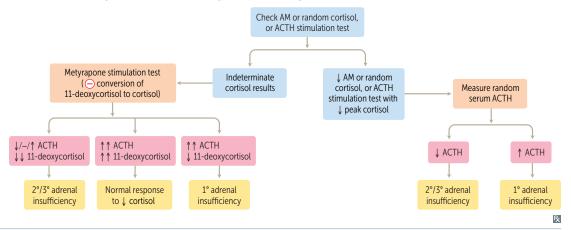
Enlargement of pre-existing ACTH–secreting pituitary adenoma after bilateral adrenalectomy for refractory Cushing disease → ↑ ACTH (hyperpigmentation), mass effect (headaches, bitemporal hemianopia).

Treatment: transsphenoidal resection, postoperative pituitary irradiation for residual tumor.

FAS1\_2019\_08-Endocrine.indd 348 11/7/19 4:30 PM

#### Adrenal insufficiency

Inability of adrenal glands to generate enough glucocorticoids +/- mineralocorticoids for the body's needs. Symptoms include weakness, fatigue, orthostatic hypotension, muscle aches, weight loss, GI disturbances, sugar and/or salt cravings. Treatment: glucocorticoid/mineralocorticoid replacement.



#### **Primary adrenal** insufficiency



- ↓ gland function → ↓ cortisol, ↓ aldosterone
- → hypotension (hyponatremic volume contraction), hyperkalemia, metabolic acidosis, skin/mucosal hyperpigmentation A († melanin synthesis due to † MSH, a byproduct of ACTH production from POMC).
- Acute—sudden onset (eg, due to massive hemorrhage). May present with shock in acute adrenal crisis.
- Chronic—Addison disease. Due to adrenal atrophy or destruction by disease (autoimmune destruction most common in the Western world; TB most common in the developing world).

Primary Pigments the skin/mucosa. Associated with autoimmune polyglandular syndromes.

#### Waterhouse-Friderichsen syndrome—acute

1° adrenal insufficiency due to adrenal hemorrhage associated with septicemia (usually Neisseria meningitidis), DIC, endotoxic shock.

#### Secondary adrenal insufficiency

Seen with ↓ pituitary ACTH production. No skin/mucosal hyperpigmentation (ACTH is not elevated), no hyperkalemia (aldosterone synthesis preserved due to functioning adrenal gland, intact RAAS).

Secondary Spares the skin/mucosa.

#### **Tertiary adrenal** insufficiency

Seen in patients with chronic exogenous steroid use, precipitated by abrupt withdrawal. Aldosterone synthesis unaffected.

Tertiary from Treatment.

#### Hyperaldosteronism

Increased secretion of aldosterone from adrenal gland. Clinical features include hypertension, ↓ or normal K<sup>+</sup>, metabolic alkalosis. 1° hyperaldosteronism does not directly cause edema due to aldosterone escape mechanism. However, certain 2° causes of hyperaldosteronism (eg, heart failure) impair the aldosterone escape mechanism, leading to worsening of edema.

#### **Primary** hyperaldosteronism

Seen with adrenal adenoma (Conn syndrome) or bilateral adrenal hyperplasia. † aldosterone, ↓ renin. Leads to treatment-resistant hypertension.

#### **Secondary** hyperaldosteronism

Seen in patients with renovascular hypertension, juxtaglomerular cell tumors (renin-producing), and edema (eg, cirrhosis, heart failure, nephrotic syndrome).

FAS1 2019 08-Endocrine.indd 349 11/7/19 4:30 PM

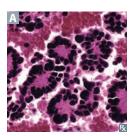
### Neuroendocrine tumors

Heterogeneous group of neoplasms originating from neuroendocrine cells (which have traits similar to nerve cells and hormone-producing cells).

Most neoplasms occur in the GI system (eg, carcinoid, gastrinoma), pancreas (eg, insulinoma, glucagonoma), and lungs (eg, small cell carcinoma). Also in thyroid (eg, medullary carcinoma) and adrenals (eg, pheochromocytoma).

Neuroendocrine cells (eg, pancreatic  $\beta$  cells, enterochromaffin cells) share a common biologic function through amine precursor uptake decarboxylase (APUD) despite differences in embryologic origin, anatomic site, and secretory products (eg, chromogranin A, neuron-specific enolase [NSE], synaptophysin, serotonin, histamine, calcitonin). Treatment: surgical resection, somatostatin analogs.

#### Neuroblastoma



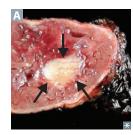
Most common tumor of the adrenal medulla in **children**, usually < 4 years old. Originates from Neural crest cells. Occurs anywhere along the sympathetic chain.

Most common presentation is abdominal distension and a firm, irregular mass that can cross the midline (vs Wilms tumor, which is smooth and unilateral). Less likely to develop hypertension than with pheochromocytoma (Neuroblastoma is Normotensive). Can also present with opsoclonus-myoclonus syndrome ("dancing eyes-dancing feet").

† HVA and VMA (catecholamine metabolites) in urine. Homer-Wright rosettes (neuroblasts surrounding a central lumen A) characteristic of neuroblastoma and medulloblastoma. Bombesin and NSE  $\oplus$ . Associated with amplification of N-myc oncogene.

#### **Pheochromocytoma**

ETIOLOGY



Most common tumor of the adrenal medulla in adults A. Derived from chromaffin cells (arise from neural crest).

May be associated with germline mutations (eg, NF-1, VHL, RET [MEN 2A, 2B]).

Rule of 10's:

10% malignant

10% bilateral

10% extra-adrenal (eg, bladder wall, organ of Zuckerkandl)

10% calcify

**10%** kids

SYMPTOMS

Most tumors secrete epinephrine, norepinephrine, and dopamine, which can cause episodic hypertension. May also secrete EPO → polycythemia.

Symptoms occur in "spells"—relapse and remit.

Episodic hyperadrenergic symptoms (5 P's):

Pressure († BP)

Pain (headache)

Perspiration

Palpitations (tachycardia)

**P**allor

FINDINGS

† catecholamines and metanephrines (eg, homovanillic acid, vanillylmandelic acid) in urine and plasma.

Chromogranin, synaptophysin and NSE ⊕.

TREATMENT

Irreversible  $\alpha$ -antagonists (eg, phenoxybenzamine) followed by  $\beta$ -blockers prior to tumor resection.  $\alpha$ -blockade must be achieved before giving  $\beta$ -blockers to avoid a hypertensive crisis. A before B.

Phenoxybenzamine for pheochromocytoma.

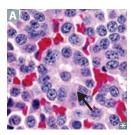
FAS1\_2019\_08-Endocrine.indd 350 11/7/19 4:30 PM

Multiple endocrine neoplasias	All MEN syndromes have autosomal dominant inheritance. "All MEN are dominant" (or so they think).	
SUBTYPE	CHARACTERISTICS	COMMENTS
MEN 1	Pituitary tumors (prolactin or GH) Pancreatic endocrine tumors—Zollinger—Ellison syndrome, insulinomas, VIPomas, glucagonomas (rare) Parathyroid adenomas Associated with mutation of MEN1 (menin, a tumor suppressor, chromosome 11), angiofibromas, collagenomas, meningiomas	Pituitary Pancreas
MEN 2A	Parathyroid hyperplasia Medullary thyroid carcinoma—neoplasm of parafollicular C cells; secretes calcitonin; prophylactic thyroidectomy required Pheochromocytoma (secretes catecholamines) Associated with mutation in RET (codes for receptor tyrosine kinase)	Thyroid (medullary carcinoma)  Pheochromocytoma
MEN 2B	Medullary thyroid carcinoma Pheochromocytoma Mucosal neuromas A (oral/intestinal ganglioneuromatosis) Associated with marfanoid habitus; mutation in RET gene	MEN 1 = 3 P's: Pituitary, Parathyroid, and Pancreas  MEN 2A = 2 P's: Parathyroid and Pheochromocytoma  MEN 2B = 1 P: Pheochromocytoma

Insulinoma	Tumor of pancreatic β cells → overproduction of insulin → hypoglycemia.  May see Whipple triad: low blood glucose, symptoms of hypoglycemia (eg, lethargy, syncope, diplopia), and resolution of symptoms after normalization of plasma glucose levels. Symptomatic patients have ↓ blood glucose and ↑ C-peptide levels (vs exogenous insulin use). ~ 10% of cases associated with MEN 1 syndrome.
	Treatment: surgical resection.
Glucagonoma	Tumor of pancreatic α cells → overproduction of glucagon.  Presents with 6 D's: Dermatitis (necrolytic migratory erythema), Diabetes (hyperglycemia), DVT,  Declining weight, Depression, Diarrhea.  Treatment: octreotide, surgical resection.
Somatostatinoma	Tumor of pancreatic δ cells → overproduction of somatostatin → ↓ secretion of secretin, cholecystokinin, glucagon, insulin, gastrin, gastric inhibitory peptide (GIP).  May present with diabetes/glucose intolerance, steatorrhea, gallstones, achlorhydria.  Treatment: surgical resection; somatostatin analogs (eg, octreotide) for symptom control.

FAS1\_2019\_08-Endocrine.indd 351 11/7/19 4:30 PM

#### **Carcinoid syndrome**



Carcinoid tumors arise from neuroendocrine cells most commonly in the intestine or lung. Rare and does not occur if tumor is limited to the GI tract.

Prominent rosettes (arrow in  $\mathbb{A}$ ), chromogranin  $\mathbb{A} \oplus$  and synaptophysin  $\oplus$ ).

Neuroendocrine cells secrete 5-HT → recurrent diarrhea, wheezing, right-sided valvular heart disease (eg, tricuspid regurgitation, pulmonic stenosis), niacin deficiency (pellagra). 5-HT undergoes hepatic first-pass metabolism and enzymatic breakdown by MAO in the lung.

Treatment: surgical resection, somatostatin analog (eg, octreotide, telotristat) for symptom control.

#### Rule of thirds:

1/3 metastasize

1/3 present with 2nd malignancy

1/3 are multiple

### Zollinger-Ellison syndrome

Gastrin-secreting tumor (gastrinoma) of pancreas or duodenum. Acid hypersecretion causes recurrent ulcers in duodenum and jejunum. Presents with abdominal pain (peptic ulcer disease, distal ulcers), diarrhea (malabsorption). Positive secretin stimulation test: gastrin levels remain elevated after administration of secretin, which normally inhibits gastrin release. May be associated with MEN 1.

#### ► ENDOCRINE—PHARMACOLOGY

## Diabetes mellitus therapy

All patients with diabetes mellitus should receive education on diet, exercise, blood glucose monitoring, and complication management. Treatment differs based on the type of diabetes and glycemic control:

- Type 1 DM—insulin replacement
- Type 2 DM—oral agents (metformin is first line), non-insulin injectables, insulin replacement; weight loss particularly helpful in lowering blood glucose
- Gestational DM—insulin replacement if nutrition therapy and exercise alone fail Regular (short-acting) insulin is preferred for DKA (IV), hyperkalemia (+ glucose), stress hyperglycemia.

To Normalize Pancreatic Function (-gliTs, -gliNs, -gliPs, -gliFs).

#### MECHANISM DRUG CLASS **ADVERSE EFFECTS** Insulin preparations Rapid acting (1-hr Bind insulin receptor (tyrosine kinase activity) Hypoglycemia, lipodystrophy, hypersensitivity peak): Lispro, Aspart, Liver: † glucose storage as glycogen reactions (rare), weight gain Muscle: † glycogen, protein synthesis Glulisine (no LAG) Short acting (2-3 hr Fat: † TG storage Lispro, aspart, glulisine Plasma insulin level peak): regular Cell membrane: † K<sup>+</sup> uptake Intermediate acting (4-10 hr peak): NPH Long acting (no real peak): detemir, glargine 10 12 18 Hours

FAS1 2019 08-Endocrine.indd 352 11/7/19 4:30 PM

### Diabetes mellitus therapy (continued)

DRUG CLASS	MECHANISM	ADVERSE EFFECTS
Increase insulin sensitivit	у	
Biguanides Metformin	<ul> <li>Inhibit mGPD → inhibition of hepatic gluconeogenesis and the action of glucagon.</li> <li>† glycolysis, peripheral glucose uptake († insulin sensitivity).</li> </ul>	GI upset, lactic acidosis (use with caution in renal insufficiency), vitamin $B_{12}$ deficiency. Weight loss (often desired).
Glitazones/ thiazolidinediones "-gliTs" Pioglitazone, rosiglitazone	Activate PPAR-γ (a nuclear receptor) → ↑ insulin sensitivity and levels of adiponectin → regulation of glucose metabolism and fatty acid storage.	Weight gain, edema, HF, ↑ risk of fractures.  Delayed onset of action (several weeks).  Rosiglitazone: ↑ risk of MI, cardiovascular death.
Increase insulin secretion	1	
Sulfonylureas (1st gen) Chlorpropamide, tolbutamide Sulfonylureas (2nd gen)	Close K <sup>+</sup> channels in pancreatic B cell	DisulFIRam-like reaction (FIRst-generation only). Rarely used. Hypoglycemia († risk in renal insufficiency),
Glipizide, glyburide  Weglitinides  "-gliNs"  Nateglinide,  repaglinide	membrane → cell depolarizes → insulin release via † Ca <sup>2+</sup> influx.	weight gain.
Increase glucose-induced	d insulin secretion	
GLP-1 analogs Exenatide, liraglutide	<ul> <li>↓ glucagon release, ↓ gastric emptying,</li> <li>↑ glucose-dependent insulin release.</li> </ul>	Nausea, vomiting, pancreatitis. Weight loss (often desired).  † satiety (often desired).
DPP-4 inhibitors "-gliPs" Linagliptin, saxagliptin, sitagliptin	Inhibit DPP-4 enzyme that deactivates GLP-1  → ↓ glucagon release, ↓ gastric emptying.  ↑ glucose-dependent insulin release.	Respiratory and urinary infections, weight neutral.  † satiety (often desired).
Decrease glucose absorp	otion	
co-transporter 2 (SGLT2) inhibitors "-gliFs" Canagliflozin, dapagliflozin, empagliflozin	Block reabsorption of glucose in proximal convoluted tubule.	Glucosuria (UTIs, vulvovaginal candidiasis), dehydration (orthostatic hypotension), hyperkalemia, weight loss. Use with caution in renal insufficiency (\$\dagger\$ efficacy with \$\dagger\$ GFR).
<b>x-glucosidase</b> <b>inhibitors</b> Acarbose, miglitol	Inhibit intestinal brush-border α-glucosidases  → delayed carbohydrate hydrolysis and glucose absorption → ↓ postprandial hyperglycemia.	GI upset, bloating. Not recommended in renal insufficiency.
Others		
Amylin analogs Pramlintide	↓ glucagon release, ↓ gastric emptying.	Hypoglycemia, nausea. † satiety (often desired).

FAS1\_2019\_08-Endocrine.indd 353 11/7/19 4:30 PM

## 354 SECTION III ENDOCRINE ► ENDOCRINE—PHARMACOLOGY

Thionamides	Propylthiouracil, methimazole.				
MECHANISM	Block thyroid peroxidase, inhibiting the oxidation of iodide as well as the organification a coupling of iodine → inhibition of thyroid hormone synthesis. PTU also blocks 5′-deiod → ↓ Peripheral conversion of T <sub>4</sub> to T <sub>3</sub> .				
CLINICAL USE	Hyperthyroidism. PTU used in first trimester of pregnancy (due to methimazole teratogenicity); methimazole used in second and third trimesters of pregnancy (due to risk of PTU-induced hepatotoxicity). Not used to treat Graves ophthalmopathy (treated with corticosteroids).				
ADVERSE EFFECTS	Skin rash, agranulocytosis (rare), aplastic anemia, hepatotoxicity.  Methimazole is a possible teratogen (can cause aplasia cutis).				
_evothyroxine, liothyro	onine				
MECHANISM	Hormone replacement for T <sub>4</sub> (levothyroxine) or T <sub>3</sub> (liothyronine).				
CLINICAL USE	Hypothyroidism, myxedema. May be abused for weight loss. Distinguish exogenous hyperthyroidism from endogenous hyperthyroidism by using a combination of TSH receptor antibodies, radioactive iodine uptake, and/or measurement of thyroid blood flow on ultrasound.				
ADVERSE EFFECTS	Tachycardia, heat intolerance, tremors, arrhythmias.				
NOVERSE EFFECTS	rueny caraia, near intorciance, tromoto, army timinas.				
-lypothalamic/pituitary	<i>y</i> drugs				
-lypothalamic/pituitary	drugs CLINICAL USE ADH antagonists				
Hypothalamic/pituitary DRUG Conivaptan, tolvaptan Demeclocycline	$ \begin{array}{c} \textbf{/ drugs} \\ \hline \textbf{CLINICAL USE} \\ \hline \textbf{ADH antagonists} \\ \hline \textbf{SIADH (block action of ADH at $V_2$-receptor)} \\ \hline \textbf{ADH antagonist, a tetracycline} \\ \end{array} $				
<b>Hypothalamic/pituitary</b> DRUG Conivaptan, tolvaptan	CLINICAL USE  ADH antagonists  SIADH (block action of ADH at $V_2$ -receptor)  ADH antagonist, a tetracycline SIADH				
Hypothalamic/pituitary DRUG Conivaptan, tolvaptan Demeclocycline Desmopressin	$\begin{array}{c} \textbf{/drugs} \\ \textbf{CLINICAL USE} \\ \textbf{ADH antagonists} \\ \textbf{SIADH (block action of ADH at V}_2\text{-receptor)} \\ \textbf{ADH antagonist, a tetracycline} \\ \textbf{SIADH} \\ \textbf{Central DI, von Willebrand disease, sleep enuresis, hemophilia A} \end{array}$				
Hypothalamic/pituitary  DRUG  Conivaptan, tolvaptan  Demeclocycline  Desmopressin  GH	CLINICAL USE  ADH antagonists  SIADH (block action of ADH at V <sub>2</sub> -receptor)  ADH antagonist, a tetracycline  SIADH  Central DI, von Willebrand disease, sleep enuresis, hemophilia A  GH deficiency, Turner syndrome				
Hypothalamic/pituitary DRUG Conivaptan, tolvaptan Demeclocycline Desmopressin GH Oxytocin Somatostatin	CLINICAL USE  ADH antagonists SIADH (block action of ADH at V <sub>2</sub> -receptor)  ADH antagonist, a tetracycline SIADH  Central DI, von Willebrand disease, sleep enuresis, hemophilia A  GH deficiency, Turner syndrome  Induction of labor (stimulates uterine contractions), control uterine hemorrhage				
Hypothalamic/pituitary DRUG Conivaptan, tolvaptan Demeclocycline Desmopressin GH Oxytocin Somatostatin (octreotide)	CLINICAL USE  ADH antagonists SIADH (block action of ADH at V <sub>2</sub> -receptor)  ADH antagonist, a tetracycline SIADH  Central DI, von Willebrand disease, sleep enuresis, hemophilia A  GH deficiency, Turner syndrome  Induction of labor (stimulates uterine contractions), control uterine hemorrhage				
Hypothalamic/pituitary DRUG Conivaptan, tolvaptan Demeclocycline Desmopressin GH Oxytocin Somatostatin (octreotide) Fludrocortisone	CUNICAL USE  ADH antagonists SIADH (block action of ADH at V <sub>2</sub> -receptor)  ADH antagonist, a tetracycline SIADH  Central DI, von Willebrand disease, sleep enuresis, hemophilia A  GH deficiency, Turner syndrome Induction of labor (stimulates uterine contractions), control uterine hemorrhage  Acromegaly, carcinoid syndrome, gastrinoma, glucagonoma, esophageal varices				

FAS1\_2019\_08-Endocrine.indd 354 11/7/19 4:30 PM

#### Cinacalcet

MECHANISM	Sensitizes Ca <sup>2+</sup> -sensing receptor (CaSR) in parathyroid gland to circulating Ca <sup>2+</sup> → ↓ PTH
CLINICAL USE	2° hyperparathyroidism in patients with CKD receiving hemodialysis, hypercalcemia in 1° hyperparathyroidism (if parathyroidectomy fails), or in parathyroid carcinoma.
ADVERSE EFFECTS	Hypocalcemia.
Sovolamor	
Sevelamer	
Sevelamer MECHANISM	Nonabsorbable phosphate binder that prevents phosphate absorption from the GI tract.
	Nonabsorbable phosphate binder that prevents phosphate absorption from the GI tract.  Hyperphosphatemia in CKD.

FAS1\_2019\_08-Endocrine.indd 355 11/7/19 4:30 PM 356 SECTION II

SECTION II ENDOCRINE → ENDOCRINE—PHARMACOLOGY

► NOTES	

FAS1\_2019\_08-Endocrine.indd 356 11/7/19 4:30 PM

## HIGH-YIELD SYSTEMS

## **Gastrointestinal**

"A good set of bowels is worth more to a man than any quantity of brains."

—Josh Billings

"Man should strive to have his intestines relaxed all the days of his life."

—Moses Maimonides

"All right, let's not panic. I'll make the money by selling one of my livers. I can get by with one."

-Homer Simpson

When studying the gastrointestinal system, be sure to understand the normal embryology, anatomy, and physiology and how it is affected in the various pathologic diseases. Study not only what a disease entails, but also its specific findings, so that you can differentiate between two similar diseases. For example, what specifically makes ulcerative colitis different than Crohn disease? Also, it is important to understand bile metabolism and which lab values increase or decrease depending on the disease process. Be comfortable with basic interpretation of abdominal x-rays, CT scans, and endoscopic images.

<b>▶</b> Embryology	358
▶ Anatomy	360
▶ Physiology	371
▶ Pathology	376
▶ Pharmacology	398

FAS1\_2019\_09-Gastrointestinal.indd 357 11/7/19 4:42 PM

#### ► GASTROINTESTINAL—EMBRYOLOGY

# Normal gastrointestinal embryology

Foregut—esophagus to duodenum at level of pancreatic duct and common bile duct insertion (ampulla of Vater).

Midgut—lower duodenum to proximal 2/3 of transverse colon.

Hindgut—distal 1/3 of transverse colon to anal canal above pectinate line.

Midgut development:

- 6th week—physiologic herniation of midgut through umbilical ring
- 10th week—returns to abdominal cavity + rotates around superior mesenteric artery (SMA), total 270° counterclockwise

#### **Ventral wall defects**

Developmental defects due to failure of rostral fold closure (eg, sternal defects [ectopia cordis]), lateral fold closure (eg, omphalocele, gastroschisis), or caudal fold closure (eg, bladder exstrophy).

	Gastroschisis	Omphalocele
ETIOLOGY	Extrusion of abdominal contents through abdominal folds (typically right of umbilicus)	Failure of lateral walls to migrate at umbilical ring → persistent midline herniation of abdominal contents into umbilical cord
COVERAGE	Not covered by peritoneum or amnion A; "the guts come out of the gap (schism) in the letter G"	Surrounded by peritoneum <b>()</b> (light gray shiny sac); "abdominal contents are <b>seal</b> ed in the letter <b>O</b> "
ASSOCIATIONS	Not associated with chromosome abnormalities; favorable prognosis	Associated with congenital anomalies (eg, trisomies 13 and 18, Beckwith-Wiedemann syndrome) and other structural abnormalities (eg, cardiac, GU, neural tube)









## Congenital umbilical hernia

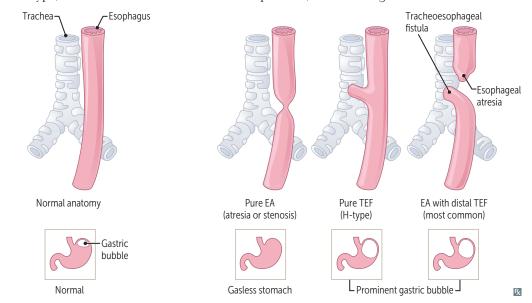
Failure of umbilical ring to close after physiologic herniation of the midgut. Small defects usually close spontaneously.

FAS1\_2019\_09-Gastrointestinal.indd 358 11/7/19 4:42 PM

## Tracheoesophageal anomalies

Esophageal atresia (EA) with distal tracheoesophageal fistula (TEF) is the most common (85%) and often presents as polyhydramnios in utero (due to inability of fetus to swallow amniotic fluid). Neonates drool, choke, and vomit with first feeding. TEFs allow air to enter stomach (visible on CXR). Cyanosis is 2° to laryngospasm (to avoid reflux-related aspiration). Clinical test: failure to pass nasogastric tube into stomach.

In H-type, the fistula resembles the letter H. In pure EA, CXR shows gasless abdomen.



#### **Intestinal atresia**



Presents with bilious vomiting and abdominal distension within first 1–2 days of life.

**Duodenal atresia**—failure to recanalize. Abdominal x-ray A shows "double bubble" (dilated stomach, proximal duodenum). Associated with Down syndrome.

**Jejunal and ileal atresia**—disruption of mesenteric vessels (typically SMA) → ischemic necrosis of fetal intestine → segmental resorption: bowel becomes discontinuous. X-ray shows dilated loops of small bowel with air-fluid levels.

## Hypertrophic pyloric stenosis



Most common cause of gastric outlet obstruction in infants (1:600). Palpable olive-shaped mass in epigastric region, visible peristaltic waves, and nonbilious projectile vomiting at  $\sim 2-6$  weeks old. More common in firstborn males; associated with exposure to macrolides.

Results in hypokalemic hypochloremic metabolic alkalosis (2° to vomiting of gastric acid and subsequent volume contraction).

Ultrasound shows thickened and lengthened pylorus A.

Treatment: surgical incision of pyloric muscles (pyloromyotomy).

FAS1\_2019\_09-Gastrointestinal.indd 359 11/7/19 4:42 PM

## Pancreas and spleen embryology



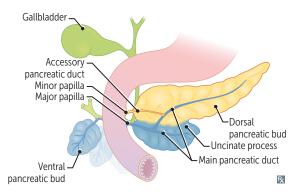
Pancreas—derived from foregut. Ventral pancreatic bud contributes to uncinate process and main pancreatic duct. The dorsal pancreatic bud alone becomes the body, tail, isthmus, and accessory pancreatic duct. Both the ventral and dorsal buds contribute to pancreatic head.

Annular pancreas—abnormal rotation of ventral pancreatic bud forms a ring of pancreatic tissue

→ encircles 2nd part of duodenum; may cause duodenal narrowing (arrows in A) and vomiting.

Pancreas divisum—ventral and dorsal parts fail to fuse at 8 weeks. Common anomaly; mostly asymptomatic, but may cause chronic abdominal pain and/or pancreatitis.

Spleen—arises in mesentery of stomach (hence is mesodermal) but has foregut supply (celiac trunk



#### ► GASTROINTESTINAL — ANATOMY

## Retroperitoneal structures

Retroperitoneal structures A are posterior to (and outside of) the peritoneal cavity. Injuries to retroperitoneal structures can cause blood or gas accumulation in retroperitoneal space.

# Duodenum/jejunum Ascending colon Peritoneum Pancreas Liver NVC Aorta Right Ridney

→ splenic artery).

#### SAD PUCKER:

Suprarenal (adrenal) glands [not shown]

Aorta and IVC

Duodenum (2nd through 4th parts)

Pancreas (except tail)

Ureters [not shown]

Colon (descending and ascending)

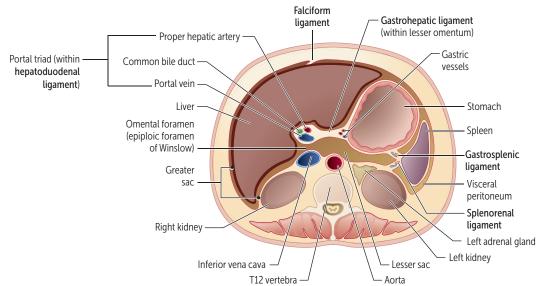
**K**idneys

Esophagus (thoracic portion) [not shown]

Rectum (partially) [not shown]



#### **Important gastrointestinal ligaments**



		T12 vertebra ─	
LIGAMENT	CONNECTS	STRUCTURES CONTAINED	NOTES
Falciform ligament	Liver to anterior abdominal wall	Ligamentum teres hepatis (derivative of fetal umbilical vein), patent paraumbilical veins	Derivative of ventral mesentery
Hepatoduodenal ligament	<b>Doduodenal</b> Liver to duodenum Portal triad: proper hepatic		Derivative of ventral mesentery Pringle maneuver—ligament is compressed manually or with a vascular clamp in omental foramen to control bleeding from hepatic inflow source Borders the omental foramen, which connects the greater and lesser sacs Part of lesser omentum
Gastrohepatic ligament	Liver to lesser curvature of stomach	Gastric vessels	Derivative of ventral mesentery Separates greater and lesser sacs on the right May be cut during surgery to access lesser sac Part of lesser omentum
Gastrocolic ligament (not shown)	Greater curvature and transverse colon	Gastroepiploic arteries	Derivative of dorsal mesentery Part of greater omentum
Gastrosplenic ligament	Greater curvature and spleen	Short gastrics, left gastroepiploic vessels	Derivative of dorsal mesentery Separates greater and lesser sacs on the left Part of greater omentum
Splenorenal ligament	Spleen to left pararenal space	Splenic artery and vein, tail of pancreas	Derivative of dorsal mesentery

FAS1\_2019\_09-Gastrointestinal.indd 361 11/7/19 4:42 PM

#### **Digestive tract** anatomy

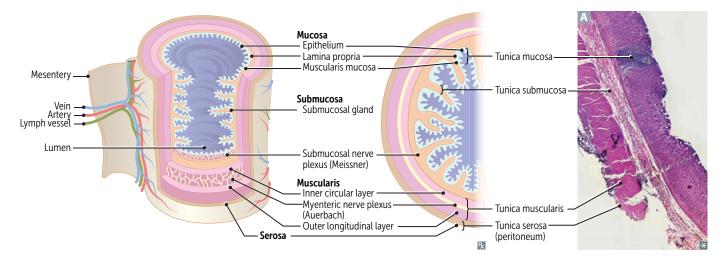
Layers of gut wall A (inside to outside—MSMS):

- Mucosa—epithelium, lamina propria, muscularis mucosa
- Submucosa—includes Submucosal nerve plexus (Meissner), Secretes fluid
- Muscularis externa—includes Myenteric nerve plexus (Auerbach), Motility
- Serosa (when intraperitoneal), adventitia (when retroperitoneal)

Ulcers can extend into submucosa, inner or outer muscular layer. Erosions are in mucosa only.

Frequency of basal electric rhythm (slow waves), which originate in the interstitial cells of Cajal:

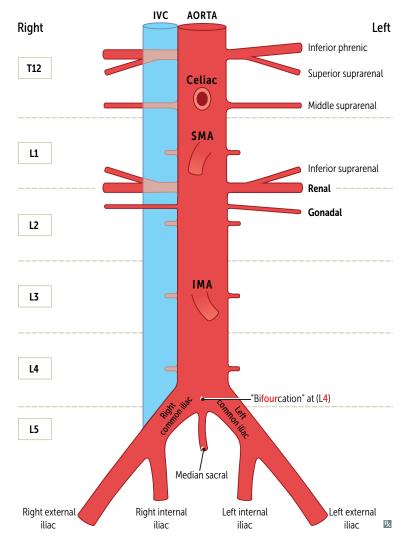
- Stomach—3 waves/min
- Duodenum—12 waves/min
- Ileum—8–9 waves/min



Esophagus	Nonkeratinized stratified squamous epithelium. Upper 1/3, striated muscle; middle and lower 2/3 smooth muscle, with some overlap at the transition.		
Stomach	Gastric glands A.		
Duodenum	Villi B and microvilli † absorptive surface. Brunner glands (HCO <sub>3</sub> secreting cells of submucosa) and crypts of Lieberkühn (contain stem cells that replace enterocytes/goblet cells and Paneth cells that secrete defensins, lysozyme, and TNF).		
Jejunum	Villi, crypts of Lieberkühn, and plicae circulares (also present in distal duodenum) 🕻.		
lleum	Peyer patches (arrow in <b>D</b> ; lymphoid aggregates in lamina propria, submucosa), plicae circulares (proximal ileum), and crypts of Lieberkühn. Largest number of goblet cells in the small intestine.		
Colon	Crypts of Lieberkühn with abundant goblet cells, but no villi 🗉.		

FAS1\_2019\_09-Gastrointestinal.indd 362 11/7/19 4:42 PM

#### **Abdominal aorta and branches**



Arteries supplying GI structures are single and branch anteriorly.

Arteries supplying non-GI structures are paired and branch laterally and posteriorly.

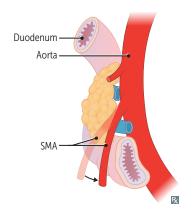
Two areas of the colon have dual blood supply from distal arterial branches ("watershed regions") → susceptible in colonic ischemia:

- Splenic flexure—SMA and IMA
- Rectosigmoid junction—the last sigmoid arterial branch from the IMA and superior rectal artery

**Nutcracker syndrome**—compression of left renal vein between superior mesenteric artery and aorta. Characterized by abdominal (flank) pain and gross hematuria (from rupture of thin-walled renal varicosities).

#### Superior mesenteric artery syndrome—

characterized by intermittent intestinal obstruction symptoms (primarily postprandial pain) when SMA and aorta compress transverse (third) portion of duodenum. Typically occurs in conditions associated with diminished mesenteric fat (eg, low body weight/malnutrition).



FAS1\_2019\_09-Gastrointestinal.indd 363 11/7/19 4:42 PM

#### **Gastrointestinal blood supply and innervation**

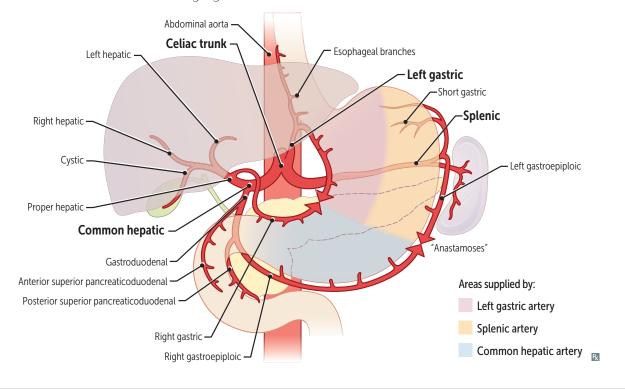
EMBRYONIC GUT REGION	ARTERY	PARASYMPATHETIC INNERVATION	VERTEBRAL LEVEL	STRUCTURES SUPPLIED
Foregut	Celiac	Vagus	T12/L1	Pharynx (vagus nerve only) and lower esophagus (celiac artery only) to proximal duodenum; liver, gallbladder, pancreas, spleen (mesoderm)
Midgut	SMA	Vagus	Ll	Distal duodenum to proximal 2/3 of transverse colon
Hindgut	IMA	Pelvic	L3	Distal 1/3 of transverse colon to upper portion of anal canal

#### **Celiac trunk**

Branches of celiac trunk: common hepatic, splenic, and left gastric. These constitute the main blood supply of the foregut.

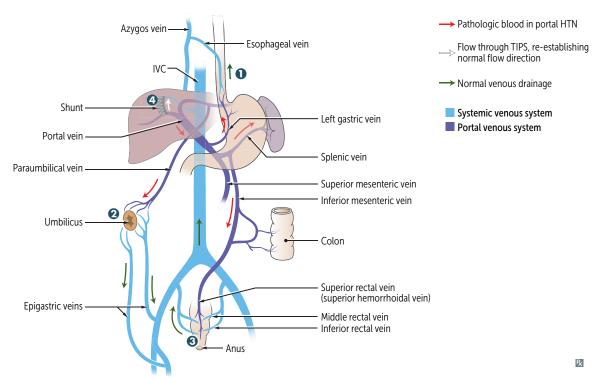
Strong anastomoses exist between:

- Left and right gastroepiploics
- Left and right gastrics



FAS1\_2019\_09-Gastrointestinal.indd 364 11/7/19 4:42 PM

## Portosystemic anastomoses



SITE OF ANASTOMOSIS	CLINICAL SIGN	PORTAL ↔ SYSTEMIC
1 Esophagus	Esophageal varices	Left gastric ↔ esophageal (drains into azygos)
2 Umbilicus	Caput medusae	Paraumbilical ↔ small epigastric veins of the anterior abdominal wall.
3 Rectum	Anorectal varices	Superior rectal ↔ middle and inferior rectal

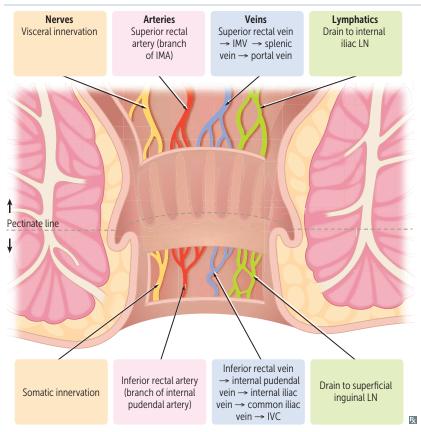
Varices of gut, butt, and caput (medusae) are commonly seen with portal hypertension.

Treatment with a transjugular intrahepatic portosystemic shunt (TIPS) between the portal vein and hepatic vein relieves portal hypertension by shunting blood to the systemic circulation, bypassing the liver. TIPS can precipitate hepatic encephalopathy due to ↓ clearance of ammonia from shunting.

FAS1\_2019\_09-Gastrointestinal.indd 365 11/7/19 4:42 PM

#### **Pectinate line**

Also called dentate line. Formed where endoderm (hindgut) meets ectoderm.



Above pectinate line: internal hemorrhoids, adenocarcinoma.

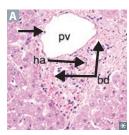
Internal hemorrhoids receive visceral innervation and are therefore **not painful**.

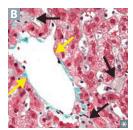
Below pectinate line: external hemorrhoids, anal fissures, squamous cell carcinoma. External hemorrhoids receive somatic innervation (inferior rectal branch of pudendal nerve) and are therefore painful if thrombosed.

Anal fissure—tear in anal mucosa below
Pectinate line. Pain while Pooping; blood
on toilet Paper. Located Posteriorly because
this area is Poorly Perfused. Innervated by
Pudendal nerve. Associated with low-fiber
diets and constipation.

FAS1\_2019\_09-Gastrointestinal.indd 366 11/7/19 4:42 PM

## Liver tissue architecture





The functional unit of the liver is made up of hexagonally arranged lobules surrounding the central vein with portal triads on the edges (consisting of a portal vein, hepatic artery, bile ducts, as well as lymphatics) A.

Apical surface of hepatocytes faces bile canaliculi. Basolateral surface faces sinusoids. Kupffer cells (specialized macrophages) located in sinusoids (black arrows in **B**; yellow arrows show hepatic venule) clear bacteria and damaged or senescent RBCs.

Hepatic stellate (Ito) cells in space of Disse store vitamin A (when quiescent) and produce extracellular matrix (when activated). Responsible for hepatic fibrosis. Zone I—periportal zone:

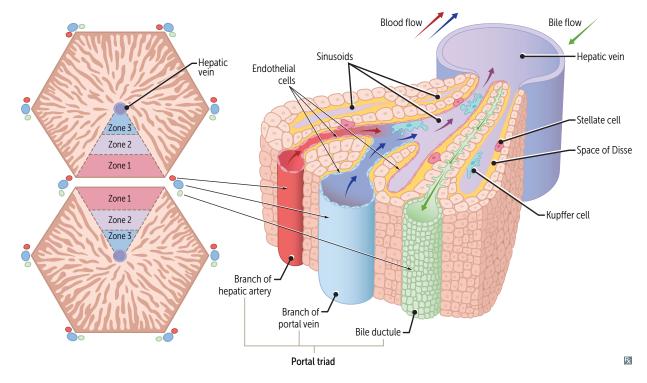
- Affected 1st by viral hepatitis
- Best oxygenated, most resistant to circulatory compromise
- Ingested toxins (eg, cocaine)

Zone **II**—intermediate zone:

Yellow fever

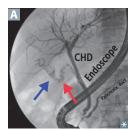
Zone III—pericentral vein (centrilobular) zone:

- Affected 1st by ischemia (least oxygenated)
- High concentration of cytochrome P-450
- Most sensitive to metabolic toxins (eg, ethanol, CCl<sub>4</sub>, halothane, rifampin, acetaminophen)
- Site of alcoholic hepatitis



FAS1\_2019\_09-Gastrointestinal.indd 367 11/7/19 4:42 PM

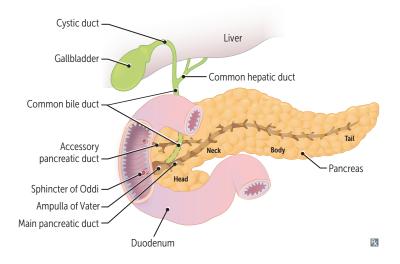
#### **Biliary structures**



Gallstones that reach the confluence of the common bile and pancreatic ducts at the ampulla of Vater can block both the common bile and pancreatic ducts (double duct sign), causing both cholangitis and pancreatitis, respectively.

Tumors that arise in head of pancreas (usually ductal adenocarcinoma) can cause obstruction of common bile duct → enlarged gallbladder with painless jaundice (Courvoisier sign).

Cholangiography shows filling defects in gallbladder (blue arrow) and cystic duct (red arrow) A.



#### **Femoral region**

ORGANIZATION

Lateral to medial: Nerve-Artery-Vein-Lymphatics.

You go from **lateral to medial** to find your **NAVeL**.

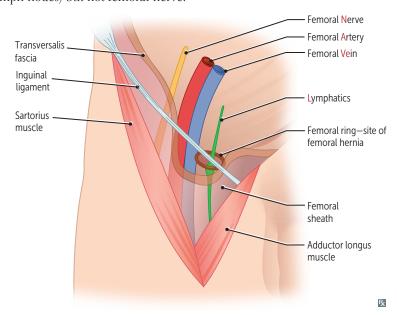
Femoral triangle

Contains femoral nerve, artery, vein.

Venous near the penis.

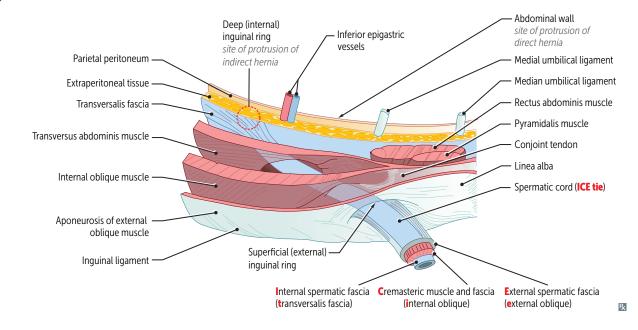
**Femoral sheath** 

Fascial tube 3–4 cm below inguinal ligament. Contains femoral vein, artery, and canal (deep inguinal lymph nodes) but not femoral nerve.

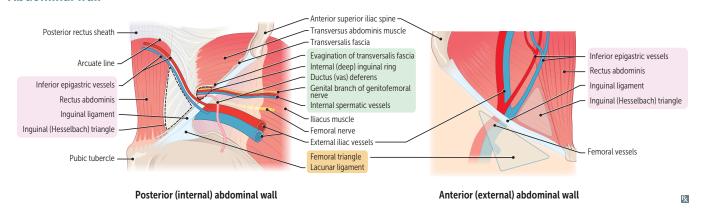


FAS1\_2019\_09-Gastrointestinal.indd 368 11/7/19 4:42 PM

#### **Inguinal canal**



#### **Abdominal wall**



FAS1\_2019\_09-Gastrointestinal.indd 369 11/7/19 4:42 PM

#### **Hernias**

Protrusion of peritoneum through an opening, usually at a site of weakness. Contents may be at risk for incarceration (not reducible back into abdomen/pelvis) and strangulation (ischemia and necrosis). Complicated hernias can present with tenderness, erythema, fever.

#### Diaphragmatic hernia



Abdominal structures enter the thorax A; may occur due to congenital defect of pleuroperitoneal membrane or from trauma. Commonly occurs on left side due to relative protection of right hemidiaphragm by liver. Most commonly a hiatal hernia, in which stomach herniates upward through the esophageal hiatus of the diaphragm.

Sliding hiatal hernia—gastroesophageal junction is displaced upward as gastric cardia slides into hiatus; "hourglass stomach." Most common type. Associated with GERD.

Paraesophageal hiatal hernia—

gastroesophageal junction is usually normal but gastric fundus protrudes into the thorax.

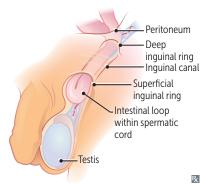


## Indirect inguinal hernia



Goes through the internal (deep) inguinal ring, external (superficial) inguinal ring, and into the groin. Enters internal inguinal ring lateral to inferior epigastric vessels. Caused by failure of processus vaginalis to close (can form hydrocele). May be noticed in infants or discovered in adulthood. Much more common in males **B**.

Follows the pathway of testicular descent. Covered by all 3 layers of spermatic fascia.



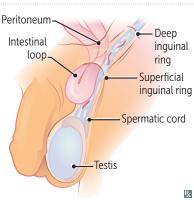
#### **Direct inguinal hernia**

Protrudes through inguinal (Hesselbach) triangle. Bulges directly through parietal peritoneum medial to the inferior epigastric vessels but lateral to the rectus abdominis. Goes through external (superficial) inguinal ring only. Covered by external spermatic fascia. Usually occurs in older men due to acquired weakness of transversalis fascia.

MDs don't LIe:

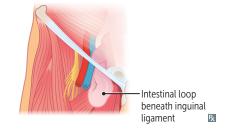
Medial to inferior epigastric vessels = Direct hernia.

Lateral to inferior epigastric vessels = Indirect hernia.



#### **Femoral** hernia

Protrudes below inguinal ligament through femoral canal below and lateral to pubic tubercle. More common in females, but overall inguinal hernias are the most common. More likely to present with incarceration or strangulation (vs inguinal hernia).



FAS1\_2019\_09-Gastrointestinal.indd 370 11/7/19 4:42 PM

## ► GASTROINTESTINAL—PHYSIOLOGY

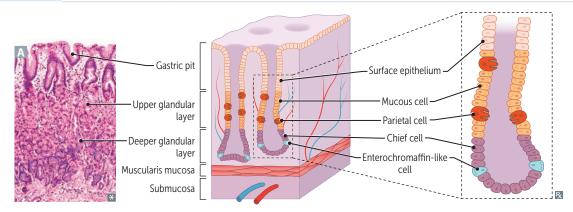
#### **Gastrointestinal regulatory substances**

REGULATORY SUBSTANCE	SOURCE	ACTION	REGULATION	NOTES
Gastrin	G cells (antrum of stomach, duodenum)	↑ gastric H <sup>+</sup> secretion ↑ growth of gastric mucosa ↑ gastric motility	† by stomach distention/ alkalinization, amino acids, peptides, vagal stimulation via gastrin-releasing peptide (GRP) ↓ by pH < 1.5	† by chronic PPI use † in chronic atrophic gastritis (eg, <i>H pylori</i> ) †† in Zollinger-Ellison syndrome (gastrinoma)
Somatostatin	D cells (pancreatic islets, GI mucosa)	<ul> <li>↓ gastric acid and pepsinogen secretion</li> <li>↓ pancreatic and small intestine fluid secretion</li> <li>↓ gallbladder contraction</li> <li>↓ insulin and glucagon release</li> </ul>	↑ by acid ↓ by vagal stimulation	Inhibits secretion of various hormones (encourages somato-stasis) Octreotide is an analog used to treat acromegaly, carcinoid syndrome, and variceal bleeding
Cholecystokinin	I cells (duodenum, jejunum)	<ul> <li>↑ pancreatic secretion</li> <li>↑ gallbladder contraction</li> <li>↓ gastric emptying</li> <li>↑ sphincter of Oddi relaxation</li> </ul>	the by fatty acids, amino acids	Acts on neural muscarinic pathways to cause pancreatic secretion
Secretin	S cells (duodenum)	<ul> <li>↑ pancreatic HCO<sub>3</sub><sup>-</sup> secretion</li> <li>↓ gastric acid secretion</li> <li>↑ bile secretion</li> </ul>	the by acid, fatty acids in lumen of duodenum	↑ HCO <sub>3</sub> - neutralizes gastric acid in duodenum, allowing pancreatic enzymes to function
Glucose- dependent insulinotropic peptide	K cells (duodenum, jejunum)	Exocrine:  ↓ gastric H <sup>+</sup> secretion Endocrine:  ↑ insulin release	the by fatty acids, amino acids, oral glucose	Also called gastric inhibitory peptide (GIP) Oral glucose load † insulin compared to IV equivalent due to GIP secretion
Motilin	Small intestine	Produces migrating motor complexes (MMCs)	† in fasting state	Motilin receptor agonists (eg, erythromycin) are used to stimulate intestinal peristalsis.
Vasoactive intestinal polypeptide	Parasympathetic ganglia in sphincters, gallbladder, small intestine	<ul> <li>intestinal water and electrolyte secretion</li> <li>relaxation of intestinal smooth muscle and sphincters</li> </ul>	↑ by distention and vagal stimulation ↓ by adrenergic input	VIPoma—non-α, non-β islet cell pancreatic tumor that secretes VIP; associated with Watery Diarrhea, Hypokalemia, Achlorhydria (WDHA syndrome)
Nitric oxide		† smooth muscle relaxation, including lower esophageal sphincter (LES)		Loss of NO secretion is implicated in † LES tone of achalasia
Ghrelin	Stomach	† appetite ("ghrowlin' stomach")	↑ in fasting state ↓ by food	↑ in Prader-Willi syndrome ↓ after gastric bypass surgery

FAS1\_2019\_09-Gastrointestinal.indd 371 11/7/19 4:42 PM

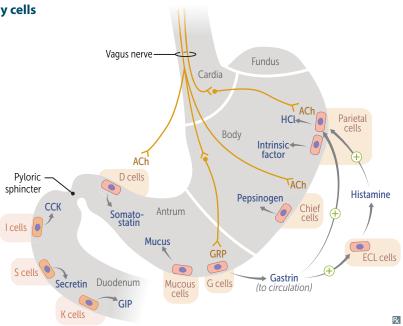
#### **Gastrointestinal secretory products**

PRODUCT	SOURCE	ACTION	REGULATION	NOTES
Intrinsic factor	Parietal cells (stomach A)	Vitamin B <sub>12</sub> -binding protein (required for B <sub>12</sub> uptake in terminal ileum)		Autoimmune destruction of parietal cells → chronic gastritis and pernicious anemia.
Gastric acid	Parietal cells (stomach)	↓ stomach pH	↑ by histamine, vagal stimulation (ACh), gastrin ↓ by somatostatin, GIP, prostaglandin, secretin	
Pepsin	Chief cells (stomach)	Protein digestion	the by vagal stimulation (ACh), local acid	Pepsinogen (inactive) is converted to pepsin (active) in the presence of H <sup>+</sup> .
Bicarbonate	Mucosal cells (stomach, duodenum, salivary glands, pancreas) and Brunner glands (duodenum)	Neutralizes acid	the by pancreatic and biliary secretion with secretin	Trapped in mucus that covers the gastric epithelium.



FAS1\_2019\_09-Gastrointestinal.indd 372 11/7/19 4:42 PM

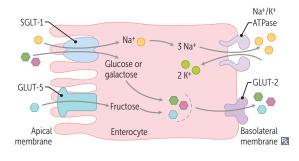
#### Locations of gastrointestinal secretory cells



Gastrin † acid secretion primarily through its effects on enterochromaffin-like (ECL) cells (leading to histamine release) rather than through its direct effect on parietal cells.

ENZYME	ROLE	NOTES
<b>α</b> -amylase	Starch digestion	Secreted in active form
Lipases	Fat digestion	
Proteases	Protein digestion	Includes trypsin, chymotrypsin, elastase, carboxypeptidases Secreted as proenzymes also called zymogen
Trypsinogen	Converted to active enzyme trypsin  → activation of other proenzymes and cleaving of additional trypsinogen molecules into active trypsin (positive feedback loop)	Converted to trypsin by enterokinase/ enteropeptidase, a brush-border enzyme on duodenal and jejunal mucosa

# Carbohydrate absorption



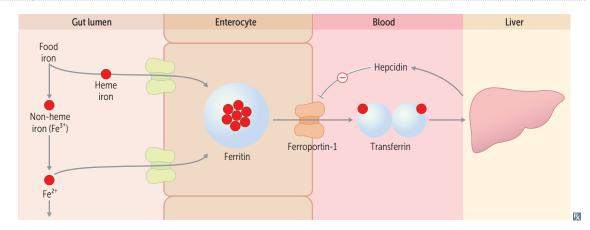
Only monosaccharides (glucose, galactose, fructose) are absorbed by enterocytes. Glucose and galactose are taken up by SGLT1 (Na<sup>+</sup> dependent). Fructose is taken up via Facilitated diffusion by GLUT5. All are transported to blood by GLUT2.

D-xylose absorption test: simple sugar that requires intact mucosa for absorption, but does not require digestive enzymes. Helps distinguish GI mucosal damage from other causes of malabsorption.

FAS1\_2019\_09-Gastrointestinal.indd 373 11/7/19 4:42 PM

#### Vitamin and mineral absorption

Iron	Absorbed as Fe <sup>2+</sup> in duodenum	Iron Fist, Bro
Folate	Absorbed in small bowel	Clinically relevant in patients with small bowel
Vitamin B <sub>12</sub>	Absorbed in terminal ileum along with bile salts, requires intrinsic factor	disease or after resection (eg, vitamin $B_{12}$ deficiency following terminal ileum resection)



#### **Peyer patches**



Unencapsulated lymphoid tissue A found in lamina propria and submucosa of ileum.

Contain specialized M cells that sample and present antigens to immune cells.

B cells stimulated in germinal centers of Peyer patches differentiate into IgA-secreting plasma cells, which ultimately reside in lamina propria. IgA receives protective secretory component and is then transported across the epithelium to the gut to deal with intraluminal antigen.

Think of IgA, the Intra-gut Antibody

#### Bile

Composed of bile salts (bile acids conjugated to glycine or taurine, making them water soluble), phospholipids, cholesterol, bilirubin, water, and ions. Cholesterol 7α-hydroxylase catalyzes rate-limiting step of bile acid synthesis.

#### Functions:

- Digestion and absorption of lipids and fatsoluble vitamins
- Cholesterol excretion (body's 1° means of eliminating cholesterol)
- Antimicrobial activity (via membrane disruption)

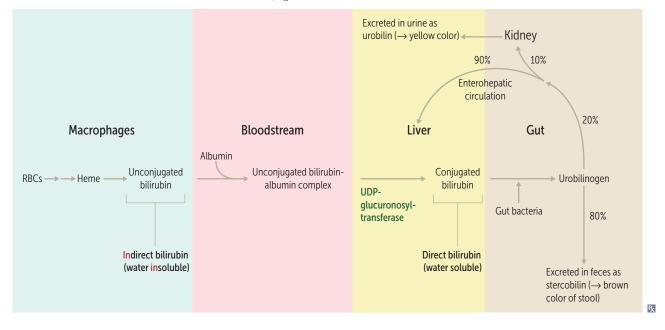
- ↓ absorption of enteric bile salts at distal ileum (as in short bowel syndrome, Crohn disease) prevents normal fat absorption
- Calcium, which normally binds oxalate, binds fat instead, so free oxalate is absorbed by gut
- → ↑ frequency of calcium oxalate kidney stones

FAS1\_2019\_09-Gastrointestinal.indd 374 11/7/19 4:42 PM

#### **Bilirubin**

Heme is metabolized by heme oxygenase to biliverdin, which is subsequently reduced to bilirubin. Unconjugated bilirubin is removed from blood by liver, conjugated with glucuronate, and excreted in bile.

Direct bilirubin: conjugated with glucuronic acid; water soluble (dissolves in water). Indirect bilirubin: unconjugated; water insoluble.



FAS1\_2019\_09-Gastrointestinal.indd 375 11/7/19 4:42 PM

#### ► GASTROINTESTINAL—PATHOLOGY

#### **Sialolithiasis**



Stone(s) in salivary gland duct A. Can occur in 3 major salivary glands (parotid, submandibular, sublingual). Single stone more common in submandibular gland (Wharton duct).

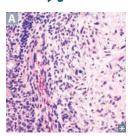
Presents as recurrent pre-/periprandial pain and swelling in affected gland.

Caused by dehydration or trauma.

Treat conservatively with NSAIDs, gland massage, warm compresses, sour candies (to promote salivary flow).

Sialadenitis—inflammation of salivary gland due to obstruction, infection, or immune-mediated mechanisms.

#### Salivary gland tumors



Most are benign and commonly affect parotid gland (80-85%). Nearly half of all submandibular gland neoplasms and most sublingual and minor salivary gland tumors are malignant. Typically present as painless mass/swelling. Facial paralysis or pain suggests malignant involvement.

- Pleomorphic adenoma (benign mixed tumor)—most common salivary gland tumor A.
   Composed of chondromyxoid stroma and epithelium and recurs if incompletely excised or ruptured intraoperatively. May undergo malignant transformation.
- Mucoepidermoid carcinoma—most common malignant tumor, has mucinous and squamous components.
- Warthin tumor (papillary cystadenoma lymphomatosum)—benign cystic tumor with germinal centers. Typically found in smokers. Bilateral in 10%; multifocal in 10%. "Warriors from Germany love smoking."

#### **Achalasia**



Failure of LES to relax due to degeneration of inhibitory neurons (containing NO and VIP) in the myenteric (Auerbach) plexus of the esophageal wall.

Manometry findings include uncoordinated or absent peristalsis with high LES resting pressure → progressive dysphagia to solids and liquids (vs obstruction—solids only). Barium swallow shows dilated esophagus with an area of distal stenosis ("bird's beak" A).

Associated with ↑ risk of esophageal cancer.

A-chalasia = absence of relaxation.

2° achalasia (pseudoachalasia) may arise from Chagas disease (*T cruzi* infection) or extraesophageal malignancies (mass effect or paraneoplastic).

Chagas disease can cause achalasia.

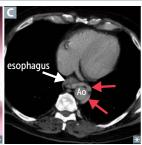
FAS1 2019 09-Gastrointestinal indd 376 11/7/19 4:42 PM

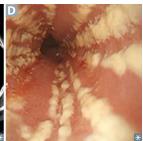
#### **Esophageal pathologies**

Diffuse esophageal spasm	Spontaneous, nonperistaltic (uncoordinated) contractions of the esophagus with normal LES pressure. Presents with dysphagia and angina-like chest pain. Barium swallow reveals "corkscrew" esophagus. Manometry is diagnostic. Treatment includes nitrates and CCBs.
Eosinophilic esophagitis	Infiltration of eosinophils in the esophagus often in atopic patients. Food allergens → dysphagia, food impaction. Esophageal rings and linear furrows often seen on endoscopy. Typically unresponsive to GERD therapy.
Esophageal perforation	Most commonly iatrogenic following esophageal instrumentation. Noniatrogenic causes include spontaneous rupture, foreign body ingestion, trauma, malignancy.  May present with pneumomediastinum (arrows in A). Subcutaneous emphysema may be due to dissecting air (signs include crepitus in the neck region or chest wall).  Boerhaave syndrome—transmural, usually distal esophageal rupture due to violent retching.
Esophageal strictures	Associated with caustic ingestion, acid reflux, and esophagitis.
Esophageal varices	Dilated submucosal veins (red arrows in <b>(E)</b> (a) in lower 1/3 of esophagus 2° to portal hypertension. Common in cirrhotics, may be source of life-threatening hematemesis.
Esophagitis	Associated with reflux, infection in immunocompromised ( <i>Candida</i> : white pseudomembrane D; HSV-1: punched-out ulcers; CMV: linear ulcers), caustic ingestion, or pill-induced esophagitis (eg, bisphosphonates, tetracycline, NSAIDs, iron, and potassium chloride).
Gastroesophageal reflux disease	Commonly presents as heartburn, regurgitation, dysphagia. May also present as chronic cough, hoarseness (laryngopharyngeal reflux). Associated with asthma. Transient decreases in LES tone.
Ma <mark>ll</mark> ory-Weiss syndrome	Partial thickness, longitudinal lacerations of gastroesophageal junction, confined to mucosa/ submucosa, due to severe vomiting. Often presents with hematemesis. Usually found in alcoholics and bulimics.
Plummer-Vinson syndrome	Triad of Dysphagia, Iron deficiency anemia, Esophageal webs. † risk of esophageal Squamous cell carcinoma ("Plumber DIES"). May be associated with glossitis.
Schatzki rings	Rings formed at gastroesophageal junction, typically due to chronic acid reflux. Can present with dysphagia.
Sclerodermal esophageal dysmotility	Esophageal smooth muscle atrophy → ↓ LES pressure and dysmotility → acid reflux and dysphagia → stricture, Barrett esophagus, and aspiration. Part of CREST syndrome.



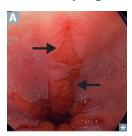




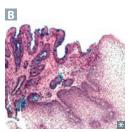


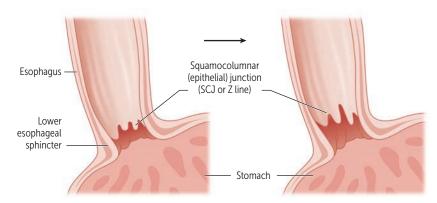
FAS1\_2019\_09-Gastrointestinal.indd 377 11/7/19 4:42 PM

#### **Barrett esophagus**



Specialized intestinal metaplasia A—replacement of nonkeratinized stratified squamous epithelium with intestinal epithelium (nonciliated columnar with goblet cells [stained blue in B]) in distal esophagus. Due to chronic gastroesophageal reflux disease (GERD). Associated with † risk of esophageal adenocarcinoma.





#### **Esophageal cancer**

Typically presents with progressive dysphagia (first solids, then liquids) and weight loss. Aggressive course due to lack of serosa in esophageal wall, allowing rapid extension. Poor prognosis due to advanced disease at presentation.

CANCER	PART OF ESOPHAGUS AFFECTED	RISK FACTORS	PREVALENCE
Squamous cell carcinoma	Upper 2/3	Alcohol, hot liquids, caustic strictures, smoking, achalasia	More common worldwide
Adenocarcinoma	Lower 1/3	Chronic GERD, Barrett esophagus, obesity, smoking, achalasia	More common in America

FAS1\_2019\_09-Gastrointestinal.indd 378 11/7/19 4:42 PM

#### **Gastritis**

Acute gastritis	Erosions can be caused by:  ■ NSAIDs→ PGE <sub>2</sub> →	Especially common among alcoholics and patients taking daily NSAIDs (eg, patients with rheumatoid arthritis)
	<ul> <li>Burns (Curling ulcer)—hypovolemia</li> <li>→ mucosal ischemia</li> </ul>	Burned by the Curling iron
	<ul> <li>Brain injury (Cushing ulcer)—↑ vagal stimulation → ↑ ACh → ↑ H<sup>+</sup> production</li> </ul>	Always Cushion the brain
Chronic gastritis	Mucosal inflammation, often leading to atrophy (hypochlorhydria → hypergastrinemia) and intestinal metaplasia († risk of gastric cancers)	
H pylori	Most common. ↑ risk of peptic ulcer disease, MALT lymphoma	Affects antrum first and spreads to body of stomach
Autoimmune	Autoantibodies to the H <sup>+</sup> /K <sup>+</sup> ATPase on parietal cells and to intrinsic factor. † risk of pernicious anemia	Affects body/fundus of stomach

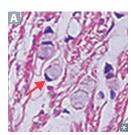
#### Ménétrier disease



Hyperplasia of gastric mucosa → hypertrophied rugae (look like brain gyri A). Causes excess mucus production with resultant protein loss and parietal cell atrophy with ↓ acid production. Precancerous.

Presents with Weight loss, Anorexia, Vomiting, Epigastric pain, Edema (due to protein loss) (WAVEE).

#### **Gastric cancer**



Most commonly gastric adenocarcinoma; lymphoma, GI stromal tumor, carcinoid (rare). Early aggressive local spread with node/liver metastases. Often presents late, with weight loss, abdominal pain, early satiety, and in some cases acanthosis nigricans or Leser-Trélat sign. Associated with blood type A.

- Intestinal—associated with H pylori, dietary nitrosamines (smoked foods), tobacco smoking, achlorhydria, chronic gastritis. Commonly on lesser curvature; looks like ulcer with raised margins.
- Diffuse—not associated with *H pylori*; most cases due to E-cadherin mutation; signet ring cells (mucin-filled cells with peripheral nuclei) A; stomach wall grossly thickened and leathery (linitis plastica).

Virchow node—involvement of left supraclavicular node by metastasis from stomach.

Krukenberg tumor—bilateral metastases to ovaries. Abundant mucin-secreting, signet ring cells.

Sister Mary Joseph nodule—subcutaneous periumbilical metastasis.

Blumer shelf—palpable mass on digital rectal exam suggesting metastasis to rectouterine pouch (pouch of Douglas).

FAS1\_2019\_09-Gastrointestinal.indd 379 11/7/19 4:42 PM

380 SECTION III

GASTROINTESTINAL ► GASTROINTESTINAL—PATHOLOGY

#### Peptic ulcer disease

	Gastric ulcer	Duodenal ulcer
PAIN	Can be Greater with meals—weight loss	Decreases with meals—weight gain
<i>H PYLORI</i> INFECTION	~ 70%	~ 90%
MECHANISM	↓ mucosal protection against gastric acid	↓ mucosal protection or ↑ gastric acid secretion
OTHER CAUSES	NSAIDs	Zollinger-Ellison syndrome
RISK OF CARCINOMA	t	Generally benign
OTHER	Biopsy margins to rule out malignancy	

#### **Ulcer complications**

•	
Hemorrhage  Gastric, duodenal (posterior > anterior). Most common complication.  Ruptured gastric ulcer on the lesser curvature of stomach → bleeding from left gastric and An ulcer on the posterior wall of duodenum → bleeding from gastroduodenal artery.	
Obstruction	Pyloric channel, duodenal.
Perforation	Duodenal (anterior > posterior).



Anterior duodenal ulcers can perforate into the anterior abdominal cavity, potentially leading to pneumoperitoneum.

May see free air under diaphragm (pneumoperitoneum) A with referred pain to the shoulder via irritation of phrenic nerve.

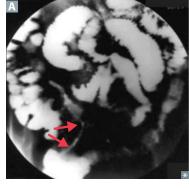
FAS1\_2019\_09-Gastrointestinal.indd 380 11/7/19 4:42 PM

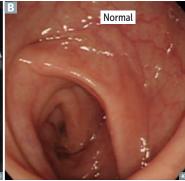
#### Can cause diarrhea, steatorrhea, weight loss, weakness, vitamin and mineral deficiencies. Screen for Malabsorption **syndromes** fecal fat (eg, Sudan stain). Celiac disease Gluten-sensitive enteropathy, celiac sprue. ↓ mucosal absorption primarily affects distal Autoimmune-mediated intolerance of duodenum and/or proximal jejunum. gliadin (gluten protein found in wheat) D-xylose test: passively absorbed in proximal → malabsorption and steatorrhea. Associated small intestine; blood and urine levels ↓ with with HLA-DQ2, HLA-DQ8, northern mucosa defects or bacterial overgrowth, European descent, dermatitis herpetiformis, normal in pancreatic insufficiency. ↓ bone density. Treatment: gluten-free diet. Findings: IgA anti-tissue transglutaminase (IgA tTG), anti-endomysial, anti-deamidated gliadin peptide antibodies; villous atrophy, crypt hyperplasia A, and intraepithelial lymphocytosis. Moderately † risk of malignancy (eg, T-cell lymphoma). Lactose intolerance Lactase deficiency. Normal-appearing villi, Lactose hydrogen breath test: ⊕ for lactose except when 2° to injury at tips of villi (eg, viral malabsorption if post-lactose breath hydrogen enteritis). Osmotic diarrhea with ↓ stool pH value rises > 20 ppm compared with baseline. (colonic bacteria ferment lactose). **Pancreatic** Due to chronic pancreatitis, cystic fibrosis, ↓ duodenal bicarbonate (and pH) and fecal insufficiency obstructing cancer. Causes malabsorption of elastase. fat and fat-soluble vitamins (A, D, E, K) as well as vitamin $B_{12}$ . **Tropical sprue** Similar findings as celiac sprue (affects small ↓ mucosal absorption affecting duodenum and bowel), but responds to antibiotics. Cause is jejunum but can involve ileum with time. unknown, but seen in residents of or recent Associated with megaloblastic anemia due to visitors to tropics. folate deficiency and, later, B<sub>12</sub> deficiency. Infection with Tropheryma whipplei PAS the foamy Whipped cream in a CAN. Whipple disease (intracellular gram ⊕); PAS ⊕ foamy macrophages in intestinal lamina propria B, mesenteric nodes. Cardiac symptoms, Arthralgias, and Neurologic symptoms are common. Diarrhea/steatorrhea occur later in disease course. Most common in older men.

FAS1\_2019\_09-Gastrointestinal.indd 381 11/7/19 4:42 PM

#### **Inflammatory bowel diseases**

	Crohn disease	Ulcerative colitis
LOCATION	Any portion of the GI tract, usually the terminal ileum and colon. <b>Skip</b> lesions, <b>rec</b> tal sparing.	Colitis = colon inflammation. Continuous colonic lesions, always with rectal involvement.
GROSS MORPHOLOGY	Transmural inflammation → fistulas.  Cobblestone mucosa, creeping fat, bowel wall thickening ("string sign" on barium swallow x-ray A), linear ulcers, fissures.	Mucosal and submucosal inflammation only.  Friable mucosa with superficial and/or deep ulcerations (compare normal ■ with diseased ☑). Loss of haustra → "lead pipe" appearance on imaging.
MICROSCOPIC MORPHOLOGY	Noncaseating granulomas and lymphoid aggregates. Th1 mediated.	Crypt abscesses and ulcers, bleeding, no granulomas. Th2 mediated.
COMPLICATIONS	Malabsorption/malnutrition, colorectal cancer (†	risk with pancolitis).
	Fistulas (eg, enterovesical fistulae, which can cause recurrent UTI and pneumaturia), phlegmon/abscess, strictures (causing obstruction), perianal disease.	Fulminant colitis, toxic megacolon, perforation.
INTESTINAL MANIFESTATION	Diarrhea that may or may not be bloody.	Bloody diarrhea.
EXTRAINTESTINAL MANIFESTATIONS	Rash (pyoderma gangrenosum, erythema nodosum), eye inflammation (episcleritis, uveitis), oral ulcerations (aphthous stomatitis), arthritis (peripheral, spondylitis).	
	Kidney stones (usually calcium oxalate), gallstones. May be ⊕ for anti-Saccharomyces cerevisiae antibodies (ASCA).	l° sclerosing cholangitis. Associated with p-ANCA.
TREATMENT	Corticosteroids, azathioprine, antibiotics (eg, ciprofloxacin, metronidazole), biologics (eg, infliximab, adalimumab).	5-aminosalicylic preparations (eg, mesalamine), 6-mercaptopurine, infliximab, colectomy.
	For Crohn, think of a fat granny and an old crone skipping down a cobblestone road away from the wreck (rectal sparing).  Stones are more common in Crohns.	Ulcerative colitis causes ULCCCERS: Ulcers Large intestine Continuous, Colorectal carcinoma, Crypt abscesses Extends proximally Red diarrhea Sclerosing cholangitis







FAS1\_2019\_09-Gastrointestinal.indd 382 11/7/19 4:42 PM

#### **SECTION III**

#### Irritable bowel syndrome

Recurrent abdominal pain associated with  $\geq 2$  of the following:

- Related to defecation
- Change in stool frequency
- Change in form (consistency) of stool

No structural abnormalities. Most common in middle-aged women. Chronic symptoms may be diarrhea-predominant, constipation-predominant, or mixed. Pathophysiology is multifaceted. First-line treatment is lifestyle modification and dietary changes.

#### **Appendicitis**



Acute inflammation of the appendix (yellow arrows in A), can be due to obstruction by fecalith (red arrow in A) (in adults) or lymphoid hyperplasia (in children).

Proximal obstruction of appendiceal lumen produces closed-loop obstruction → ↑ intraluminal pressure → stimulation of visceral afferent nerve fibers at T8-T10 → initial diffuse periumbilical pain → inflammation extends to serosa and irritates parietal peritoneum. Pain localized to RLQ/ McBurney point (1/3 the distance from right anterior superior iliac spine to umbilicus). Nausea, fever; may perforate → peritonitis; may elicit psoas, obturator, and Rovsing signs, guarding and rebound tenderness on exam.

Differential: diverticulitis (elderly), ectopic pregnancy (use hCG to rule out), pseudoappendicitis. Treatment: appendectomy.

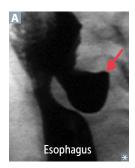
#### Diverticula of the GI tract

Diverticula of the G			
Diverticulum	Blind pouch A protruding from the alimentary tract that communicates with the lumen of the gut. Most diverticula (esophagus, stomach, duodenum, colon) are acquired and are termed "false diverticula."	"True" diverticulum—all gut wall layers outpouch (eg, Meckel).  "False" diverticulum or pseudodiverticulum—only mucosa and submucosa outpouch.  Occur especially where vasa recta perforate muscularis externa.	
Diverticulosis	Many false diverticula of the colon <b>B</b> , commonly sigmoid. Common (in ~ 50% of people > 60 years). Caused by <b>†</b> intraluminal pressure and focal weakness in colonic wall. Associated with obesity and diets low in fiber, high in total fat/red meat.	Often asymptomatic or associated with vague discomfort.  Complications include diverticular bleeding (painless hematochezia), diverticulitis.	
Diverticulitis	Inflammation of diverticula with wall thickening (red arrows in () classically causing LLQ pain, fever, leukocytosis. Treat with antibiotics.	Complications: abscess, fistula (colovesical fistula → pneumaturia), obstruction (inflammatory stenosis), perforation (white arrows in () (→ peritonitis).	



FAS1\_2019\_09-Gastrointestinal.indd 383 11/7/19 4:42 PM

#### Zenker diverticulum



Pharyngoesophageal **false** diverticulum A. Esophageal dysmotility causes herniation of mucosal tissue at Killian triangle between the thyropharyngeal and cricopharyngeal parts of the inferior pharyngeal constrictor. Presenting symptoms: dysphagia, obstruction, gurgling, aspiration, foul breath, neck mass. Most common in elderly males.

#### Elder MIKE has bad breath:

**Elderly** 

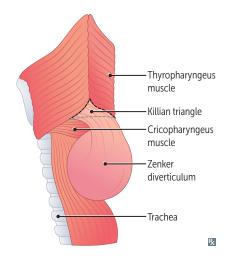
Males

Inferior pharyngeal constrictor

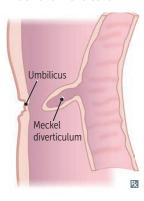
Killian triangle

Esophageal dysmotility

Halitosis



#### **Meckel diverticulum**



True diverticulum. Persistence of the vitelline (omphalomesenteric) duct. May contain ectopic acid–secreting gastric mucosa and/or pancreatic tissue. Most common congenital anomaly of GI tract. Can cause hematochezia/melena (less common), RLQ pain, intussusception, volvulus, or obstruction near terminal ileum.

Contrast with omphalomesenteric cyst = cystic dilation of vitelline duct.

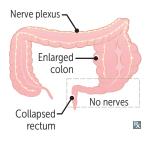
Diagnosis: 99mTc-pertechnetate scan (aka Meckel scan) for uptake by heterotopic gastric mucosa.

The rule of 2's:

- 2 times as likely in males.
- 2 inches long.
- 2 feet from the ileocecal valve.
- 2% of population.

Commonly presents in first 2 years of life. May have 2 types of epithelia (gastric/pancreatic).

#### Hirschsprung disease



Congenital megacolon characterized by lack of ganglion cells/enteric nervous plexuses (Auerbach and Meissner plexuses) in distal segment of colon. Due to failure of neural crest cell migration. Associated with loss of function mutations in *RET*.

Presents with bilious emesis, abdominal distention, and failure to pass meconium within 48 hours → chronic constipation.

Normal portion of the colon proximal to the aganglionic segment is dilated, resulting in a "transition zone."

Risk † with Down syndrome.

Explosive expulsion of feces (squirt sign)

→ empty rectum on digital exam.

Diagnosed by absence of ganglionic cells on rectal suction biopsy.

Treatment: resection.

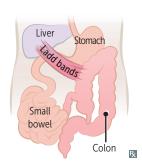
**RET** mutation in the **REcT**um.

FAS1\_2019\_09-Gastrointestinal.indd 384 11/7/19 4:42 PM

#### **Malrotation**

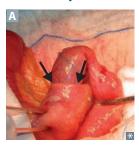


Anomaly of midgut rotation during fetal development → improper positioning of bowel (small bowel clumped on the right side) A, formation of fibrous bands (Ladd bands). Can lead to volvulus, duodenal obstruction.



**SECTION III** 

#### Intussusception



Telescoping A of proximal bowel segment into a distal segment, commonly at the ileocecal junction. Most commonly idiopathic, but may be due to lead point.

Compromised blood supply → intermittent, severe, abdominal pain often with "currant jelly" dark red stools.

Majority of cases in infants, unusual in adults. Most common pathologic lead point:

- Children—Meckel diverticulum
- Adults—intraluminal mass/tumor

On physical exam, patient may draw their legs to chest to ease pain, sausage shaped mass on palpation.

Imaging—Ultrasound/CT may show "target sign." B

May be associated with IgA vasculitis (HSP), recent viral infection (eg, adenovirus; Peyer patch hypertrophy creates lead point).

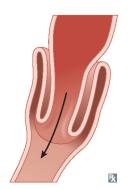
FAS1\_2019\_09-Gastrointestinal.indd 385 11/7/19 4:42 PM

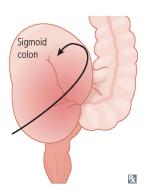
#### **Volvulus**



Twisting of portion of bowel around its mesentery; can lead to obstruction and infarction. Can occur throughout the GI tract.

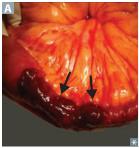
- Midgut volvulus more common in infants and children (minors)
- Sigmoid volvulus (coffee bean sign on x-ray
   A) more common in seniors (elderly)





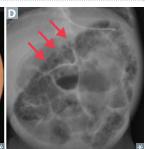
#### Other intestinal disorders

Acute mesenteric ischemia	Critical blockage of intestinal blood flow (often embolic occlusion of SMA) → small bowel necrosis A → abdominal pain out of proportion to physical findings. May see red "currant jelly" stools.
Adhesion	Fibrous band of scar tissue; commonly forms after surgery. Most common cause of small bowel obstruction, demonstrated by multiple dilated small bowel loops on x-ray (arrows in B).
Angiodysplasia	Tortuous dilation of vessels  → hematochezia. Most often found in the right-sided colon. More common in older patients. Confirmed by angiography. Associated with end-stage renal disease, von Willebrand disease, aortic stenosis.
Chronic mesenteric ischemia	"Intestinal angina": atherosclerosis of celiac artery, SMA, or IMA → intestinal hypoperfusion → postprandial epigastric pain → food aversion and weight loss.
Colonic ischemia	Reduction in intestinal blood flow causes ischemia. Crampy abdominal pain followed by hematochezia. Commonly occurs at watershed areas (splenic flexure, rectosigmoid junction). Typically affects elderly. Thumbprint sign on imaging due to mucosal edema/hemorrhage.
lleus	Intestinal hypomotility without obstruction → constipation and ↓ flatus; distended/tympanic abdomen with ↓ bowel sounds. Associated with abdominal surgeries, opiates, hypokalemia, sepsis. Treatment: bowel rest, electrolyte correction, cholinergic drugs (stimulate intestinal motility).
Meconium ileus	Meconium plug obstructs intestine, prevents stool passage at birth. Associated with cystic fibrosis.
Necrotizing enterocolitis	Seen in premature, formula-fed infants with immature immune system. Necrosis of intestinal mucosa (most commonly terminal ileum and proximal colon) with possible perforation, which can lead to pneumatosis intestinalis (arrows in D), pneumoperitoneum, portal venous gas.



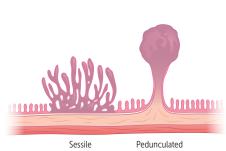


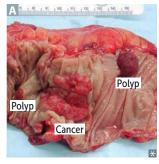




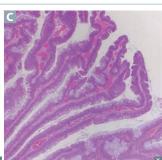
FAS1\_2019\_09-Gastrointestinal.indd 386 11/7/19 4:42 PM

Colonic polyps	Growths of tissue within the colon A. Grossly characterized as flat, sessile, or pedunculated on the basis of protrusion into colonic lumen. Generally classified by histologic type.	
HISTOLOGIC TYPE	CHARACTERISTICS	
Generally non-neoplasti	ic	
Hamartomatous polyps	Solitary lesions do not have significant risk of transformation. Growths of normal colonic tissue with distorted architecture. Associated with Peutz-Jeghers syndrome and juvenile polyposis.	
Hyperplastic polyps	Most common; generally smaller and predominantly located in rectosigmoid region. Occasionally evolves into serrated polyps and more advanced lesions.	
Inflammatory pseudopolyps	Due to mucosal erosion in inflammatory bowel disease.	
Mucosal polyps	Small, usually < 5 mm. Look similar to normal mucosa. Clinically insignificant.	
Submucosal polyps	May include lipomas, leiomyomas, fibromas, and other lesions.	
Malignant potential		
Adenomatous polyps	Neoplastic, via chromosomal instability pathway with mutations in <i>APC</i> and <i>KRAS</i> . Tubular <b>B</b> histology has less malignant potential than villous <b>C</b> ("villous histology is villainous"); tubulovillous has intermediate malignant potential. Usually asymptomatic; may present with occult bleeding.	
Serrated polyps	Neoplastic. Characterized by CpG island methylator phenotype (CIMP; cytosine base followed by guanine, linked by a phosphodiester bond). Defect may silence MMR gene (DNA mismatch repair) expression. Mutations lead to microsatellite instability and mutations in BRAF. "Sawtooth" pattern of crypts on biopsy. Up to 20% of cases of sporadic CRC.	









#### **Polyposis syndromes**

Familial adenomatous polyposis	Autosomal dominant mutation of <i>APC</i> tumor suppressor gene on chromosome 5q22. 2-hit hypothesis. Thousands of polyps arise starting after puberty; pancolonic; always involves rectum. Prophylactic colectomy or else 100% progress to CRC.
Gardner syndrome	FAP + osseous and soft tissue tumors (eg, osteomas of skull or mandible), congenital hypertrophy of retinal pigment epithelium, impacted/supernumerary teeth.
Turcot syndrome	FAP or Lynch syndrome + malignant CNS tumor (eg, medulloblastoma, glioma). <b>Tur</b> cot = <b>Tur</b> ban.
Peutz-Jeghers syndrome	Autosomal dominant syndrome featuring numerous hamartomas throughout GI tract, along with hyperpigmented macules on mouth, lips, hands, genitalia. Associated with † risk of breast and GI cancers (eg, colorectal, stomach, small bowel, pancreatic).
Juvenile polyposis syndrome	Autosomal dominant syndrome in children (typically < 5 years old) featuring numerous hamartomatous polyps in the colon, stomach, small bowel. Associated with † risk of CRC.

FAS1\_2019\_09-Gastrointestinal.indd 387 11/7/19 4:42 PM

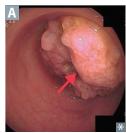
#### GASTROINTESTINAL → GASTROINTESTINAL—PATHOLOGY

#### Lynch syndrome

Previously called hereditary nonpolyposis colorectal cancer (HNPCC). Autosomal dominant mutation of mismatch repair genes (eg, MLH1, MSH2) with subsequent microsatellite instability. ~ 80% progress to CRC. Proximal colon is always involved. Associated with endometrial, ovarian, and skin cancers.

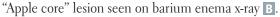
#### **Colorectal cancer**

#### DIAGNOSIS



Iron deficiency anemia in males (especially > 50 years old) and postmenopausal females raises suspicion. Screening:

- Low risk: screen at age 50 with colonoscopy (polyp seen in A); alternatives include flexible sigmoidoscopy, fecal occult blood testing (FOBT), fecal immunochemical testing (FIT), FIT-fecal DNA, CT colonography
- Patients with a first-degree relative who has colon cancer: screen at age 40 with colonoscopy, or 10 years prior to the relative's presentation
- Patients with IBD: distinct screening protocol



CEA tumor marker: good for monitoring recurrence, should not be used for screening.

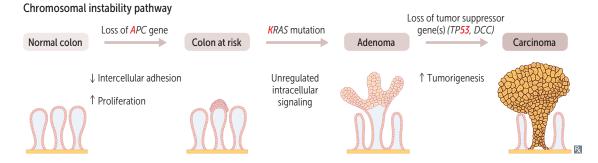


EPIDEMIOLOGY	Most patients are $> 50$ years old. $\sim 25\%$ have a family history.
PRESENTATION	Rectosigmoid > ascending > descending.
	Right side (cecal, ascending) associated with occult bleeding; left side (rectosigmoid) associated
	with hematochezia and obstruction (narrower lumen).
	Ascending—exophytic mass, iron deficiency anemia, weight loss.
	Descending—infiltrating mass, partial obstruction, colicky pain, hematochezia.
	Can present with S bovis (gallolyticus) bacteremia/endocarditis or as an episode of diverticulitis.
RISK FACTORS	Adenomatous and serrated polyps, familial cancer syndromes, IBD, tobacco use, diet of processed meat with low fiber.

FAS1\_2019\_09-Gastrointestinal.indd 388 11/7/19 4:42 PM Molecular pathogenesis of colorectal cancer Chromosomal instability pathway: mutations in APC cause FAP and most sporadic cases of CRC via adenoma-carcinoma sequence; (firing order of events is "AK-53").

Microsatellite instability pathway: mutations or methylation of mismatch repair genes (eg, MLH1) cause Lynch syndrome and some sporadic CRC (via serrated polyp pathway).

Overexpression of COX-2 has been linked to colorectal cancer, NSAIDs may be chemopreventive.



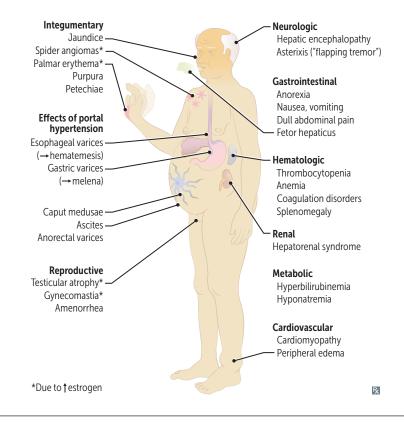
#### **Cirrhosis and portal hypertension**





**Cirrhosis**—diffuse bridging fibrosis (via stellate cells) and regenerative nodules (red arrows in A; white arrows show splenomegaly) disrupt normal architecture of liver; † risk for hepatocellular carcinoma (white arrow in B). Etiologies include alcohol, nonalcoholic steatohepatitis, chronic viral hepatitis, autoimmune hepatitis, biliary disease, genetic/metabolic disorders.

Portal hypertension—† pressure in portal venous system. Etiologies include cirrhosis (most common cause in Western countries), vascular obstruction (eg, portal vein thrombosis, Budd-Chiari syndrome), schistosomiasis.



FAS1 2019 09-Gastrointestinal.indd 389 11/7/19 4:42 PM 390 SECTION III

#### GASTROINTESTINAL → GASTROINTESTINAL—PATHOLOGY

# Spontaneous bacterial peritonitis

Also called 1° bacterial peritonitis. Common and potentially fatal bacterial infection in patients with cirrhosis and ascites. Often asymptomatic, but can cause fevers, chills, abdominal pain, ileus, or worsening encephalopathy. Commonly caused by gram  $\ominus$  organisms (eg, E coli, Klebsiella) or less commonly gram  $\oplus$  Streptococcus.

Diagnosis: paracentesis with ascitic fluid absolute neutrophil count (ANC) > 250 cells/mm<sup>3</sup>. Empiric first-line treatment is 3rd generation cephalosporin (eg, cefotaxime).

_		4	and the second second
Seriim	markers	of liver	pathology
JCIGIII	III al IXCI 3		putilology

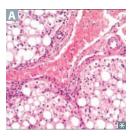
ENZYMES RELEASED IN LIVER DAMAG			
Aspartate aminotransferase and alanine aminotransferase	† in most liver disease: ALT > AST † in alcoholic liver disease: AST > ALT (AST usually will not exceed 500 U/L in alcoholic hepatitis)  AST > ALT in nonalcoholic liver disease suggests progression to advanced fibrosis or cirrhosis  ††† aminotransferases (>1000 U/L): differential includes drug-induced liver injury (eg, acetaminophen toxicity), ischemic hepatitis, acute viral hepatitis, autoimmune hepatitis		
Alkaline phosphatase	† in cholestasis (eg, biliary obstruction), infiltrativ	ve disorders, bone disease	
γ-glutamyl transpeptidase	† in various liver and biliary diseases (just as ALF alcohol use	can), but not in bone disease; associated with	
FUNCTIONAL LIVER MARKERS			
Bilirubin	† in various liver diseases (eg, biliary obstruction,	alcoholic or viral hepatitis, cirrhosis), hemolysis	
Albumin	↓ in advanced liver disease (marker of liver's biosynthetic function)		
Prothrombin time	† in advanced liver disease (‡ production of clotting factors, thereby measuring the liver's biosynthetic function)		
Platelets	↓ in advanced liver disease (↓ thrombopoietin, liver sequestration) and portal hypertension (splenomegaly/splenic sequestration)		
Reye syndrome	Rare, often fatal childhood hepatic encephalopathy.  Associated with viral infection (especially VZV and influenza) that has been treated with aspirin. Aspirin metabolites ↓ β-oxidation by reversible inhibition of mitochondrial enzymes.  Findings: mitochondrial abnormalities, fatty liver (microvesicular fatty changes), hypoglycemia, vomiting, hepatomegaly, coma.	Avoid aspirin in children, except in those with Kawasaki disease. Salicylates aren't a ray (Reye) of sunSHINE for kids: Steatosis of liver/hepatocytes Hypoglycemia/Hepatomegaly Infection (VZV, influenza) Not awake (coma) Encephalopathy	

FAS1\_2019\_09-Gastrointestinal.indd 390 11/7/19 4:42 PM

#### **Alcoholic liver disease**

## Macrovesicular fatty change A that may be **Hepatic steatosis** reversible with alcohol cessation. Requires sustained, long-term consumption. **Alcoholic hepatitis** Make a to**AST** with alcohol: Swollen and necrotic hepatocytes with **AST** > ALT (ratio usually > 2:1). neutrophilic infiltration. Mallory bodies B (intracytoplasmic eosinophilic inclusions of damaged keratin filaments). **Alcoholic cirrhosis** Final and usually irreversible form. Sclerosis around central vein (arrows in C) may be seen in early disease. Regenerative nodules surrounded by fibrous bands in response to chronic liver injury → portal hypertension and end-stage liver disease.

## Nonalcoholic fatty liver disease



Metabolic syndrome (insulin resistance); obesity → fatty infiltration of hepatocytes A → cellular "ballooning" and eventual necrosis. May cause cirrhosis and HCC. Independent of alcohol use. ALT > AST (Lipids)

## Hepatic encephalopathy

Cirrhosis → portosystemic shunts → ↓ NH<sub>3</sub> metabolism → neuropsychiatric dysfunction. Reversible neuropsychiatric dysfunction ranging from disorientation/asterixis (mild) to difficult arousal or coma (severe).

#### Triggers:

- † NH, production and absorption (due to GI bleed, constipation, infection).
- \$\dagger\$ NH<sub>2</sub> removal (due to renal failure, diuretics, bypassed hepatic blood flow post-TIPS).

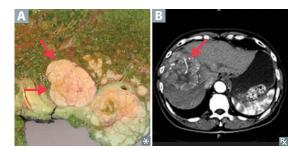
Treatment: lactulose († NH<sub>4</sub>+ generation) and rifaximin (↓ NH<sub>3</sub>-producing gut bacteria).

FAS1\_2019\_09-Gastrointestinal.indd 391 11/7/19 4:42 PM

## Hepatocellular carcinoma/hepatoma

Most common 1° malignant tumor of liver in adults A. Associated with HBV (+/– cirrhosis) and all other causes of cirrhosis (including HCV, alcoholic and nonalcoholic fatty liver disease, autoimmune disease, hemochromatosis, Wilson disease, α<sub>1</sub>-antitrypsin deficiency) and specific carcinogens (eg, aflatoxin from Aspergillus). May lead to Budd-Chiari syndrome. Findings: jaundice, tender hepatomegaly, ascites, polycythemia, anorexia. Spreads hematogenously.

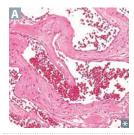
Diagnosis: † α-fetoprotein; ultrasound or contrast CT/MRI **B**, biopsy.



#### Other liver tumors

#### Angiosarcoma

# Cavernous hemangioma



Malignant tumor of endothelial origin; associated with exposure to arsenic, vinyl chloride.

Most common benign liver tumor (venous malformation) **A**; typically occurs at age 30–50 years. Biopsy contraindicated because of risk of hemorrhage.

#### Hepatic adenoma

Rare, benign liver tumor, often related to oral contraceptive or anabolic steroid use; may regress spontaneously or rupture (abdominal pain and shock).

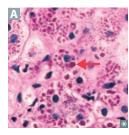
#### Metastases

GI malignancies, breast and lung cancer. Most common overall; metastases are rarely solitary.

#### **Budd-Chiari syndrome**

Thrombosis or compression of hepatic veins with centrilobular congestion and necrosis → congestive liver disease (hepatomegaly, ascites, varices, abdominal pain, liver failure). Absence of JVD. Associated with hypercoagulable states, polycythemia vera, postpartum state, HCC. May cause nutmeg liver (mottled appearance).

# $\alpha_1$ -antitrypsin deficiency



Misfolded gene product protein aggregates in hepatocellular ER → cirrhosis with PAS ⊕ globules ♠ in liver. Codominant trait. Often presents in young patients with liver damage and dyspnea without a history of smoking.

In lungs,  $\downarrow \alpha_1$ -antitrypsin  $\rightarrow$  uninhibited elastase in alveoli  $\rightarrow \downarrow$  elastic tissue  $\rightarrow$  panacinar emphysema.

FAS1\_2019\_09-Gastrointestinal.indd 392 11/7/19 4:42 PM

#### GASTROINTESTINAL

#### **Jaundice**



Abnormal yellowing of the skin and/or sclera A due to bilirubin deposition. Hyperbilirubinemia 2° to ↑ production or ↓ clearance (impaired hepatic uptake, conjugation, excretion).

**HOT Liver**—common causes of † bilirubin

level:

**H**emolysis

Obstruction

Tumor

Liver disease

#### **Conjugated (direct)** hyperbilirubinemia

Biliary tract obstruction: gallstones, cholangiocarcinoma, pancreatic or liver cancer, liver fluke. Biliary tract disease:

- 1° sclerosing cholangitis
- 1° biliary cholangitis

Excretion defect: Dubin-Johnson syndrome, Rotor syndrome.

#### Unconjugated (indirect) hyperbilirubinemia

Hemolytic, physiologic (newborns), Crigler-Najjar, Gilbert syndrome.

#### Mixed (direct and indirect) hyperbilirubinemia

Hepatitis, cirrhosis.

#### **Physiologic** neonatal jaundice

At birth, immature UDP-glucuronosyltransferase → unconjugated hyperbilirubinemia → jaundice/ kernicterus (deposition of unconjugated, lipid-soluble bilirubin in the brain, particularly basal ganglia).

Occurs after first 24 hours of life and usually resolves without treatment in 1–2 weeks. Treatment: phototherapy (non-UV) isomerizes unconjugated bilirubin to water-soluble form.

#### **Biliary atresia**

Most common reason for pediatric liver transplantation.

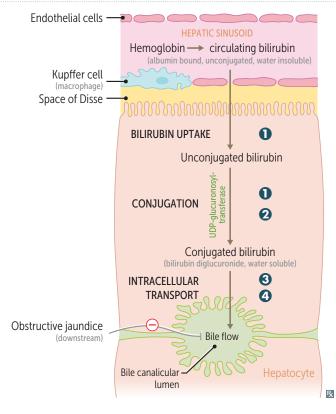
Fibro-obliterative destruction of extrahepatic bile ducts → cholestasis.

Often presents as a newborn with persistent jaundice after 2 weeks of life, darkening urine, acholic stools, hepatomegaly.

Labs: † direct bilirubin and GGT.

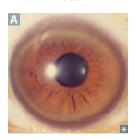
FAS1\_2019\_09-Gastrointestinal.indd 393 11/7/19 4:42 PM

Hereditary hyperbilirubinemias	All autosomal recessive.
Gilbert syndrome	Mildly \(\psi\) UDP-glucuronosyltransferase conjugation and impaired bilirubin uptake. Asymptomatic or mild jaundice usually with stress, illness, or fasting. \(\fat{\tau}\) unconjugated bilirubin without overt hemolysis.  Relatively common, benign condition.
2 Crigler-Najjar syndrome, type I	Absent UDP-glucuronosyltransferase. Presents early in life, but some patients may not have neurologic signs until later in life.  Findings: jaundice, kernicterus (bilirubin deposition in brain), † unconjugated bilirubin.  Treatment: plasmapheresis and phototherapy (does not conjugate UCB; but does † polarity and † water solubility to allow excretion). Liver transplant is curative.  Type II is less severe and responds to phenobarbital, which † liver enzyme synthesis.
<b>3</b> Dubin-Johnson syndrome	Conjugated hyperbilirubinemia due to defective liver excretion. Grossly black ( <b>D</b> ark) liver due to impaired excretion of epinephrine metabolites. Benign.
Rotor syndrome	Similar to Dubin-Johnson syndrome, but milder in presentation without black (Regular) liver. Due to impaired hepatic uptake and excretion.



FAS1\_2019\_09-Gastrointestinal.indd 394 11/7/19 4:42 PM

#### Wilson disease

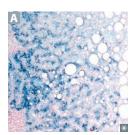


Also called hepatolenticular degeneration. Autosomal recessive mutations in hepatocyte copper-transporting ATPase (ATP7B gene; chromosome 13) → ↓ copper incorporation into apoceruloplasmin and excretion into bile → ↓ serum ceruloplasmin. Copper accumulates, especially in liver, brain, cornea, kidneys; † urine copper.

Presents before age 40 with liver disease (eg, hepatitis, acute liver failure, cirrhosis), neurologic disease (eg, dysarthria, dystonia, tremor, parkinsonism), psychiatric disease, Kayser-Fleischer rings (deposits in Descemet membrane of cornea) A, hemolytic anemia, renal disease (eg, Fanconi

Treatment: chelation with penicillamine or trientine, oral zinc. Liver transplant in acute liver failure related to Wilson disease.

#### Hemochromatosis



Autosomal recessive. On HFE gene, located on chromosome 6; associated with HLA-A3. Leads to abnormal iron sensing and ↑ intestinal absorption (↑ ferritin, ↑ iron, ↓ TIBC → ↑ transferrin saturation). Iron overload can also be 2° to chronic transfusion therapy (eg, β-thalassemia major). Iron accumulates, especially in liver, pancreas, skin, heart, pituitary, joints. Hemosiderin (iron) can be identified on liver MRI or biopsy with Prussian blue stain A.

Presents after age 40 when total body iron > 20 g; iron loss through menstruation slows progression in women. Classic triad of cirrhosis, diabetes mellitus, skin pigmentation ("bronze diabetes"). Also causes restrictive cardiomyopathy (classic) or dilated cardiomyopathy (reversible), hypogonadism, arthropathy (calcium pyrophosphate deposition; especially metacarpophalangeal joints). HCC is common cause of death.

Treatment: repeated phlebotomy, iron (Fe) chelation with deferasirox, deferoxamine, deferiprone.

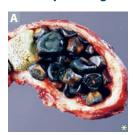
#### **Biliary tract disease**

May present with pruritus, jaundice, dark urine, light-colored stool, hepatosplenomegaly. Typically with cholestatic pattern of LFTs († conjugated bilirubin, † cholesterol, † ALP † GGT)

	PATHOLOGY	EPIDEMIOLOGY	ADDITIONAL FEATURES
Primary sclerosing cholangitis	Unknown cause of concentric "onion skin" bile duct fibrosis → alternating strictures and dilation with "beading" of intra- and extrahepatic bile ducts on ERCP, magnetic resonance cholangiopancreatography (MRCP).	Classically in middle-aged men with ulcerative colitis.	Associated with ulcerative colitis. p-ANCA ⊕. ↑ IgM. Can lead to 2° biliary cholangitis. ↑ risk of cholangiocarcinoma and gallbladder cancer.
Primary biliary cholangitis	Autoimmune reaction  → lymphocytic infiltrate  +/- granulomas  → destruction of lobular bile ducts.	Classically in middle-aged women.	Anti-mitochondrial antibody ⊕,  † IgM. Associated with other autoimmune conditions (eg, Hashimoto thyroiditis, rheumatoid arthritis, celiac disease). Treatment: ursodiol.
Secondary biliary cirrhosis	Extrahepatic biliary obstruction  → ↑ pressure in intrahepatic ducts → injury/ fibrosis and bile stasis.	Patients with known obstructive lesions (gallstones, biliary strictures, pancreatic carcinoma).	May be complicated by ascending cholangitis.

FAS1 2019 09-Gastrointestinal.indd 395 11/7/19 4:42 PM

## Cholelithiasis and related pathologies



↑ cholesterol and/or bilirubin, ↓ bile salts, and gallbladder stasis all cause stones.

#### 2 types of stones:

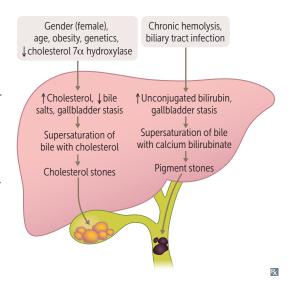
- Cholesterol stones (radiolucent with 10–20% opaque due to calcifications)—80% of stones.
   Associated with obesity, Crohn disease, advanced age, estrogen therapy, multiparity, rapid weight loss, Native American origin.
- Pigment stones A (black = radiopaque, Ca²+ bilirubinate, hemolysis; brown = radiolucent, infection). Associated with Crohn disease, chronic hemolysis, alcoholic cirrhosis, advanced age, biliary infections, total parenteral nutrition (TPN).

Risk factors (4 F's):

- 1. Female
- 2. **F**at
- 3. Fertile (multiparity)
- 4. Forty

Most common complication is cholecystitis; can also cause acute pancreatitis, ascending cholangitis.

Diagnose with ultrasound. Treat with elective cholecystectomy if symptomatic.



#### RELATED PATHOLOGIES

#### CHARACTERISTICS

#### **Biliary colic**

Associated with nausea/vomiting and dull RUQ pain. Neurohormonal activation (eg, by CCK after a fatty meal) triggers contraction of gallbladder, forcing stone into cystic duct. Labs are normal, ultrasound shows cholelithiasis.

#### Choledocholithiasis

Presence of gallstone(s) in common bile duct, often leading to elevated ALP, GGT, direct bilirubin, and/or AST/ALT.

#### Cholecystitis





Acute or chronic inflammation of gallbladder.

Calculous cholecystitis—most common type; due to gallstone impaction in the cystic duct resulting in inflammation and gallbladder wall thickening (arrows in B); can produce 2° infection.

Acalculous cholecystitis—due to gallbladder stasis, hypoperfusion, or infection (CMV); seen in critically ill patients.

Murphy sign: inspiratory arrest on RUQ palpation due to pain. Pain may radiate to right shoulder (due to irritation of phrenic nerve). † ALP if bile duct becomes involved (eg, ascending cholangitis).

Diagnose with ultrasound or cholescintigraphy (HIDA scan). Failure to visualize gallbladder on HIDA scan suggests obstruction.

Gallstone ileus—fistula between gallbladder and GI tract → stone enters GI lumen → obstructs at ileocecal valve (narrowest point); can see air in biliary tree (pneumobilia). Rigler triad: radiographic findings of pneumobilia, small bowel obstruction, gallstone (usually in iliac fossa).

FAS1\_2019\_09-Gastrointestinal.indd 396 11/7/19 4:42 PM

#### Cholelithiasis and related pathologies (continued)

#### Porcelain gallbladder



Calcified gallbladder due to chronic cholecystitis; usually found incidentally on imaging **C**. Treatment: prophylactic cholecystectomy generally recommended due to † risk of gallbladder cancer (mostly adenocarcinoma).

#### **Ascending cholangitis**

Infection of biliary tree usually due to obstruction that leads to stasis/bacterial overgrowth. Charcot triad of cholangitis includes jaundice, fever, RUQ pain. Reynolds pentad is Charcot triad plus altered mental status and shock (hypotension).

#### **Acute pancreatitis**

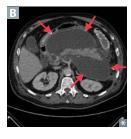


Autodigestion of pancreas by pancreatic enzymes (A shows pancreas [yellow arrows] surrounded by edema [red arrows]).

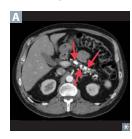
Causes: Idiopathic, Gallstones, Ethanol, Trauma, Steroids, Mumps, Autoimmune disease, Scorpion sting, Hypercalcemia/Hypertriglyceridemia (> 1000 mg/dL), ERCP, Drugs (eg, sulfa drugs, NRTIs, protease inhibitors). I GET SMASHED.

Diagnosis by 2 of 3 criteria: acute epigastric pain often radiating to the back, † serum amylase or lipase (more specific) to 3× upper limit of normal, or characteristic imaging findings.

Complications: pseudocyst B (lined by granulation tissue, not epithelium), abscess, necrosis, hemorrhage, infection, organ failure (ALI/ARDS, shock, renal failure), hypocalcemia (precipitation of Ca<sup>2+</sup> soaps).



#### **Chronic pancreatitis**



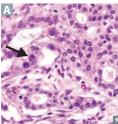
Chronic inflammation, atrophy, calcification of the pancreas A. Major causes include alcohol abuse and genetic predisposition (ie, cystic fibrosis); can be idiopathic. Complications include pancreatic insufficiency and pseudocysts.

Pancreatic insufficiency (typically when <10% pancreatic function) may manifest with steatorrhea, fat-soluble vitamin deficiency, diabetes mellitus.

Amylase and lipase may or may not be elevated (almost always elevated in acute pancreatitis).

FAS1 2019 09-Gastrointestinal.indd 397 11/7/19 4:42 PM

## Pancreatic adenocarcinoma





Very aggressive tumor arising from pancreatic ducts (disorganized glandular structure with cellular infiltration A); often metastatic at presentation, with average survival ~ 1 year after diagnosis. Tumors more common in pancreatic head B (lead to obstructive jaundice). Associated with CA 19-9 tumor marker (also CEA, less specific).

#### Risk factors:

- Tobacco use
- Chronic pancreatitis (especially > 20 years)
- Diabetes
- Age > 50 years
- Jewish and African-American males

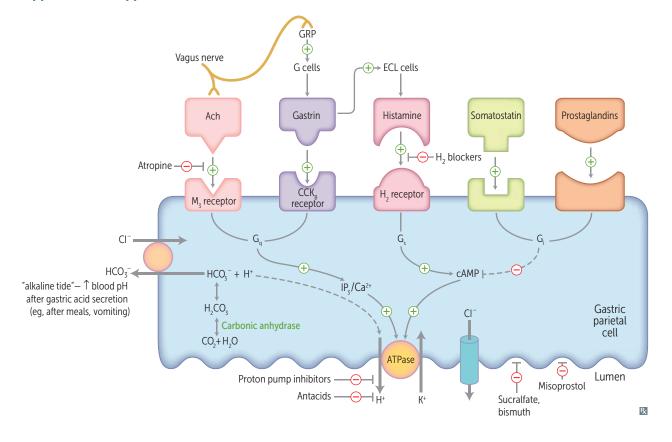
#### Often presents with:

- Abdominal pain radiating to back
- Weight loss (due to malabsorption and anorexia)
- Migratory thrombophlebitis—redness and tenderness on palpation of extremities (Trousseau syndrome)
- Obstructive jaundice with palpable, nontender gallbladder (Courvoisier sign)

Treatment: Whipple procedure (pancreaticoduodenectomy), chemotherapy, radiation therapy.

#### ► GASTROINTESTINAL—PHARMACOLOGY

#### **Acid suppression therapy**



FAS1\_2019\_09-Gastrointestinal.indd 398 11/7/19 4:42 PM

Histamine-2 blockers	Cimetidine, ranitidine, famotidine, nizatidine.	Take $H_2$ blockers before you dine. Think "table for 2" to remember $H_2$ .	
MECHANISM	Reversible block of histamine H₂-receptors → ↓ H	f+ secretion by parietal cells.	
CLINICAL USE	Peptic ulcer, gastritis, mild esophageal reflux.		
ADVERSE EFFECTS	Cimetidine is a potent inhibitor of cytochrome P-450 (multiple drug interactions); it also has antiandrogenic effects (prolactin release, gynecomastia, impotence, ↓ libido in males); can cross blood-brain barrier (confusion, dizziness, headaches) and placenta. Both cimetidine and ranitidine ↓ renal excretion of creatinine. Other H₂ blockers are relatively free of these effects.		
Proton pump inhibitors	Omeprazole, lansoprazole, esomeprazole, pantop	razole, dexlansoprazole.	
MECHANISM	Irreversibly inhibit H+/K+ ATPase in stomach paris	etal cells.	
CLINICAL USE	Peptic ulcer, gastritis, esophageal reflux, Zollinge <i>H pylori</i> , stress ulcer prophylaxis.	r-Ellison syndrome, component of therapy for	
ADVERSE EFFECTS	↑ risk of <i>C difficile</i> infection, pneumonia, acute ir ↓ serum Mg <sup>2+</sup> and ↓ Ca <sup>2+</sup> absorption (potentially		
Antacids	Can affect absorption, bioavailability, or urinary of urinary pH or by delaying gastric emptying. All can cause hypokalemia. Overuse can also cause the following problems:	excretion of other drugs by altering gastric and	
Aluminum hydroxide	Constipation, Hypophosphatemia, Osteodystrophy, Proximal muscle weakness, Seizures	Aluminimum amount of feces CHOPS	
Calcium carbonate	Hypercalcemia (milk-alkali syndrome), rebound acid ↑	Can chelate and ↓ effectiveness of other drugs (eg, tetracycline)	
Magnesium hydroxide	Diarrhea, hyporeflexia, hypotension, cardiac arrest	$Mg^{2+} = Must go 2$ the bathroom	
Bismuth, sucralfate			
MECHANISM	Bind to ulcer base, providing physical protection a gradient in the mucous layer. Sucralfate requires blockers.	- ,	
CLINICAL USE	† ulcer healing, travelers' diarrhea (bismuth). Bismuth also used in quadruple therapy for <i>H pylori</i> gastritis.		
Misoprostol			
MECHANISM	PGE <sub>1</sub> analog. † production and secretion of gastri	c mucous barrier, ↓ acid production.	
CLINICAL USE	Prevention of NSAID-induced peptic ulcers (NSAIDs block PGE <sub>1</sub> production). Also used off-label for induction of labor (ripens cervix).		
ADVERSE EFFECTS	Diarrhea. Contraindicated in women of childbearing potential (abortifacient).		

11/7/19 4:42 PM FAS1\_2019\_09-Gastrointestinal.indd 399

## GASTROINTESTINAL ► GASTROINTESTINAL—PHARMACOLOGY

Octreotide			
MECHANISM	Long-acting somatostatin analog; inhibits secretion of various splanchnic vasodilatory hormones.		
CLINICAL USE	Acute variceal bleeds, acromegaly, VIPoma, carcinoid tumors.		
ADVERSE EFFECTS	Nausea, cramps, steatorrhea. † risk of cholelithiasis due to CCK inhibition.		
Sulfasalazine			
MECHANISM	A combination of sulfapyridine (antibacterial) and 5-aminosalicylic acid (anti-inflammatory). Activated by colonic bacteria.		
CLINICAL USE	Ulcerative colitis, Crohn disease (colitis component).		
ADVERSE EFFECTS	Malaise, nausea, sulfonamide toxicity, reversible oligospermia.		
Loperamide			
MECHANISM	Agonist at $\mu$ -opioid receptors; slows gut motility. Poor CNS penetration (low addictive potential).		
CLINICAL USE	Diarrhea.		
ADVERSE EFFECTS	Constipation, nausea.		
Ondansetron			
MECHANISM	5-HT₃ antagonist; ↓ vagal stimulation. Powerful central-acting antiemetic.		
CLINICAL USE	Control vomiting postoperatively and in patients undergoing cancer chemotherapy.		
ADVERSE EFFECTS	Headache, constipation, QT interval prolongation, serotonin syndrome.		
Metoclopramide			
MECHANISM	$D_2$ receptor antagonist. † resting tone, contractility, LES tone, motility, promotes gastric emptying. Does not influence colon transport time.		
CLINICAL USE	Diabetic and postoperative gastroparesis, antiemetic, persistent GERD.		
ADVERSE EFFECTS	† parkinsonian effects, tardive dyskinesia. Restlessness, drowsiness, fatigue, depression, diarrhea. Drug interaction with digoxin and diabetic agents. Contraindicated in patients with small bowel obstruction, Parkinson disease (due to D <sub>2</sub> -receptor blockade), ↓ seizure threshold.		
Orlistat			
MECHANISM	Inhibits gastric and pancreatic lipase → ↓ breakdown and absorption of dietary fats. Taken with fat-containing meals.		
CLINICAL USE	Weight loss.		
ADVERSE EFFECTS	Abdominal pain, flatulence, bowel urgency/frequent bowel movements, steatorrhea; ↓ absorption of fat-soluble vitamins.		

FAS1\_2019\_09-Gastrointestinal.indd 400 11/7/19 4:42 PM

Laxatives	Indicated for constipation or patients on opiates requiring a bowel regimen.			
	EXAMPLES	MECHANISM	ADVERSE EFFECTS	
<b>Bulk-forming laxatives</b>	Psyllium, methylcellulose	Soluble fibers draw water into gut lumen, forming a viscous liquid that promotes peristalsis	Bloating	
Osmotic laxatives	Magnesium hydroxide, magnesium citrate, polyethylene glycol, lactulose	Provides osmotic load to draw water into GI lumen Lactulose also treats hepatic encephalopathy: gut flora degrade lactulose into metabolites (lactic acid, acetic acid) that promote nitrogen excretion as NH <sub>4</sub> <sup>+</sup>	Diarrhea, dehydration; may be abused by bulimics	
Stimulants	Senna	Enteric nerve stimulation  → colonic contraction	Diarrhea, melanosis coli	
Emollients	Docusate	Promotes incorporation of water and fat into stool	Diarrhea	
Aprepitant				
MECHANISM	Substance P antagonist. Blocks I	$NK_1$ (neurokinin-1) receptors in bi	rain.	
CLINICAL USE	Antiemetic for chemotherapy-induced nausea and vomiting.			

FAS1\_2019\_09-Gastrointestinal.indd 401 11/7/19 4:42 PM

402 SECTION III GASTROINTESTINAL

► NOTES	

11/7/19 4:42 PM FAS1\_2019\_09-Gastrointestinal.indd 402

## HIGH-YIELD SYSTEMS

# Hematology and Oncology

"You're always somebody's type! (blood type, that is)"

-BloodLink

"All the soarings of my mind begin in my blood."

-Rainer Maria Rilke

"The best blood will at some time get into a fool or a mosquito."

-Austin O'Malley

When studying hematology, pay close attention to the many cross connections to immunology. Make sure you master the different types of anemias. Be comfortable interpreting blood smears. When reviewing oncologic drugs, focus on mechanisms and adverse effects rather than details of clinical uses, which may be lower yield.

Please note that solid tumors are covered in their respective organ system chapters.

<b>▶</b> Embryology	404
▶ Anatomy	406
▶ Physiology	410
▶ Pathology	414
▶ Pharmacology	435

FAS1\_2019\_10-HemaOncol.indd 403 11/7/19 5:04 PM

#### ► HEMATOLOGY AND ONCOLOGY—EMBRYOLOGY

#### **Fetal erythropoiesis**

Fetal erythropoiesis occurs in:

- Yolk sac (3–8 weeks)
- Liver (6 weeks-birth)
- **S**pleen (10–28 weeks)
- Bone marrow (18 weeks to adult)

# Hemoglobin development

Embryonic globins:  $\zeta$  and  $\epsilon$ .

Fetal hemoglobin (HbF) =  $\alpha_2 \gamma_2$ .

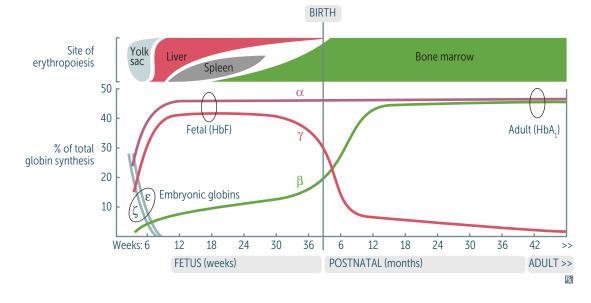
Adult hemoglobin  $(HbA_1) = \alpha_2 \beta_2$ . HbF has higher affinity for  $O_2$  due to less avid binding of 2,3-BPG, allowing HbF to extract

binding of 2,3-BPG, allowing HbF to extract  $O_2$  from maternal hemoglobin (HbA<sub>1</sub> and HbA<sub>2</sub>) across the placenta. HbA<sub>2</sub> ( $\alpha_2 \delta_2$ ) is a form of adult hemoglobin present in small amounts.

Young Liver Synthesizes Blood.

From fetal to adult hemoglobin:

Alpha Always; Gamma Goes, Becomes Beta.



FAS1\_2019\_10-HemaOncol.indd 404 11/7/19 5:04 PM

#### **Blood groups**

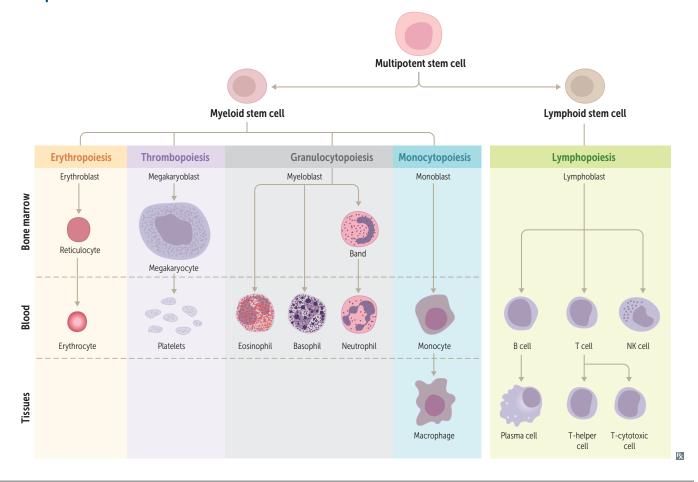
	ABO classification			Rh classification		
	A	В	АВ	0	<b>Rh</b> ⊕	Rh⊝
RBC type	A	B	AB	0		
Group antigens on RBC surface	A	В	A & B	None	Rh (D)	None
Antibodies in plasma	Anti-B	Anti-A	None	Anti-A Anti-B	None	Anti-D IgG
Clinical relevance	Receive B or AB → hemolytic reaction	Receive A or AB  → hemolytic reaction	Universal recipient of RBCs; universal donor of plasma	Receive any non-O  → hemolytic reaction Universal donor of RBCs; universal recipient of plasma	Can receive either Rh⊕ or Rh⊖ blood	Treat mother with anti-D IgG during and after each pregnancy to prevent anti-D IgG formation

Hemolytic disease of the newborn	Also known as erythroblastosis fetalis.			
	Rh hemolytic disease of the newborn	ABO hemolytic disease of the newborn		
INTERACTION	$Rh \ominus$ mother; $Rh \oplus$ fetus.	Type O mother; type A or B fetus.		
MECHANISM	First pregnancy: mother exposed to fetal blood (often during delivery) → formation of maternal anti-D IgG.  Subsequent pregnancies: anti-D IgG crosses the placenta → attacks fetal RBCs → hemolysis in the fetus.	Pre-existing maternal anti-A and/or anti-B IgG antibodies cross placenta → hemolysis in the fetus.		
PRESENTATION	Hydrops fetalis, jaundice shortly after birth, kernicterus.	Mild jaundice in the neonate within 24 hours of birth. Unlike Rh HDN, can occur in firstborn babies and is usually less severe.		
TREATMENT/PREVENTION	Prevent by administration of anti-D IgG to Rh  ☐ pregnant women during third trimester and early postpartum period (if fetus Rh ⊕).  Prevents maternal anti-D IgG production.	Treatment: phototherapy or exchange transfusion.		

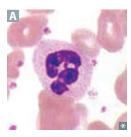
FAS1\_2019\_10-HemaOncol.indd 405 11/7/19 5:04 PM

#### ► HEMATOLOGY AND ONCOLOGY—ANATOMY

#### **Hematopoiesis**



#### **Neutrophils**

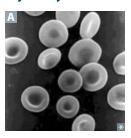


Acute inflammatory response cells. Numbers † in bacterial infections. Phagocytic. Multilobed nucleus A. Specific granules contain leukocyte alkaline phosphatase (LAP), collagenase, lysozyme, and lactoferrin. Azurophilic granules (lysosomes) contain proteinases, acid phosphatase, myeloperoxidase, and β-glucuronidase.

Hypersegmented neutrophils (nucleus has 6+ lobes) are seen in vitamin B<sub>12</sub>/ folate deficiency. A left shift with † band cells (immature neutrophils) reflects states of † myeloid proliferation (eg, bacterial infections, CML). Important neutrophil chemotactic agents: C5a, IL-8, LTB<sub>4</sub>, kallikrein, platelet-activating factor.

FAS1\_2019\_10-HemaOncol.indd 406 11/7/19 5:04 PM

#### **Erythrocytes**



Carry O, to tissues and CO, to lungs. Anucleate and lack organelles; biconcave A, with large surface area-to-volume ratio for rapid gas exchange. Life span of 120 days. Source of energy is glucose (90% used in glycolysis, 10% used in HMP shunt). Membranes contain Cl<sup>-</sup>/HCO<sub>2</sub> antiporter, which allow RBCs to export HCO<sub>2</sub> and transport CO<sub>2</sub> from the periphery to the lungs for elimination.

Eryth = red; cyte = cell.

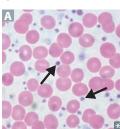
► HEMATOLOGY AND ONCOLOGY—ANATOMY

Erythrocytosis = polycythemia =  $\uparrow$  Hct. Anisocytosis = varying sizes. Poikilocytosis = varying shapes.

Reticulocyte = immature RBC; reflects erythroid proliferation.

Bluish color (polychromasia) on Wright-Giemsa stain of reticulocytes represents residual ribosomal RNA.

#### **Thrombocytes** (platelets)



Involved in 1° hemostasis. Small cytoplasmic fragments A derived from megakaryocytes. Life span of 8–10 days. When activated by endothelial injury, aggregate with other platelets and interact with fibrinogen to form platelet plug. Contain dense granules (Ca<sup>2+</sup>, ADP, Serotonin, Histamine; CASH) and α granules (vWF, fibrinogen, fibronectin, platelet factor 4). Approximately 1/3 of platelet pool is stored in the spleen.

Thrombocytopenia or ↓ platelet function results in petechiae.

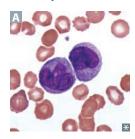
vWF receptor: GpIb.

Fibrinogen receptor: GpIIb/IIIa.

Thrombopoietin stimulates megakaryocyte proliferation.

Alfa granules contain vWF, fibrinogen, fibronectin, platelet factor four.

#### **Monocytes**

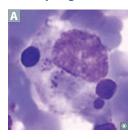


Found in blood, differentiate into macrophages

Large, kidney-shaped nucleus A. Extensive "frosted glass" cytoplasm.

Mono = one (nucleus); cyte = cell.

#### **Macrophages**

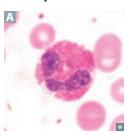


Phagocytose bacteria, cellular debris, and senescent RBCs. Long life in tissues. Differentiate from circulating blood monocytes **A**. Activated by  $\gamma$ -interferon. Can function as antigen-presenting cell via MHC II. Important cellular component of granulomas (eg, TB, sarcoidosis).

Macro = large; phage = eater.Macrophage naming varies by specific tissue type (eg, Kupffer cells in liver, histiocytes in connective tissue, Langerhans cells in skin, osteoclasts in bone, microglial cells in brain). Lipid A from bacterial LPS binds CD14 on macrophages to initiate septic shock.

FAS1 2019 10-HemaOncol.indd 407 11/7/19 5:04 PM

#### **Eosinophils**



Defend against helminthic infections (major basic protein). Bilobate nucleus. Packed with large eosinophilic granules of uniform size A. Highly phagocytic for antigenantibody complexes.

Produce histaminase, major basic protein (MBP, a helminthotoxin), eosinophil peroxidase, eosinophil cationic protein, and eosinophilderived neurotoxin.

Eosin = pink dye; philic = loving. Causes of eosinophilia = PACCMAN:

**P**arasites

**A**sthma

Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)

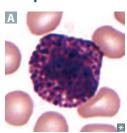
Chronic adrenal insufficiency

Myeloproliferative disorders

Allergic processes

Neoplasia (eg, Hodgkin lymphoma)

#### **Basophils**

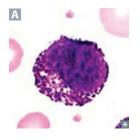


Mediate allergic reaction. Densely basophilic granules A contain heparin (anticoagulant) and histamine (vasodilator). Leukotrienes synthesized and released on demand.

Basophilic—stains readily with basic stains.

Basophilia is uncommon, but can be a sign of myeloproliferative disorders, particularly CML.

#### **Mast cells**



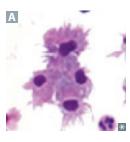
Mediate local tissue allergic reactions. Contain basophilic granules ⚠. Originate from same precursor as basophils but are not the same cell type. Can bind the Fc portion of IgE to membrane. Activated by tissue trauma, C3a and C5a, surface IgE cross-linking by antigen (IgE receptor aggregation) → degranulation → release of histamine, heparin, tryptase, and eosinophil chemotactic factors.

Involved in type I hypersensitivity reactions.

Cromolyn sodium prevents mast cell
degranulation (used for asthma prophylaxis).

Vancomycin, opioids, and radiocontrast dye can
elicit IgE-independent mast cell degranulation.

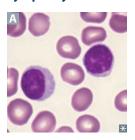
#### Dendritic cells



Highly phagocytic antigen-presenting cells (APCs) A. Function as link between innate and adaptive immune systems. Express MHC class II and Fc receptors on surface.

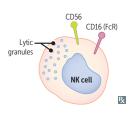
FAS1\_2019\_10-HemaOncol.indd 408 11/7/19 5:04 PM

#### Lymphocytes



Refer to B cells, T cells, and NK cells. B cells and T cells mediate adaptive immunity. NK cells are part of the innate immune response. Round, densely staining nucleus with small amount of pale cytoplasm A.

#### **Natural killer cells**



Important in innate immunity, especially against intracellular pathogens. Larger than B and T cells, with distinctive cytoplasmic lytic granules (containing perforin and granzymes) that, when released, act on target cells to induce apoptosis. Distinguish between healthy and infected cells by identifying cell surface proteins (induced by stress, malignant transformation, or microbial infections).

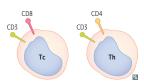
#### **B** cells



Mediate humoral immune response. Originate from stem cells in bone marrow and matures in marrow. Migrate to peripheral lymphoid tissue (follicles of lymph nodes, white pulp of spleen, unencapsulated lymphoid tissue). When antigen is encountered, B cells differentiate into plasma cells (which produce antibodies) and memory cells. Can function as an APC.

 $\mathbf{B} = \mathbf{B}$ one marrow.

#### T cells



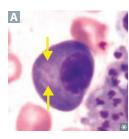
Mediate cellular immune response. Originate from stem cells in the bone marrow, but mature in the thymus. Differentiate into cytotoxic T cells (express CD8, recognize MHC I), helper T cells (express CD4, recognize MHC II), and regulatory T cells. CD28 (costimulatory signal) necessary for T-cell activation. Most circulating lymphocytes are T cells (80%).

T = Thymus.

CD4+ helper T cells are the primary target of HIV.

Rule of 8: MHC II  $\times$  CD4 = 8; MHC I  $\times$  CD8 = 8.

#### Plasma cells



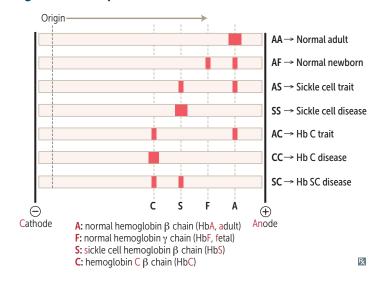
Produce large amounts of antibody specific to a particular antigen. "Clock-face" chromatin distribution and eccentric nucleus, abundant RER, and well-developed Golgi apparatus (arrows in A). Found in bone marrow and normally do not circulate in peripheral blood.

Multiple myeloma is a plasma cell dyscrasia.

FAS1\_2019\_10-HemaOncol.indd 409 11/7/19 5:04 PM

#### ► HEMATOLOGY AND ONCOLOGY—PHYSIOLOGY

#### **Hemoglobin electrophoresis**



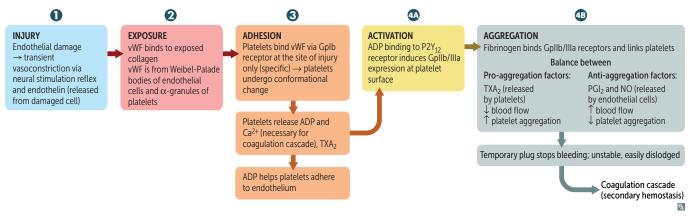
On a gel, hemoglobin migrates from the negatively charged cathode to the positively charged anode. HbA migrates the farthest, followed by HbF, HbS, and HbC. This is because the missense mutations in HbS and HbC replace glutamic acid ⊖ with valine (neutral) and lysine ⊕, respectively, making HbC and HbS more positively charged than HbA.

A Fat Santa Claus can't (cathode → anode) go far.

FAS1\_2019\_10-HemaOncol.indd 410 11/7/19 5:04 PM

0

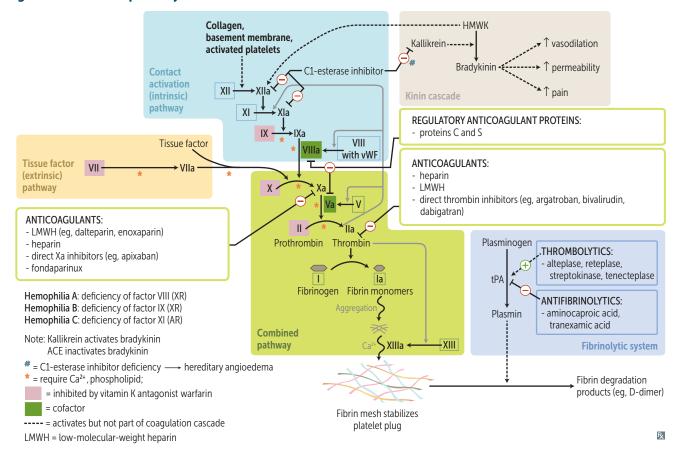
#### Platelet plug formation (primary hemostasis)



#### Formation of insoluble fibrin mesh. **Thrombogenesis** Aspirin irreversibly inhibits cyclooxygenase, thereby inhibiting TXA, synthesis. Clopidogrel, prasugrel, and ticlopidine inhibit ADP-induced expression of GpIIb/IIIa by irreversibly blocking $P2Y_{12}$ receptor. Abciximab, eptifibatide, and tirofiban inhibit GpIIb/IIIa directly. Ristocetin activates vWF to bind GpIb. Failure of aggregation with ristocetin assay occurs in Clopidogrel, prasugrel, Platelet von Willebrand disease and Bernard-Soulier ticlopidine syndrome. vWF Inside vWF carries/protects factor VIII; volksWagen Aspirin platelets Fibrinogen Factories make gr8 cars. Fibrinogen Arachidonic ADP (P2Y<sub>12</sub>) receptor acid 4A Deficiency: Glanzmann thrombasthenia $\ominus$ Activated Protein C protein C Abciximab, Deficiency: Bernard-Thrombin-Gpllb/Illa eptifibatide, Vascular endothelial cells Soulier syndrome thrombomodulin insertion tirofiban complex 3 Deficiency: von (vWF + factor VIII) Inside Willebrand Subendothelial endothelial vWI disease Thromboplastin collagen 2 cells LtPA, PGI<sub>2</sub>

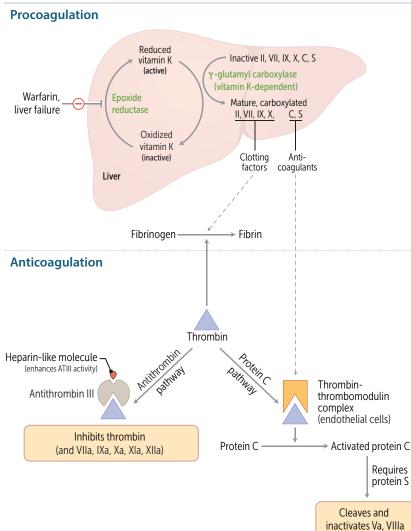
FAS1\_2019\_10-HemaOncol.indd 411 11/7/19 5:04 PM

#### **Coagulation and kinin pathways**



FAS1\_2019\_10-HemaOncol.indd 412 11/7/19 5:04 PM

#### Vitamin K-dependent coagulation



Vitamin K deficiency: ↓ synthesis of factors II, VII, IX, X, protein C, protein S.

Warfarin inhibits vitamin K epoxide reductase. Vitamin K administration can potentially reverse inhibitory effect of warfarin on clotting factor synthesis (delayed). FFP or PCC administration reverses action of warfarin immediately and can be given with vitamin K in cases of severe bleeding.

Neonates lack enteric bacteria, which produce vitamin K. Early administration of vitamin K overcomes neonatal deficiency/coagulopathy. Factor VII (seven)—shortest half-life. Factor II (two)—longest (tallest) half-life.

Antithrombin inhibits thrombin (factor IIa) and factors VIIa, IXa, Xa, XIa, XIIa.

Heparin enhances the activity of antithrombin. Principal targets of antithrombin: thrombin and factor Xa.

Factor V Leiden mutation produces a factor V resistant to inhibition by activated protein C. tPA is used clinically as a thrombolytic.

FAS1\_2019\_10-HemaOncol.indd 413 11/7/19 5:04 PM

Ŗ

## ► HEMATOLOGY AND ONCOLOGY—PATHOLOGY

RBC morphology			
ТҮРЕ	EXAMPLE	ASSOCIATED PATHOLOGY	NOTES
Acanthocytes ("spur cells")		Liver disease, abetalipoproteinemia	Projections of varying size at irregular intervals.
Echinocytes ("burr cells")	R	Liver disease, ESRD, pyruvate kinase deficiency	Smaller and more uniform projections than acanthocytes
Dacrocytes ("teardrop cells")		Bone marrow infiltration (eg, myelofibrosis)	RBC "sheds a <b>tear</b> " because it's mechanically squeezed out of its home in the bone marrow
Schistocytes (eg, "helmet" cells)		MAHAs (eg, DIC, TTP/HUS, HELLP syndrome), mechanical hemolysis (eg, heart valve prosthesis)	Fragmented RBCs
Degmacytes ("bite cells")		G6PD deficiency	Due to removal of Heinz bodies by splenic macrophages
Elliptocytes		Hereditary elliptocytosis	Caused by mutation in genes encoding RBC membrane proteins (eg, spectrin)

FAS1\_2019\_10-HemaOncol.indd 414 11/7/19 5:04 PM

## **HEMATOLOGY AND ONCOLOGY** ► HEMATOLOGY AND ONCOLOGY—PATHOLOGY

#### **RBC** morphology (continued)

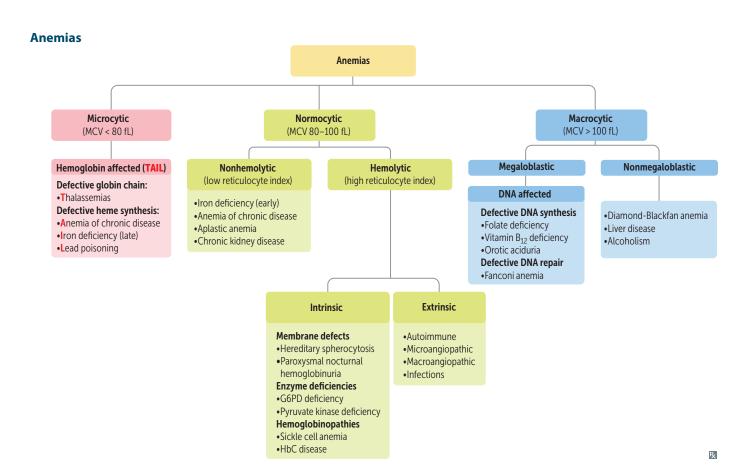
TYPE	EXAMPLE	ASSOCIATED PATHOLOGY	NOTES
Spherocytes		Hereditary spherocytosis, autoimmune hemolytic anemia	Small, spherical cells without central pallor
Macro-ovalocytes		Megaloblastic anemia (also hypersegmented PMNs)	
Target cells	R	HbC disease, Asplenia, Liver disease, Thalassemia	"HALT," said the hunter to his target
Sickle cells	*	Sickle cell anemia	Sickling occurs with low O <sub>2</sub> conditions (eg, high altitude, acidosis)

11/7/19 5:04 PM FAS1\_2019\_10-HemaOncol.indd 415

#### **RBC inclusions**

EXAMPLE	ASSOCIATED PATHOLOGY	NOTES
*	Sideroblastic anemias (eg, lead poisoning, myelodysplastic syndromes, alcoholism)	Perinuclear mitochondria with excess iron (forming ring in ringed sideroblasts) Require Prussian blue stain to be visualized
*	Functional hyposplenia (eg, sickle cell disease), asplenia	Basophilic nuclear remnants (do not contain iron) Usually removed by splenic macrophages
×	Sideroblastic anemias, thalassemias	Basophilic ribosomal precipitates (do not contain iron)
*	Sideroblastic anemia	Basophilic granules (contain iron)
R	G6PD deficiency	Denatured and precipitated hemoglobin (contain iron) Phagocytic removal of Heinz bodies → bite cells Requires supravital stain (eg, crystal violet) to be visualized
	*	Sideroblastic anemias (eg, lead poisoning, myelodysplastic syndromes, alcoholism)  Functional hyposplenia (eg, sickle cell disease), asplenia  Sideroblastic anemias, thalassemias  Sideroblastic anemia  G6PD deficiency

FAS1\_2019\_10-HemaOncol.indd 416 11/7/19 5:05 PM



#### **Reticulocyte index**

Also called corrected reticulocyte count. Used to correct falsely elevated reticulocyte count in anemia. Measures appropriate bone marrow response to anemic conditions (effective erythropoiesis). High reticulocyte index (RI) indicates compensatory RBC production; low RI indicates inadequate response to correct anemia. Calculated as:

> RI = reticulocyte % × actual Hct/normal Hct [normal Hct  $\approx 45\%$ ]

FAS1\_2019\_10-HemaOncol.indd 417 11/7/19 5:05 PM

Microcytic,
-------------

#### hypochromic anemias

MCV < 80 fL

#### Iron deficiency

↓ iron due to chronic bleeding (eg, GI loss, menorrhagia), malnutrition, absorption disorders, GI surgery (eg, gastrectomy), or ↑ demand (eg, pregnancy) → ↓ final step in heme synthesis.

Labs: ↓ iron, ↑ TIBC, ↓ ferritin, ↑ free erythrocyte protoporphyrin, ↑ RDW, ↓ RI. Microcytosis and

hypochromasia († central pallor) A.

Symptoms: fatigue, conjunctival pallor **B**, pica (persistent craving and compulsive eating of nonfood substances), spoon nails (koilonychia).

May manifest as glossitis, cheilosis, Plummer-Vinson syndrome (triad of iron deficiency anemia, esophageal webs, and dysphagia).

#### α-thalassemia

 $\alpha$ -globin gene deletions on chromosome  $16 \rightarrow 4$   $\alpha$ -globin synthesis. *cis* deletion (deletions occur on same chromosome) prevalent in Asian populations; *trans* deletion (deletions occur on separate chromosomes) prevalent in African populations. Normal is  $\alpha\alpha/\alpha\alpha$ .

NUMBER OF $\alpha$ -GLOBIN GENES DELETED	DISEASE	CLINICAL OUTCOME
$1 \; (\alpha \; \alpha/\alpha \; -)$	lpha-thalassemia minima	No anemia (silent carrier)
2 ( $\alpha$ -/ $\alpha$ -; trans) or ( $\alpha$ $\alpha$ /; cis)	α-thalassemia minor	Mild microcytic, hypochromic anemia; <i>cis</i> deletion may worsen outcome for the carrier's offspring
3 (/- α)	Hemoglobin H disease (HbH); excess β-globin forms $β_4$	Moderate to severe microcytic hypochromic anemia
4 (/)	Hemoglobin Barts disease; no α-globin, excess γ-globin forms γ <sub>4</sub>	Hydrops fetalis; incompatible with life

#### β-thalassemia

Point mutations in splice sites and promoter sequences on chromosome  $11 \rightarrow \ \downarrow \beta$ -globin synthesis. Prevalent in Mediterranean populations.

**β**-thalassemia minor (heterozygote): β chain is underproduced. Usually asymptomatic. Diagnosis confirmed by † HbA, (> 3.5%) on electrophoresis.

HbS/ $\beta$ -thalassemia heterozygote: mild to moderate sickle cell disease depending on amount of  $\beta$ -globin production.

FAS1\_2019\_10-HemaOncol.indd 418 11/7/19 5:05 PM

#### Microcytic, hypochromic anemias (continued)

#### **Lead poisoning**

Lead inhibits ferrochelatase and ALA dehydratase → ↓ heme synthesis and ↑ RBC protoporphyrin. Also inhibits rRNA degradation → RBCs retain aggregates of rRNA (basophilic stippling).

Symptoms of **LEAD** poisoning:

- Lead Lines on gingivae (Burton lines) and on metaphyses of long bones D on x-ray.
- Encephalopathy and Erythrocyte basophilic stippling.
- Abdominal colic and sideroblastic Anemia.
- Drops—wrist and foot drop. Dimercaprol and EDTA are 1st line of treatment.

**Suc**cimer used for chelation for kids (It "sucks" to be a kid who eats lead).

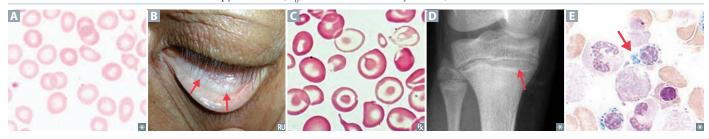
Exposure risk † in old houses with chipped paint.

#### Sideroblastic anemia

Causes: genetic (eg, X-linked defect in ALA synthase gene), acquired (myelodysplastic syndromes), and reversible (alcohol is most common; also lead poisoning, vitamin B<sub>6</sub> deficiency, copper deficiency, drugs [eg, isoniazid, linezolid]).

Lab findings: † iron, normal/‡ TIBC, † ferritin. Ringed sideroblasts (with iron-laden, Prussian blue–stained mitochondria) seen in bone marrow **E**. Peripheral blood smear: basophilic stippling of RBCs. Some acquired variants may be normocytic or macrocytic.

Treatment: pyridoxine (B<sub>6</sub>, cofactor for ALA synthase).



#### **Interpretation of iron studies**

	Iron deficiency	Chronic disease	Hemochromatosis	Pregnancy/ OCP use
Serum iron	<b>†</b>	ţ	†	_
Transferrin or TIBC	1	↓a	Ţ	†
Ferritin	Į.	†	<b>†</b>	_
% transferrin saturation (serum iron/TIBC)	††	<b>—/↓</b>	††	ţ

 $\uparrow \downarrow = 1^{\circ}$  disturbance.

Transferrin—transports iron in blood.

TIBC—indirectly measures transferrin.

Ferritin—1° iron storage protein of body.

<sup>a</sup>Evolutionary reasoning—pathogens use circulating iron to thrive. The body has adapted a system in which iron is stored within the cells of the body and prevents pathogens from acquiring circulating iron.

FAS1\_2019\_10-HemaOncol.indd 419 11/7/19 5:05 PM

## **HEMATOLOGY AND ONCOLOGY** ► HEMATOLOGY AND ONCOLOGY—PATHOLOGY

Macrocytic anemias	MCV > 100  fL.	
	DESCRIPTION	FINDINGS
Megaloblastic anemia	Impaired DNA synthesis → maturation of nucleus of precursor cells in bone marrow delayed relative to maturation of cytoplasm.  Causes: vitamin B <sub>12</sub> deficiency, folate deficiency, medications (eg, hydroxyurea, phenytoin, methotrexate, sulfa drugs).	RBC macrocytosis, hypersegmented neutrophils (arrow in A), glossitis.
Folate deficiency	Causes: malnutrition (eg, alcoholics), malabsorption, drugs (eg, methotrexate, trimethoprim, phenytoin), † requirement (eg, hemolytic anemia, pregnancy).	† homocysteine, normal methylmalonic acid. <b>No neurologic symptoms</b> (vs B <sub>12</sub> deficiency).
Vitamin B <sub>12</sub> (cobalamin) deficiency	Causes: pernicious anemia, malabsorption (eg, Crohn disease), pancreatic insufficiency, gastrectomy, insufficient intake (eg, veganism), Diphyllobothrium latum (fish tapeworm).	↑ homocysteine, ↑ methylmalonic acid.  Neurologic symptoms: reversible dementia, subacute combined degeneration (due to involvement of B₁₂ in fatty acid pathways and myelin synthesis): spinocerebellar tract, lateral corticospinal tract, dorsal column dysfunction. Folate supplementation in vitamin B₁₂ deficiency can correct the anemia, but worsens neurologic symptoms.  Historically diagnosed with the Schilling test, a test that determines if the cause is dietary insufficiency vs malabsorption.  Anemia 2° to insufficient intake may take several years to develop due to liver's ability to store B₁₂ (as opposed to folate deficiency).
Orotic aciduria	Inability to convert orotic acid to UMP (de novo pyrimidine synthesis pathway) because of defect in UMP synthase.  Autosomal recessive. Presents in children as failure to thrive, developmental delay, and megaloblastic anemia refractory to folate and B₁₂. No hyperammonemia (vs ornithine transcarbamylase deficiency—↑ orotic acid with hyperammonemia).	Orotic acid in urine. Treatment: uridine monophosphate or uridine triacetate to bypass mutated enzyme.
Nonmegaloblastic anemia	Macrocytic anemia in which DNA synthesis is normal. Causes: alcoholism, liver disease.	RBC macrocytosis without hypersegmented neutrophils.
Diamond-Blackfan anemia	A congenital form of pure red cell aplasia.  Rapid-onset anemia within 1st year of life due to intrinsic defect in erythroid progenitor cells.	↑ % HbF (but ↓ total Hb). Short stature, craniofacial abnormalities, and upper extremity malformations (triphalangeal thumbs) in up to 50% of cases.

11/7/19 5:05 PM FAS1\_2019\_10-HemaOncol.indd 420

Normocytic, normochromic anemias	Normocytic, normochromic anemias are classified as nonhemolytic or hemolytic. The hemolytic anemias are further classified according to the cause of the hemolysis (intrinsic vs extrinsic to the RBC) and by the location of the hemolysis (intravascular vs extravascular). Hemolysis can lead to increases in LDH, reticulocytes, unconjugated bilirubin, pigmented gallstones, and urobilinogen in urine.
Intravascular hemolysis	Findings: \(\psi\) haptoglobin, \(\dagger\) schistocytes on blood smear. Characteristic hemoglobinuria, hemosiderinuria, and urobilinogen in urine. Notable causes are mechanical hemolysis (eg, prosthetic valve), paroxysmal nocturnal hemoglobinuria, microangiopathic hemolytic anemias.
Extravascular hemolysis	Mechanism: macrophages in spleen clear RBCs. Findings: spherocytes in peripheral smear (most commonly due to hereditary spherocytosis and autoimmune hemolytic anemia), no hemoglobinuria/hemosiderinuria. Can present with urobilinogen in urine.

	DESCRIPTION	FINDINGS
Anemia of chronic disease	Inflammation (eg, ↑ IL-6) → ↑ hepcidin (released by liver, binds ferroportin on intestinal mucosal cells and macrophages, thus inhibiting iron transport) → ↓ release of iron from macrophages and ↓ iron absorption from gut. Associated with conditions such as chronic infections, neoplastic disorders, chronic kidney disease, and autoimmune diseases (eg, SLE, rheumatoid arthritis).	↓ iron, ↓ TIBC, ↑ ferritin. Normocytic, but can become microcytic. Treatment: address underlying cause of inflammation, judicious use of blood transfusion, consider erythropoiesis-stimulating agents such as EPO (eg, in chronic kidney disease).
Aplastic anemia	<ul> <li>Caused by failure or destruction of hematopoietic stem cells due to:</li> <li>Radiation and drugs (eg, benzene, chloramphenicol, alkylating agents, antimetabolites)</li> <li>Viral agents (eg, EBV, HIV, hepatitis viruses)</li> <li>Fanconi anemia (autosomal recessive DNA repair defect → bone marrow failure); normocytosis or macrocytosis on CBC</li> <li>Idiopathic (immune mediated, 1° stem cell defect); may follow acute hepatitis</li> </ul>	

11/7/19 5:05 PM FAS1\_2019\_10-HemaOncol.indd 421

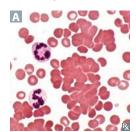
#### **Intrinsic hemolytic anemias**

	DESCRIPTION	FINDINGS
Hereditary spherocytosis	Primarily autosomal dominant. Due to defect in proteins interacting with RBC membrane skeleton and plasma membrane (eg, ankyrin, band 3, protein 4.2, spectrin).  Small, round RBCs with less surface area and no central pallor (↑ MCHC) → premature removal by spleen (extravascular hemolysis).	Splenomegaly, aplastic crisis (parvovirus B19 infection).  Labs: ↓ mean fluorescence of RBCs in eosin  5-maleimide (EMA) binding test, ↑ fragility in osmotic fragility test. Normal to ↓ MCV with abundance of RBCs.  Treatment: splenectomy.
G6PD deficiency	X-linked recessive. G6PD defect  → ↓ NADPH → ↓ reduced glutathione  → ↑ RBC susceptibility to oxidative stress (eg, sulfa drugs, antimalarials, fava beans)  → hemolysis.  Causes extravascular and intravascular hemolysis.	Back pain, hemoglobinuria a few days after oxidant stress.  Labs: blood smear shows RBCs with Heinz bodies and bite cells.  "Stress makes me eat bites of fava beans with Heinz ketchup."
Pyruvate kinase deficiency	Autosomal recessive. Pyruvate kinase defect  → ↓ ATP → rigid RBCs → extravascular hemolysis. Increases levels of 2,3-BPG  → ↓ hemoglobin affinity for O₂.	Hemolytic anemia in a newborn.
Paroxysmal nocturnal hemoglobinuria	Hematopoietic stem cell mutation  → ↑ complement-mediated intravascular hemolysis, especially at night. Acquired PIGA mutation → impaired GPI anchor synthesis for decay-accelerating factor (DAF/CD55) and membrane inhibitor of reactive lysis (MIRL/ CD59), which protect RBC membrane from complement.	Triad: Coombs ⊝ hemolytic anemia, pancytopenia, venous thrombosis (eg, Budd-Chiari syndrome).  Pink/red urine in morning. Associated with aplastic anemia, acute leukemias.  Labs: CD55/59 ⊖ RBCs on flow cytometry.  Treatment: eculizumab (targets terminal complement protein C5).
Sickle cell anemia	Point mutation in β-globin gene → single amino acid substitution (glutamic acid → valine). Mutant HbA is termed HbS. Causes extravascular and intravascular hemolysis.  Pathogenesis: low O₂, high altitude, or acidosis precipitates sickling (deoxygenated HbS polymerizes) → anemia, vaso-occlusive disease.  Newborns are initially asymptomatic because of ↑ HbF and ↓ HbS.  Heterozygotes (sickle cell trait) have resistance to malaria.  8% of African Americans carry an HbS allele.  Sickle cells are crescent-shaped RBCs A.  "Crew cut" on skull x-ray due to marrow expansion from ↑ erythropoiesis (also seen in thalassemias).	<ul> <li>Complications in sickle cell disease:</li> <li>Aplastic crisis (transient arrest of erythropoiesis due to parvovirus B19).</li> <li>Autosplenectomy (Howell-Jolly bodies)  → ↑ risk of infection by encapsulated organisms (eg, S pneumoniae).</li> <li>Splenic infarct/sequestration crisis.</li> <li>Salmonella osteomyelitis.</li> <li>Painful vaso-occlusive crises: dactylitis (painful swelling of hands/feet), priapism, acute chest syndrome (respiratory distress, new pulmonary infiltrates on CXR, common cause of death), avascular necrosis, stroke.</li> <li>Sickling in renal medulla (↓ Po<sub>2</sub>) → renal papillary necrosis → hematuria.</li> <li>Hb electrophoresis: ↓↓ HbA, ↑ HbF, ↑↑ HbS.</li> <li>Treatment: hydroxyurea (↑ HbF), hydration.</li> </ul>
HbC disease	Glutamic acid–to-ly <mark>C</mark> ine (lysine) mutation in β-globin. Causes extravascular hemolysis.	Patients with HbSC (1 of each mutant gene) have milder disease than HbSS patients. Blood smear in homozygotes: hemoglobin Crystals inside RBCs, target cells.

FAS1\_2019\_10-HemaOncol.indd 422 11/7/19 5:05 PM

#### **Extrinsic hemolytic anemias**

#### Autoimmune hemolytic anemia



#### DESCRIPTION

A normocytic anemia that is usually idiopathic and Coombs ⊕. Two types:

- Warm AIHA-chronic anemia in which IgG causes RBC agglutination. Seen in SLE and CLL and with certain drugs (eg, α-methyldopa). "Warm weather is Good."
- Cold AIHA–acute anemia in which IgM

   + complement causes RBC agglutination
   upon exposure to cold → painful, blue
   fingers and toes. Seen in CLL, Mycoplasma pneumoniae infections, infectious
   Mononucleosis.

#### FINDINGS

Spherocytes and agglutinated RBCs A on peripheral blood smear.

Warm AIHA treatment: steroids, rituximab, splenectomy (if refractory).

Cold AIHA treatment: cold avoidance, rituximab.

Direct Coombs test—anti-Ig antibody (Coombs reagent) added to patient's RBCs. RBCs agglutinate if RBCs are coated with Ig.

For comparison, Indirect Coombs test—normal RBCs added to patient's serum. If serum has anti-RBC surface Ig, RBCs agglutinate when Coombs reagent added.

	Patient component	Reagent(s)	⊕ Result (agglutination)	← Result (no agglutination)
Direct Coombs		公.	454	*
_	RBCs +/- anti-RBC Ab	Anti-human globulin (Coombs reagent)	⊕ Result Anti-RBC Ab present	Result Anti-RBC Ab absent
Indirect Coombs	~ ~ ~ \ ~ ~ \ ~ ~ \	Donor blood	The state of the s	4
	Patient serum +/ – anti-donor RBC Ab	Anti-human globulin (Coombs reagent)	⊕ Result Anti-donor RBC Ab present	Result Anti-donor RBC Ab absent

## Microangiopathic hemolytic anemia

RBCs are damaged when passing through obstructed or narrowed vessels. Causes intravascular hemolysis.

Seen in DIC, TTP/HUS, SLE, HELLP syndrome, hypertensive emergency.

peripheral blood smear due to mechanical destruction (*schisto* = to split) of RBCs.

Macroangiopathic hemolytic anemia

Prosthetic heart valves and aortic stenosis may also cause hemolytic anemia 2° to mechanical destruction of RBCs.

Schistocytes on peripheral blood smear.

Hemolytic anemia due † destruction to infection

† destruction of RBCs (eg, malaria, Babesia).

FAS1\_2019\_10-HemaOncol.indd 423 11/7/19 5:05 PM

424

SECTION III

**HEMATOLOGY AND ONCOLOGY** ► HEMATOLOGY AND ONCOLOGY—PATHOLOGY

#### Leukopenias

=		
CELL TYPE	CELL COUNT	CAUSES
Neutropenia	Absolute neutrophil count < 1500 cells/mm <sup>3</sup> Severe infections typical when < 500 cells/mm <sup>3</sup>	Sepsis/postinfection, drugs (including chemotherapy), aplastic anemia, SLE, radiation
Lymphopenia	Absolute lymphocyte count < 1500 cells/mm³ (< 3000 cells/mm³ in children)	HIV, DiGeorge syndrome, SCID, SLE, corticosteroids <sup>a</sup> , radiation, sepsis, postoperative
Eosinopenia	Absolute eosinophil count < 30 cells/mm³	Cushing syndrome, corticosteroids <sup>a</sup>

<sup>&</sup>lt;sup>a</sup>Corticosteroids cause neutrophilia, despite causing eosinopenia and lymphopenia. Corticosteroids ↓ activation of neutrophil adhesion molecules, impairing migration out of the vasculature to sites of inflammation. In contrast, corticosteroids sequester eosinophils in lymph nodes and cause apoptosis of lymphocytes.

#### **Neutrophil left shift**

† neutrophil precursors, such as band cells and metamyelocytes, in peripheral blood. Usually seen with neutrophilia in the acute response to infection or inflammation. Called leukoerythroblastic reaction when left shift is seen with immature RBCs. Occurs with severe anemia (physiologic response) or marrow response (eg, fibrosis, tumor taking up space in marrow).

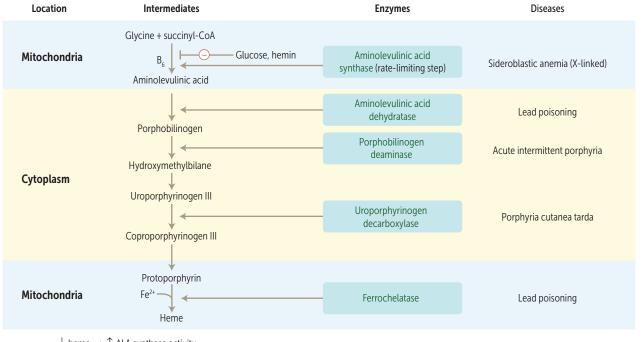
A left shift is a shift to a more immature cell in the maturation process.

FAS1\_2019\_10-HemaOncol.indd 424 11/7/19 5:05 PM

#### Heme synthesis, porphyrias, and lead poisoning

The porphyrias are hereditary or acquired conditions of defective heme synthesis that lead to the accumulation of heme precursors. Lead inhibits specific enzymes needed in heme synthesis, leading to a similar condition.

CONDITION	AFFECTED ENZYME	ACCUMULATED SUBSTRATE	PRESENTING SYMPTOMS
Lead poisoning	Ferrochelatase and ALA dehydratase	Protoporphyrin, ALA (blood)	Microcytic anemia (basophilic stippling in peripheral smear A, ringed sideroblasts in bone marrow), GI and kidney disease.  Children—exposure to lead paint → mental deterioration.  Adults—environmental exposure (eg, batteries, ammunition) → headache, memory loss, demyelination (peripheral neuropathy).
Acute intermittent porphyria	Porphobilinogen deaminase, previously called uroporphyrinogen I synthase (autosomal dominant mutation)	Porphobilinogen, ALA	Symptoms (5 P's):  Painful abdomen  Port wine–colored Pee  Polyneuropathy  Psychological disturbances  Precipitated by drugs (eg, cytochrome P-450 inducers), alcohol, starvation  Treatment: hemin and glucose.
Porphyria cutanea tarda  B	Uroporphyrinogen decarboxylase	Uroporphyrin (tea- colored urine)	Blistering cutaneous photosensitivity and hyperpigmentation <b>B</b> .  Most common porphyria. Exacerbated with alcohol consumption.  Causes: familial, hepatitis C.  Treatment: phlebotomy, sun avoidance, antimalarials (eg, hydroxychloroquine).



 $\downarrow$  heme  $\rightarrow$   $\uparrow$  ALA synthase activity

 $\uparrow$  heme  $\rightarrow \downarrow$  ALA synthase activity

Ŗ

FAS1\_2019\_10-HemaOncol.indd 425 11/7/19 5:05 PM

#### Iron poisoning

	Acute	Chronic	
FINDINGS	High mortality rate associated with accidental ingestion by children (adult iron tablets may look like candy).	Seen in patients with 1° (hereditary) or 2° (eg, chronic blood transfusions for thalassemia or sickle cell disease) hemochromatosis.	
MECHANISM	Cell death due to formation of free radicals and peroxidation of membrane lipids.		
SYMPTOMS/SIGNS	Abdominal pain, vomiting, GI bleeding. Radiopaque pill seen on x-ray. May progress to anion gap metabolic acidosis and multiorgan failure. Leads to scarring with GI obstruction.	Arthropathy, cirrhosis, cardiomyopathy, diabetes mellitus and skin pigmentation ("bronze diabetes"), hypogonadism.	
TREATMENT	Chelation (eg, deferoxamine, deferasirox), gastric lavage.	Phlebotomy (patients without anemia) or chelation.	

#### **Coagulation disorders**

PT—tests function of common and extrinsic pathway (factors I, II, V, VII, and X). Defect → ↑ PT (Play Tennis outside [extrinsic pathway]).

INR (international normalized ratio) = patient PT/control PT. 1 = normal, > 1 = prolonged. Most common test used to follow patients on warfarin, which prolongs INR.

PTT—tests function of common and intrinsic pathway (all factors except VII and XIII). Defect
→ ↑ PTT (Play Table Tennis inside).

Coagulation disorders can be due to clotting factor deficiencies or acquired factor inhibitors. Diagnosed with a mixing study, in which normal plasma is added to patient's plasma. Clotting factor deficiencies should correct (the PT or PTT returns to within the appropriate normal range), whereas factor inhibitors will not correct.

DISORDER	PT	PTT	MECHANISM AND COMMENTS
Hemophilia A, B, or C	_	1	<ul> <li>Intrinsic pathway coagulation defect († PTT).</li> <li>A: deficiency of factor VIII; X-linked recessive.</li> <li>B: deficiency of factor IX; X-linked recessive.</li> <li>C: deficiency of factor XI; autosomal recessive.</li> <li>Hemorrhage in hemophilia—hemarthroses (bleeding into joints, eg, knee A), easy bruising, bleeding after trauma or surgery (eg, dental procedures).</li> <li>Treatment: desmopressin + factor VIII concentrate (A); factor IX concentrate (B); factor XI concentrate (C).</li> </ul>
Vitamin K deficiency	<b>†</b>	†	General coagulation defect. Bleeding time normal.  Lactivity of factors II, VII, IX, X, protein C, protein S.

FAS1\_2019\_10-HemaOncol.indd 426 11/7/19 5:05 PM

#### ► HEMATOLOGY AND ONCOLOGY—PATHOLOGY **HEMATOLOGY AND ONCOLOGY**

#### **Platelet disorders**

All platelet disorders have † bleeding time (BT), mucous membrane bleeding, and microhemorrhages (eg, petechiae, epistaxis). Platelet count (PC) is usually low, but may be normal in qualitative disorders.

DISORDER	PC	ВТ	NOTES
Bernard-Soulier syndrome	<b>-/↓</b>	†	Defect in adhesion. ↓ GpIb → ↓ platelet-to-vWF adhesion. Labs: abnormal ristocetin test, large platelets.
Glanzmann thrombasthenia	-	<b>†</b>	Defect in aggregation. $\downarrow$ GpIIb/IIIa ( $\downarrow$ integrin $\alpha_{IIb}\beta_3$ ) $\rightarrow \downarrow$ platelet-to-platelet aggregation and defective platelet plug formation. Labs: blood smear shows no platelet clumping.
Immune thrombocytopenia	1	1	Destruction of platelets in spleen. Anti-GpIIb/IIIa antibodies → splenic macrophages phagocytose platelets. May be idiopathic or 2° to autoimmune disorders (eg, SLE), viral illness (eg, HIV, HCV), malignancy (eg, CLL), or drug reactions.  Labs: ↑ megakaryocytes on bone marrow biopsy, ↓ platelet count.  Treatment: steroids, IVIG, rituximab, TPO receptor agonists (eg, eltrombopag, romiplostim), or splenectomy for refractory ITP.

## **Thrombotic**

Disorders overlap significantly in symptomatology.

	Thrombotic thrombocytopenic purpura	Hemolytic-uremic syndrome	
EPIDEMIOLOGY	Typically females	Typically children	
PATHOPHYSIOLOGY	Inhibition or deficiency of ADAMTS13 (a vWF metalloprotease) → ↓ degradation of vWF multimers → ↑ large vWF multimers → ↑ platelet adhesion and aggregation (microthrombi formation)	Commonly caused by Shiga-like toxin from EHEC (serotype O157:H7) infection	
PRESENTATION	Triad of thrombocytopenia (‡ platelets), microan † LDH), acute kidney injury († Cr)	ngiopathic hemolytic anemia (‡ Hb, schistocytes,	
DIFFERENTIATING SYMPTOMS	Triad + fever + neurologic symptoms	Triad + bloody diarrhea	
LABS	Normal PT and PTT helps distinguish TTP an DIC (coagulation pathway is activated)	d HUS (coagulation pathway is not activated) from	
TREATMENT	Plasmapheresis, steroids, rituximab	Supportive care	

FAS1\_2019\_10-HemaOncol.indd 427 11/7/19 5:05 PM 428 SECTION III

**HEMATOLOGY AND ONCOLOGY** ► HEMATOLOGY AND ONCOLOGY—PATHOLOGY

#### Mixed platelet and coagulation disorders

DISORDER	PC	ВТ	PT	PTT	NOTES
von Willebrand disease	_	Ť	_	<b>—/1</b>	Intrinsic pathway coagulation defect: ↓ vWF  → ↑ PTT (vWF carries/protects factor VIII).  Defect in platelet plug formation: ↓ vWF  → defect in platelet-to-vWF adhesion.  Autosomal dominant. Mild but most common inherited bleeding disorder. No platelet aggregation with ristocetin cofactor assay.  Treatment: desmopressin, which releases vWF stored in endothelium.
Disseminated intravascular coagulation	1	t	t	t	Widespread clotting factor activation  → deficiency in clotting factors → bleeding state.  Causes: Snake bites, Sepsis (gram ⊕),  Trauma, Obstetric complications, acute  Pancreatitis, Malignancy, Nephrotic syndrome, Transfusion (SSTOP Making New Thrombi).  Labs: schistocytes, ↑ fibrin degradation products (D-dimers), ↓ fibrinogen, ↓ factors V and VIII.

#### Hereditary thrombosis syndromes leading to hypercoagulability

DISEASE	DESCRIPTION
Antithrombin deficiency	<ul> <li>Autosomal dominant inherited deficiency of antithrombin: has no direct effect on the PT, PTT, or thrombin time but diminishes the increase in PTT following heparin administration.</li> <li>Can also be acquired: renal failure/nephrotic syndrome → antithrombin loss in urine → ↓ inhibition of factors IIa and Xa.</li> </ul>
Factor V Leiden	Autosomal dominant, most common cause of inherited hypercoagulability in Caucasians.  Production of mutant factor V (guanine → adenine DNA point mutation → Arg506Gln mutation near the cleavage site) that is resistant to degradation by activated protein C. Complications include DVT, cerebral vein thrombosis, recurrent pregnancy loss.
Protein C or S deficiency	↓ ability to inactivate factors Va and VIIIa. ↑ risk of thrombotic skin necrosis with hemorrhage after administration of warfarin. If this occurs, think protein C deficiency. Together, protein C Cancels, and protein S Stops, coagulation.
Prothrombin gene mutation	Mutation in 3′ untranslated region → ↑ production of prothrombin → ↑ plasma levels and venous clots.

FAS1\_2019\_10-HemaOncol.indd 428 11/7/19 5:05 PM

#### ► HEMATOLOGY AND ONCOLOGY—PATHOLOGY **HEMATOLOGY AND ONCOLOGY**

#### **Blood transfusion therapy**

COMPONENT	DOSAGE EFFECT	CLINICAL USE	
Packed RBCs	† Hb and O <sub>2</sub> carrying capacity	Acute blood loss, severe anemia	
Platelets	† platelet count († ~ 5000/mm³/unit)	Stop significant bleeding (thrombocytopenia, qualitative platelet defects)	
<b>Fresh frozen</b> plasma/prothrombin  complex concentrate  † coagulation factor levels; FFP contains all coagulation factors and plasma proteins; PCC generally contains factors II, VII, IX, and X, a well as protein C and S			
Cryoprecipitate	Contains fibrinogen, factor VIII, factor XIII, vWF, and fibronectin	Coagulation factor deficiencies involving fibrinogen and factor VIII	

Blood transfusion risks include infection transmission (low), transfusion reactions, iron overload (may lead to 2° hemochromatosis), hypocalcemia (citrate is a Ca<sup>2+</sup> chelator), and hyperkalemia (RBCs may lyse in old blood units).

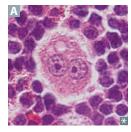
#### Leukemia vs lymphoma

Leukemia	Lymphoid or myeloid neoplasm with widespread involvement of bone marrow. Tumor cells are usually found in peripheral blood.
Lymphoma	Discrete tumor mass arising from lymph nodes. Presentations often blur definitions.

#### **Hodgkin vs** non-Hodgkin lymphoma

Hodgkin	Non-Hodgkin
Both may present with constitutional ("B") signs/sloss.	symptoms: low-grade fever, night sweats, weight
Localized, single group of nodes with contiguous spread (stage is strongest predictor of prognosis). Better prognosis.	Multiple lymph nodes involved; extranodal involvement common; noncontiguous spread. Worse prognosis.
Characterized by Reed-Sternberg cells.	Majority involve B cells; a few are of T-cell lineage.
Bimodal distribution: young adulthood and > 55 years; more common in men except for nodular sclerosing type.	Can occur in children and adults.
Associated with EBV.	May be associated with autoimmune diseases and viral infections (eg, HIV, EBV, HTLV).

#### **Hodgkin lymphoma**



Contains Reed-Sternberg cells: distinctive tumor giant cells; binucleate or bilobed with the 2 halves as mirror images ("owl eyes" A). RS cells are CD15+ and CD30+ B-cell origin. 2 owl eyes  $\times$  15 = 30.

	9
SUBTYPE	NOTES
Nodular sclerosis	Most common
Lymphocyte rich	Best prognosis
Mixed cellularity	Eosinophilia, seen in immunocompromised patients
Lymphocyte depleted	Seen in immunocompromised patients

FAS1\_2019\_10-HemaOncol.indd 429 11/7/19 5:05 PM

#### Non-Hodgkin lymphoma

ТҮРЕ	OCCURS IN	GENETICS	COMMENTS
Neoplasms of mature B c	ells		
Burkitt lymphoma	Adolescents or young adults	t(8;14)—translocation of c-myc (8) and heavy-chain Ig (14)	"Starry sky" appearance, sheets of lymphocytes with interspersed "tingible body" macrophages (arrows in A). Associated with EBV.  Jaw lesion B in endemic form in Africa; pelvis or abdomen in sporadic form.
Diffuse large B-cell lymphoma	Usually older adults, but 20% in children	Mutations in BCL-2, BCL-6	Most common type of non-Hodgkin lymphoma in adults.
Follicular lymphoma	Adults	t(14;18)—translocation of heavy-chain Ig (14) and <i>BCL</i> -2 (18)	Indolent course with painless "waxing and waning" lymphadenopathy. Bcl-2 normally inhibits apoptosis.
Mantle cell lymphoma	Adult males >> adult females	t(11;14)—translocation of cyclin D1 (11) and heavy-chain Ig (14), CD5+	Very aggressive, patients typically present with late-stage disease.
Marginal zone lymphoma	Adults	t(11;18)	Associated with chronic inflammation (eg, Sjögren syndrome, chronic gastritis [MALT lymphoma]).
Primary central nervous system lymphoma	Adults	EBV related; associated with HIV/ AIDS	Considered an AIDS-defining illness. Variable presentation: confusion, memory loss, seizures. CNS mass (often single, ring-enhancing lesion on MRI) in immunocompromised patients , needs to be distinguished from toxoplasmosis via CSF analysis or other lab tests.
Neoplasms of mature T c	ells		
Adult T-cell lymphoma	Adults	Caused by HTLV (associated with IV drug abuse)	Adults present with cutaneous lesions; common in Japan (T-cell in Tokyo), West Africa, and the Caribbean.  Lytic bone lesions, hypercalcemia.
Mycosis fungoides/ Sézary syndrome	Adults		Mycosis fungoides: skin patches and plaques (cutaneous T-cell lymphoma), characterized by atypical CD4+ cells with "cerebriform" nuclei and intraepidermal neoplastic cell aggregates (Pautrier microabscess). May progress to Sézary syndrome (T-cell leukemia).
	A	B	

FAS1\_2019\_10-HemaOncol.indd 430 11/7/19 5:05 PM

#### Plasma cell dyscrasias

M spike →  $\overline{\text{Albumin}}$   $\alpha_1$   $\alpha_2$   $\beta$ 

Characterized by monoclonal immunoglobulin (Ig) overproduction due to plasma cell disorder. Labs: serum protein electrophoresis (SPEP) or free light chain (FLC) assay for initial tests (M spike on SPEP represents overproduction of a monoclonal Ig fragment). For urinalysis, use 24-hr urine protein electrophoresis (UPEP) to detect light chain, as routine urine dipstick detects only albumin.

► HEMATOLOGY AND ONCOLOGY—PATHOLOGY

Confirm with bone marrow biopsy.

#### Multiple myeloma

Overproduction of IgG (55% of cases) > IgA.

Clinical features: CRAB

- HyperCalcemia
- Renal involvement
- Anemia
- Bone lytic lesions ("punched out" on X-ray A) → Back pain.

Peripheral blood smear shows Rouleaux formation B (RBCs stacked like poker chips).

Urinalysis shows Ig light chains (Bence Jones proteinuria) with  $\Theta$  urine dipstick.

Bone marrow analysis shows > 10% monoclonal plasma cells with clock-face chromatin [ and intracytoplasmic inclusions containing IgG.

Complications: † infection risk, 1° amyloidosis (AL).

#### Waldenstrom macroglobulinemia

Overproduction of IgM (macroglobulinemia because IgM is the largest Ig).

Clinical features:

- Peripheral neuropathy
- No CRAB findings
- Hyperviscosity syndrome:
  - Headache
  - Blurry vision
  - Raynaud phenomenon
  - Retinal hemorrhages

Bone marrow analysis shows >10% small lymphocytes with IgM-containing vacuoles (lymphoplasmacytic lymphoma).

Complication: thrombosis.

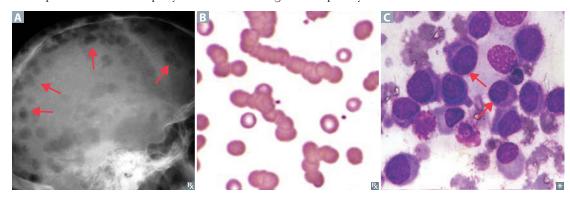
#### Monoclonal gammopathy of undetermined significance

Overproduction of any Ig type.

Usually asymptomatic. No CRAB findings.

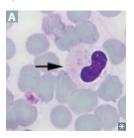
Bone marrow analysis shows < 10% monoclonal plasma cells.

Complication: 1-2% risk per year of transitioning to multiple myeloma.



FAS1 2019 10-HemaOncol.indd 431 11/7/19 5:05 PM

#### Myelodysplastic **syndromes**



Stem cell disorders involving ineffective hematopoiesis → defects in cell maturation of nonlymphoid lineages. Caused by de novo mutations or environmental exposure (eg, radiation, benzene, chemotherapy). Risk of transformation to AML.

**HEMATOLOGY AND ONCOLOGY** 

Pseudo-Pelger-Huet anomaly—neutrophils with bilobed ("duet") nuclei A. Typically seen after chemotherapy.

#### Leukemias

Unregulated growth and differentiation of WBCs in bone marrow → marrow failure → anemia (\dagger RBCs), infections (\dagger mature WBCs), and hemorrhage (\dagger platelets). Usually presents with † circulating WBCs (malignant leukocytes in blood); rare cases present with normal/4 WBCs. Leukemic cell infiltration of liver, spleen, lymph nodes, and skin (leukemia cutis) possible.

TYPE

NOTES

#### Lymphoid neoplasms

#### **Acute lymphoblastic** leukemia/lymphoma

Most frequently occurs in children; less common in adults (worse prognosis). T-cell ALL can present as mediastinal mass (presenting as SVC-like syndrome). Associated with Down syndrome. Peripheral blood and bone marrow have ††† lymphoblasts A.

TdT+ (marker of pre-T and pre-B cells), CD10+ (marker of pre-B cells).

Most responsive to therapy. May spread to CNS and testes.  $t(12;21) \rightarrow better prognosis.$ 

#### **Chronic lymphocytic** leukemia/small lymphocytic lymphoma

Age > 60 years. Most common adult leukemia. CD20+, CD23+, CD5+ B-cell neoplasm. Often asymptomatic, progresses slowly; smudge cells B in peripheral blood smear; autoimmune hemolytic anemia. CLL = Crushed Little Lymphocytes (smudge cells).

Richter transformation—CLL/SLL transformation into an aggressive lymphoma, most commonly diffuse large B-cell lymphoma (DLBCL).

#### Hairy cell leukemia

Adult males. Mature B-cell tumor. Cells have filamentous, hair-like projections (fuzzy appearing on LM C). Peripheral lymphadenopathy is uncommon.

Causes marrow fibrosis → dry tap on aspiration. Patients usually present with massive splenomegaly and pancytopenia.

Stains TRAP (tartrate-resistant acid phosphatase)  $\oplus$  (trapped in a hairy situation). TRAP stain largely replaced with flow cytometry. Associated with BRAF mutations. Treatment: cladribine, pentostatin.

#### Myeloid neoplasms

#### **Acute myelogenous** leukemia

Median onset 65 years. Auer rods □; myeloperoxidase ⊕ cytoplasmic inclusions seen mostly in APL (formerly M3 AML); ††† circulating myeloblasts on peripheral smear.

Risk factors: prior exposure to alkylating chemotherapy, radiation, myeloproliferative disorders, Down syndrome. APL: t(15;17), responds to all-trans retinoic acid (vitamin A) and arsenic, which induce differentiation of promyelocytes; DIC is a common presentation.

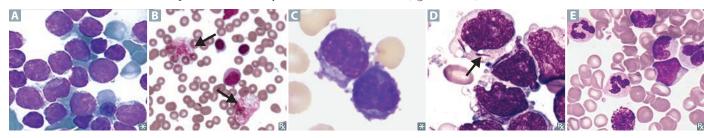
FAS1 2019 10-HemaOncol.indd 432 11/7/19 5:05 PM

#### Leukemias (continued)

## Chronic myelogenous leukemia

Peak incidence: 45—85 years; median age: 64 years. Defined by the Philadelphia chromosome (t[9;22], BCR-ABL) and myeloid stem cell proliferation. Presents with dysregulated production of mature and maturing granulocytes (eg, neutrophils, metamyelocytes, myelocytes, basophils and splenomegaly. May accelerate and transform to AML or ALL ("blast crisis").

Very low leukocyte alkaline phosphatase (LAP) as a result of low activity in malignant neutrophils, vs benign neutrophilia (leukemoid reaction) in which LAP is † due to † leukocyte count with neutrophilia in response to stressors (eg, infections, medications, severe hemorrhage). Responds to ber-abl tyrosine kinase inhibitors (eg, imatinib).



# Chronic myeloproliferative disorders

Malignant hematopoietic neoplasms with varying impacts on WBCs and myeloid cell lines.

#### Polycythemia vera

Primary polycythemia. Disorder of † RBCs, usually due to acquired *JAK2* mutation. May present as intense itching after shower (aquagenic pruritus). Rare but classic symptom is erythromelalgia (severe, burning pain and red-blue coloration) due to episodic blood clots in vessels of the extremities A.

↓ EPO (vs 2° polycythemia, which presents with endogenous or artificially † EPO). Treatment: phlebotomy, hydroxyurea, ruxolitinib (JAK1/2 inhibitor).

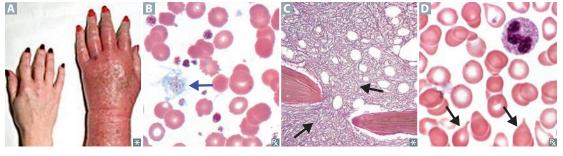
## Essential thrombocythemia

Characterized by massive proliferation of megakaryocytes and platelets. Symptoms include bleeding and thrombosis. Blood smear shows markedly increased number of platelets, which may be large or otherwise abnormally formed **B**. Erythromelalgia may occur.

#### Myelofibrosis

Obliteration of bone marrow with fibrosis due to † fibroblast activity. Associated with massive splenomegaly and "teardrop" RBCs . "Bone marrow cries because it's fibrosed and is a dry tap."

	RBCs	WBCs	PLATELETS	PHILADELPHIA CHROMOSOME	JAK2 MUTATIONS
Polycythemia vera	1	<b>†</b>	<b>†</b>	$\ominus$	$\oplus$
Essential thrombocythemia	-	_	<b>†</b>	$\Theta$	⊕ (30–50%)
Myelofibrosis	1	Variable	Variable	$\ominus$	⊕ (30–50%)
CML	1	1	1	$\oplus$	$\Theta$



FAS1\_2019\_10-HemaOncol.indd 433 11/7/19 5:05 PM

#### **Polycythemia**

	PLASMA VOLUME	RBC MASS	O <sub>2</sub> SATURATION	EPO LEVELS	ASSOCIATIONS
Relative	<b>4</b>	_	_	_	Dehydration, burns.
Appropriate absolute	-	1	1	<b>†</b>	Lung disease, congenital heart disease, high altitude.
Inappropriate absolute	_	†	_	†	Exogenous EPO: athlete abuse ("blood doping"). Inappropriate EPO secretion: malignancy (eg, renal cell carcinoma, hepatocellular carcinoma).
Polycythemia vera	t	††	_	ţ	EPO ↓ in PCV due to negative feedback suppressing renal EPO production.

**HEMATOLOGY AND ONCOLOGY** 

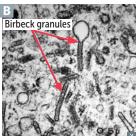
#### **Chromosomal translocations**

TRANSLOCATION	ASSOCIATED DISORDER	NOTES	
t(8;14)	Burkitt (Burk-8) lymphoma (c-myc activation)	The Ig heavy chain genes on chromosome 14	
t(11;14)	Mantle cell lymphoma (cyclin Dl activation)	are constitutively expressed. When other genes (eg, <i>c-myc</i> and <i>BCL-2</i> ) are translocate next to this heavy chain gene region, they a	
t(11;18)	Marginal zone lymphoma		
t(14;18)	Follicular lymphoma (BCL-2 activation)	overexpressed.	
t(15;17)	APL (M3 type of AML; responds to all-trans retinoic acid)		
t(9;22) ( <b>Philadelphia</b> chromosome)	CML (BCR-ABL hybrid), ALL (less common, poor prognostic factor); Philadelphia CreaML cheese		

## Langerhans cell histiocytosis

Collective group of proliferative disorders of Langerhans cells. Presents in a child as lytic bone lesions and skin rash or as recurrent otitis media with a mass involving the mastoid bone. Cells are functionally immature and do not effectively stimulate primary T cells via antigen presentation. Cells express S-100 (mesodermal origin) and CDla. Birbeck granules ("tennis rackets" or rod shaped on EM) are characteristic .

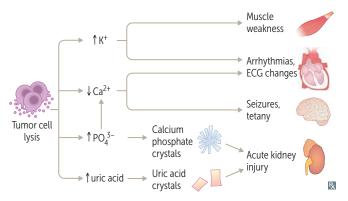




FAS1\_2019\_10-HemaOncol.indd 434 11/7/19 5:05 PM

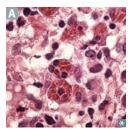
**<sup>↑</sup>** = 1° disturbance

#### **Tumor lysis syndrome**



Oncologic emergency triggered by massive tumor cell lysis, most often in lymphomas/ leukemias. Release of K<sup>+</sup> → hyperkalemia, release of PO<sub>4</sub> <sup>3-</sup> → hyperphosphatemia, hypocalcemia due to Ca<sup>2+</sup> sequestration by PO<sub>4</sub> <sup>3-</sup>. ↑ nucleic acid breakdown → hyperuricemia → acute kidney injury. Prevention and treatment include aggressive hydration, allopurinol, rasburicase.

## Hemophagocytic lymphohistiocytosis



Systemic overactivation of macrophages and cytotoxic T cells → fever, pancytopenia, hepatosplenomegaly, ↑↑↑ serum ferritin levels. Can be inherited or 2° to strong immunologic activation (eg, after EBV infection, malignancy). Bone marrow biopsy shows macrophages phagocytosing marrow elements A.

#### ► HEMATOLOGY AND ONCOLOGY—PHARMACOLOGY

Direct thrombin inhibitors	Bivalirudin, Argatroban, Dabigatran (only oral agent in class).	
MECHANISM	Directly inhibits activity of free and clot-associated thrombin.	
CLINICAL USE	Venous thromboembolism, atrial fibrillation. Can be used in HIT, when heparin is <b>BAD</b> for the patient. Does not require lab monitoring.	
ADVERSE EFFECTS	Bleeding; can reverse dabigatran with idarucizumab. Consider PCC and/or antifibrinolytics (eg, tranexamic acid) if no reversal agent available.	

FAS1\_2019\_10-HemaOncol.indd 435 11/7/19 5:05 PM

**HEMATOLOGY AND ONCOLOGY** 

MECHANISM	Activates antithrombin, which ↓ action of IIa (the	rombin) and factor Xa. Short half-life.
CLINICAL USE	Immediate anticoagulation for pulmonary embo venous thrombosis (DVT). Used during pregna	lism (PE), acute coronary syndrome, MI, deep
ADVERSE EFFECTS	Bleeding, thrombocytopenia (HIT), osteoporosis (antidote), use protamine sulfate (positively chaheparin).	
NOTES	÷ · · · · · · · · · · · · · · · · · · ·	er bioavailability and 2-4× longer half life than about aneously and without laboratory monitoring learance of unfractionated heparin) and are
	Heparin-induced thrombocytopenia (HIT) typ heparin-bound platelet factor 4 (PF4). Antibody thrombosis and thrombocytopenia. Highest risl characterized by nonimmunologic milder drop	v-heparin-PF4 complex activates platelets → k with unfractionated heparin. <b>HIT type 1</b>
Warfarin		
MECHANISM	Inhibits epoxide reductase, which interferes with γ-carboxylation of vitamin K-dependent clotting factors II, VII, IX, X, and proteins C, S. Metabolism affected by polymorphisms in the gene for vitamin K epoxide reductase complex (VKORCI). In laboratory assay, has effect on EXtrinsic pathway and ↑ PT. Long half-life.	The <b>EX-P</b> residen <b>T</b> went to war(farin).
CLINICAL USE	Chronic anticoagulation (eg, venous thromboembolism prophylaxis, and prevention of stroke in atrial fibrillation). Not used in pregnant women (because warfarin, unlike heparin, crosses placenta). Follow PT/INR.	
ADVERSE EFFECTS	Bleeding, teratogenic, skin/tissue necrosis A, drug-drug interactions. Initial risk of hypercoagulation: protein C has a shorter half-life than factors II and X.	For reversal of warfarin, give vitamin K. For rapid reversal, give fresh frozen plasma (FFP) or PCC. Heparin "bridging": heparin frequently used



Initial risk of hypercoagulation: protein C has a shorter half-life than factors II and X. Existing protein C depletes before existing factors II and X deplete, and before warfarin can reduce factors II and X production → hypercoagulation. Skin/tissue necrosis

→ hypercoagulation. Skin/tissue necrosis within first few days of large doses believed to be due to small vessel microthrombosis.

Heparin "bridging": heparin frequently used when starting warfarin. Heparin's activation of antithrombin enables anticoagulation during initial, transient hypercoagulable state caused by warfarin. Initial heparin therapy reduces risk of recurrent venous thromboembolism and skin/tissue necrosis.

Metabolized by cytochrome P-450.

FAS1\_2019\_10-HemaOncol.indd 436 11/7/19 5:05 PM

#### Heparin vs warfarin

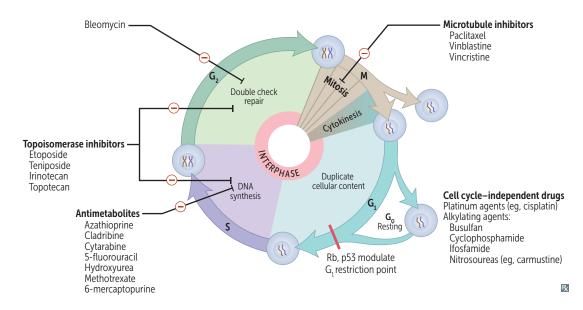
	Heparin	Warfarin	
ROUTE OF ADMINISTRATION	Parenteral (IV, SC)	Oral	
SITE OF ACTION	Blood	Liver	
ONSET OF ACTION	Rapid (seconds)	Slow, limited by half-lives of normal clotting factors	
MECHANISM OF ACTION	Activates antithrombin, which ↓ the action of IIa (thrombin) and factor Xa	Impairs synthesis of vitamin K-dependent clotting factors II, VII, IX, and X, and anticlotting proteins C and S	
DURATION OF ACTION	Hours	Days	
AGENTS FOR REVERSAL	Protamine sulfate	Vitamin K, FFP, PCC	
MONITORING	PTT (intrinsic pathway)	PT/INR (extrinsic pathway)	
CROSSES PLACENTA	No	Yes (teratogenic)	
Direct factor Xa nhibitors	Api <b>Xa</b> ban, rivaro <b>Xa</b> ban.		
MECHANISM	Bind to and directly inhibit factor Xa.		
CLINICAL USE	Treatment and prophylaxis for DVT and PE; stroke prophylaxis in patients with atrial fibrillation. Oral agents do not usually require coagulation monitoring.		
ADVERSE EFFECTS	Bleeding. Reverse with andeXanet alfa.		
Thrombolytics	Alteplase (tPA), reteplase (rPA), streptokinase, ter	necteplase (TNK-tPA).	
MECHANISM	Directly or indirectly aid conversion of plasminogen to plasmin, which cleaves thrombin and fibrir clots. † PT, † PTT, no change in platelet count.		
CLINICAL USE	Early MI, early ischemic stroke, direct thrombol	ysis of severe PE.	
ADVERSE EFFECTS	Bleeding. Contraindicated in patients with active recent surgery, known bleeding diatheses, or seantifibrinolytics (eg, aminocaproic acid, tranex corrections (eg, cryoprecipitate, FFP, PCC).	evere hypertension. Nonspecific reversal with	
ADP receptor inhibitor	s Clopidogrel, prasugrel, ticagrelor (reversible), tic	lopidine.	
MECHANISM	Irreversibly block ADP (P2Y <sub>12</sub> ) receptor, which p expression of glycoproteins IIb/IIIa on platelet	orevents subsequent platelet aggregation. Prevent surface.	
CLINICAL USE	Acute coronary syndrome; coronary stenting. ↓ i	ncidence or recurrence of thrombotic stroke.	
ADVERSE EFFECTS	Neutropenia (ticlopidine). TTP may be seen.		

FAS1\_2019\_10-HemaOncol.indd 437 11/7/19 5:05 PM

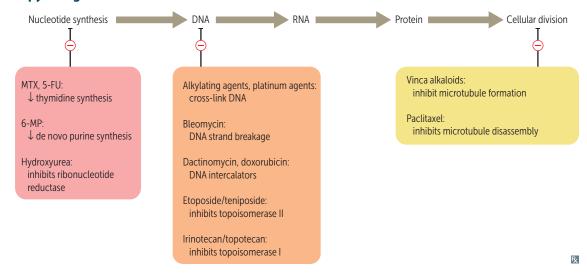
#### Glycoprotein IIb/IIIa

inhibitors	Abciximab, eptifibatide, tirofiban.
MECHANISM	Bind to the glycoprotein receptor IIb/IIIa (fibrinogen receptor) on activated platelets, preventing aggregation. Abciximab is made from monoclonal antibody Fab fragments.
CLINICAL USE	Unstable angina, percutaneous coronary intervention.
ADVERSE EFFECTS	Bleeding, thrombocytopenia.

#### Cancer therapy—cell cycle



#### **Cancer therapy—targets**



FAS1\_2019\_10-HemaOncol.indd 438 11/7/19 5:05 PM

#### **Antitumor antibiotics**

DRUG	MECHANISM	CLINICAL USE	ADVERSE EFFECTS
Bleomycin	Induces free radical formation  → breaks in DNA strands.	Testicular cancer, Hodgkin lymphoma.	Pulmonary fibrosis, skin hyperpigmentation. Minimal myelosuppression.
Dactinomycin (actinomycin D)	Intercalates into DNA, preventing RNA synthesis.	Wilms tumor, Ewing sarcoma, rhabdomyosarcoma. Used for childhood tumors.	Myelosuppression.
Anthracyclines (eg, doxorubicin, daunorubicin)	Generate free radicals. Intercalate in DNA → breaks in DNA → ↓ replication. Interferes with topoisomerase II enzyme.	Solid tumors, leukemias, lymphomas.	Cardiotoxicity (dilated cardiomyopathy), myelosuppression, alopecia. Dexrazoxane (iron chelating agent) used to prevent cardiotoxicity.

FAS1\_2019\_10-HemaOncol.indd 439 11/7/19 5:05 PM

#### **Antimetabolites**

DRUG	MECHANISM <sup>a</sup>	CLINICAL USE	ADVERSE EFFECTS
Azathioprine, 6-mercaptopurine	Purine (thiol) analogs  → ↓ de novo purine synthesis. Activated by HGPRT. Azathioprine is metabolized into 6-MP.	Preventing organ rejection, rheumatoid arthritis, IBD, SLE; used to wean patients off steroids in chronic disease and to treat steroid-refractory chronic disease.	Myelosuppression; GI, liver toxicity.  Azathioprine and 6-MP are metabolized by xanthine oxidase; thus both have † risk of toxicity with allopurinol or febuxostat.
Cladribine	Purine analog → multiple mechanisms (eg, inhibition of DNA polymerase, DNA strand breaks).	Hairy cell leukemia.	Myelosuppression, nephrotoxicity, and neurotoxicity.
Cytarabine (arabinofuranosyl cytidine)	Pyrimidine analog → DNA chain termination. At higher concentrations, inhibits DNA polymerase.	Leukemias (AML), lymphomas.	Myelosuppression with megaloblastic anemia.  CYTarabine causes panCYTopenia.
5-fluorouracil	Pyrimidine analog bioactivated to 5-FdUMP, which covalently complexes with thymidylate synthase and folic acid. Capecitabine is a prodrug.  This complex inhibits thymidylate synthase  → ↓ dTMP → ↓ DNA synthesis.	Colon cancer, pancreatic cancer, actinic keratosis, basal cell carcinoma (topical). Effects enhanced with the addition of leucovorin.	Myelosuppression, palmar- plantar erythrodysesthesia (hand-foot syndrome).
Methotrexate	Folic acid analog that competitively inhibits dihydrofolate reductase  → ↓ dTMP → ↓ DNA synthesis.	Cancers: leukemias (ALL), lymphomas, choriocarcinoma, sarcomas. Non-neoplastic: ectopic pregnancy, medical abortion (with misoprostol), rheumatoid arthritis, psoriasis, IBD, vasculitis.	Myelosuppression, which is reversible with leucovorin (folinic acid) "rescue." Hepatotoxicity. Mucositis (eg, mouth ulcers). Pulmonary fibrosis. Folate deficiency, which may be teratogenic (neural tube defects) without supplementation. Nephrotoxicity.

<sup>&</sup>lt;sup>a</sup>All are S-phase specific except cladribine, which is cell cycle nonspecific.

FAS1\_2019\_10-HemaOncol.indd 440 11/7/19 5:05 PM

#### **Alkylating agents**

DRUG	MECHANISM	CLINICAL USE	ADVERSE EFFECTS
Busulfan	Cross-links DNA.	Used to ablate patient's bone marrow before bone marrow transplantation.	Severe myelosuppression (in almost all cases), pulmonary fibrosis, hyperpigmentation.
Cyclophosphamide, ifosfamide	Cross-link DNA at guanine. Require bioactivation by liver. A nitrogen mustard.	Solid tumors, leukemia, lymphomas, rheumatic disease (eg, SLE, granulomatosis with polyangiitis).	Myelosuppression; SIADH; Fanconi syndrome (ifosfamide); hemorrhagic cystitis and bladder cancer, prevented with mesna (sulfhydryl group of mesna binds toxic metabolites) and adequate hydration.
Nitrosoureas (eg, carmustine, lomustine)	Require bioactivation. Cross blood-brain barrier → CNS. Cross-link DNA.	Brain tumors (including glioblastoma multiforme).	CNS toxicity (convulsions, dizziness, ataxia).
Procarbazine	Cell cycle phase–nonspecific alkylating agent, mechanism unknown. Also a weak MAO inhibitor.	Hodgkin lymphoma, brain tumors.	Bone marrow suppression, pulmonary toxicity, leukemia, disulfiram-like reaction, tyramine-induced hypertensive crisis with consumption of tyramine-rich foods (eg, aged cheese, wine, fava beans).

#### **Microtubule inhibitors**

DRUG	MECHANISM	CLINICAL USE	ADVERSE EFFECTS
Paclitaxel, other taxanes	Hyperstabilize polymerized microtubules in M phase so that mitotic spindle cannot break down (anaphase cannot occur).	Ovarian and breast carcinomas.	Myelosuppression, neuropathy, hypersensitivity.  Taxes stabilize society.
Vincristine, vinblastine	Vinca alkaloids that bind β-tubulin and inhibit its polymerization into microtubules → prevent mitotic spindle formation (M-phase arrest).	Solid tumors, leukemias, Hodgkin and non-Hodgkin lymphomas.	Vineristine: neurotoxicity (areflexia, peripheral neuritis), constipation (including paralytic ileus). Crisps the nerves. Vinblastine: bone marrow suppression. Blasts the bone marrow.

FAS1\_2019\_10-HemaOncol.indd 441 11/7/19 5:05 PM

#### Cisplatin, carboplatin, oxaliplatin

Cross-link DNA.
Testicular, bladder, ovary, GI, and lung carcinomas.
Nephrotoxicity (including Fanconi syndrome), peripheral neuropathy, ototoxicity. Prevent nephrotoxicity with amifostine (free radical scavenger) and chloride (saline) diuresis.

#### Etoposide, teniposide

MECHANISM	Inhibit topoisomerase II $\rightarrow$ † DNA degradation (cell cycle arrest in $G_2$ and $S$ phases).
CLINICAL USE	Solid tumors (particularly testicular and small cell lung cancer), leukemias, lymphomas.
ADVERSE EFFECTS	Myelosuppression, alopecia.

#### Irinotecan, topotecan

MECHANISM	Inhibit topoisomerase I and prevent DNA unwinding and replication.		
CLINICAL USE	Colon cancer (irinotecan); ovarian and small cell lung cancers (topotecan).		
ADVERSE EFFECTS	Severe myelosuppression, diarrhea.		

#### Hydroxyurea

MECHANISM	Inhibits ribonucleotide reductase → ↓ DNA Synthesis (S-phase specific).
CLINICAL USE	Myeloproliferative disorders (eg, CML, polycythemia vera), sickle cell disease († HbF).
ADVERSE EFFECTS	Severe myelosuppression, megaloblastic anemia.

#### Bevacizumab

MECHANISM	Monoclonal antibody against VEGF. Inhibits angiogenesis (BeVacizumab inhibits Blood Vessel formation).
CLINICAL USE	Solid tumors (eg, colorectal cancer, renal cell carcinoma), wet age-related macular degeneration.
ADVERSE EFFECTS	Hemorrhage, blood clots, and impaired wound healing.

#### **Erlotinib**

MECHANISM	EGFR tyrosine kinase inhibitor.
CLINICAL USE	Non-small cell lung cancer.
ADVERSE EFFECTS	Rash, diarrhea.

#### Cetuximab, panitumumab

MECHANISM	Monoclonal antibodies against EGFR.			
CLINICAL USE	Stage IV colorectal cancer (wild-type KRAS), head and neck cancer.			
ADVERSE EFFECTS	Rash, elevated LFTs, diarrhea.			

FAS1\_2019\_10-HemaOncol.indd 442 11/7/19 5:05 PM

MECHANISM	Tyrosine kinase inhibitors of bcr-abl (encoded by Philadelphia chromosome fusion gene in CML) and c-kit (common in GI stromal tumors).				
CLINICAL USE	CML, GI stromal tumors (GISTs).				
ADVERSE EFFECTS	Fluid retention.				
Rituximab					
MECHANISM	Monoclonal antibody against CD20, which is found on most B-cell neoplasms.				
CLINICAL USE	Non-Hodgkin lymphoma, CLL, ITP, rheumatoid arthritis, TTP, AIHA.				
ADVERSE EFFECTS	↑ risk of progressive multifocal leukoencephalopathy.				
Bortezomib, carfil	zomib				
MECHANISM	Proteasome inhibitors, induce arrest at G2-M phase and apoptosis.				
CLINICAL USE	Multiple myeloma, mantle cell lymphoma.				
ADVERSE EFFECTS	Peripheral neuropathy, herpes zoster reactivation.				
Tamoxifen, raloxif					
MECHANISM	Selective estrogen receptor modulators (SERMs)—receptor antagonists in breast and agonists in bone. Block the binding of estrogen to ER $\oplus$ cells.				
CLINICAL USE	Breast cancer treatment (tamoxifen only) and prevention. Raloxifene also useful to prevent osteoporosis.				
CEMICAL 03E					
ADVERSE EFFECTS					
ADVERSE EFFECTS	osteoporosis.  Tamoxifen—partial agonist in endometrium, which † the risk of endometrial cancer.  Raloxifene—no † in endometrial carcinoma (so you can relax!), because it is an estrogen receptor antagonist in endometrial tissue.				
ADVERSE EFFECTS	osteoporosis.  Tamoxifen—partial agonist in endometrium, which † the risk of endometrial cancer.  Raloxifene—no † in endometrial carcinoma (so you can relax!), because it is an estrogen receptor antagonist in endometrial tissue.				
ADVERSE EFFECTS  Trastuzumab	osteoporosis.  Tamoxifen—partial agonist in endometrium, which † the risk of endometrial cancer.  Raloxifene—no † in endometrial carcinoma (so you can relax!), because it is an estrogen recepto antagonist in endometrial tissue.  Both † risk of thromboembolic events (eg, DVT, PE) and "hot flashes."  Monoclonal antibody against HER-2 (c-erbB2), a tyrosine kinase receptor. Helps kill cancer cells that overexpress HER-2 through inhibition of HER-2 initiated cellular signaling and antibody-				

FAS1\_2019\_10-HemaOncol.indd 443 11/7/19 5:05 PM

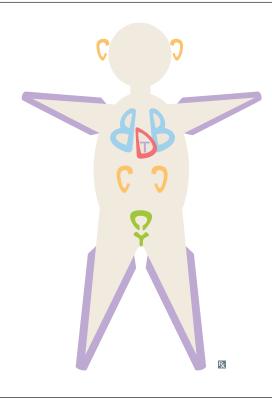
#### Dabrafenib, vemurafenib

MECHANISM	Small molecule inhibitors of <i>BRAF</i> oncogene ⊕ melanoma. <b>VEmuRAF-enib</b> is for <b>V</b> 600 <b>E</b> -
	mutated BRAF inhibition. Often co-administered with MEK inhibitors (eg, trametinib).
CLINICAL USE	Metastatic melanoma.

#### Rasburicase

MECHANISM	Recombinant uricase that catalyzes metabolism of uric acid to allantoin.
CLINICAL USE	Prevention and treatment of tumor lysis syndrome.

#### **Key chemotoxicities**



Cisplatin/Carboplatin → ototoxicity

Vincristine → peripheral neuropathy
Bleomycin, Busulfan → pulmonary fibrosis
Doxorubicin → cardiotoxicity
Trastuzumab → cardiotoxicity
Cisplatin/Carboplatin → nephrotoxicity

**CY**clophosphamide → hemorrhagic cystitis

Nonspecific common toxicities of nearly all cytotoxic chemotherapies include myelosuppression (neutropenia, anemia, thrombocytopenia), GI toxicity (nausea, vomiting, mucositis), alopecia.

FAS1\_2019\_10-HemaOncol.indd 444 11/7/19 5:05 PM

#### HIGH-YIELD SYSTEMS

# Musculoskeletal, Skin, and Connective Tissue

"Rigid, the skeleton of habit alone upholds the human frame."

-Virginia Woolf

"Beauty may be skin deep, but ugly goes clear to the bone."

—Redd Foxx

"The function of muscle is to pull and not to push, except in the case of the genitals and the tongue."

—Leonardo da Vinci

"To thrive in life you need three bones. A wishbone. A backbone. And a funny bone."

-Reba McEntire

This chapter provides information you will need to understand certain anatomical dysfunctions, rheumatic diseases, and dermatologic conditions. Be able to interpret 3D anatomy in the context of radiologic imaging. For the rheumatic diseases, create instructional cases or personas that include the most likely presentation and symptoms: risk factors, gender, important markers (eg, autoantibodies), and other epidemiologic factors. Doing so will allow you to answer the higher order questions that are likely to be asked on the exam.

▶ Anatomy and Physiology 446
 ▶ Pathology 459
 ▶ Dermatology 473
 ▶ Pharmacology 485

FAS1\_2019\_11-Musculo.indd 445 11/7/19 5:23 PM

#### ▶ MUSCULOSKELETAL, SKIN, AND CONNECTIVE TISSUE—ANATOMY AND PHYSIOLOGY

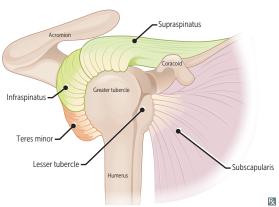
#### **Rotator cuff muscles**



Shoulder muscles that form the rotator cuff:

- Supraspinatus (suprascapular nerve)—
   abducts arm initially (before the action
   of the deltoid); most common rotator
   cuff injury (trauma or degeneration and
   impingement → tendinopathy or tear [arrow
   in A]), assessed by "empty/full can" test
- Infraspinatus (suprascapular nerve) externally rotates arm; pitching injury
- teres minor (axillary nerve)—adducts and externally rotates arm
- Subscapularis (upper and lower subscapular nerves)—internally rotates and adducts arm Innervated primarily by C5-C6.

SItS (small t is for teres minor).



#### **Arm abduction**

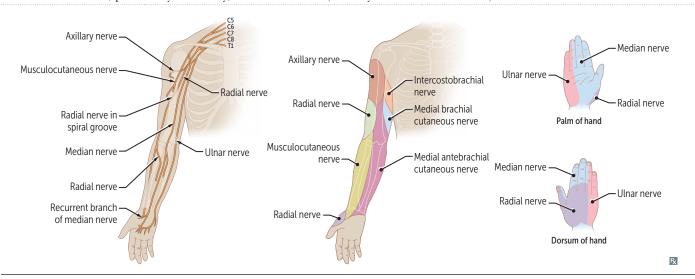
DEGREE	MUSCLE	NERVE	
0°–15°	Supraspinatus	Suprascapular	
15°-100°	Deltoid	Axillary	
>90°	Trapezius	Accessory	
> 100° Serratus Anterior		Long Thoracic (SALT)	

FAS1\_2019\_11-Musculo.indd 446 11/7/19 5:23 PM

#### **Upper extremity nerves**

NERVE	CAUSES OF INJURY	PRESENTATION		
Axillary (C5-C6)	Fractured surgical neck of humerus Anterior dislocation of humerus	Flattened deltoid Loss of arm abduction at shoulder (> 15°) Loss of sensation over deltoid and lateral arm		
Musculocutaneous (C5-C7)	Upper trunk compression	↓ biceps (C5-6) reflex Weakness of forearm flexion and supination Loss of sensation over lateral forearm		
Radial (C5-T1)  Compression of axilla, eg, due to crutches or sleeping with arm over chair ("Saturday nigh palsy")  Midshaft fracture of humerus Repetitive pronation/supination of forearm, eg due to screwdriver use ("finger drop")		Wrist drop: loss of elbow, wrist, and finger extension  I grip strength (wrist extension necessary for maximal action of flexors)  Loss of sensation over posterior arm/forearm and dorsal hand		
Median (C5-T1)  Supracondylar fracture of humerus → proximal lesion of the nerve  Carpal tunnel syndrome and wrist laceration  → distal lesion of the nerve		"Ape hand" and "Pope's blessing"  Loss of wrist flexion, flexion of lateral fingers, thumb opposition, lumbricals of index and middle fingers  Loss of sensation over thenar eminence and dorsal and palmar aspects of lateral 3½ fingers with proximal lesion		
Ulnar (C8-T1)	Fracture of medial epicondyle of humerus "funny bone" (proximal lesion) Fractured hook of hamate (distal lesion) from fall on outstretched hand	"Ulnar claw" on digit extension Radial deviation of wrist upon flexion (proximalesion) Loss of wrist flexion, flexion of medial fingers, abduction and adduction of fingers (interessed actions of medial 2 lumbrical muscles Loss of sensation over medial 1½ fingers including hypothenar eminence		
Recurrent branch of median nerve (C5-T1)	Superficial laceration of palm	"Ape hand" Loss of thenar muscle group: opposition, abduction, and flexion of thumb No loss of sensation		

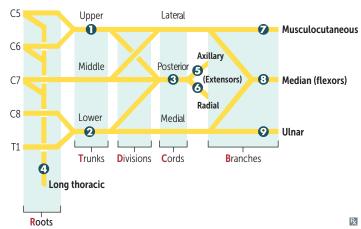
Humerus fractures, proximally to distally, follow the ARM (Axillary → Radial → Median)



FAS1\_2019\_11-Musculo.indd 447 11/7/19 5:23 PM

#### **Brachial plexus lesions**

- Erb palsy ("waiter's tip")
- Klumpke palsy (claw hand)
- 3 Wrist drop
- Winged scapula
- **6** Deltoid paralysis
- "Saturday night palsy" (wrist drop)
- Difficulty flexing elbow, variable sensory loss
- ② Decreased thumb function, "Pope's blessing"
- ② Intrinsic muscles of hand, claw hand



Randy Travis Drinks Cold Beer

CONDITION	INJURY	CAUSES	MUSCLE DEFICIT	FUNCTIONAL DEFICIT	PRESENTATION
Erb palsy ("waiter's tip")	Traction or tear of <b>upper</b> trunk: traction on neck during delivery Adults—trauma	traction on neck	Deltoid, supraspinatus	Abduction (arm hangs by side)	
		Infraspinatus	Lateral rotation (arm medially rotated)		
			Biceps brachii Herb gets DIBs on tips	Flexion, supination (arm extended and pronated)	
Klumpke palsy	Traction or tear of <b>lower</b> trunk: C8-T1 roots	Infants—upward force on arm during delivery Adults—trauma (eg, grabbing a tree branch to break a fall)	Intrinsic hand muscles: lumbricals, interossei, thenar, hypothenar	Total claw hand: lumbricals normally flex MCP joints and extend DIP and PIP joints	399
Thoracic outlet syndrome	Compression of lower trunk and subclavian vessels, most commonly within the scalene triangle	Cervical rib (arrows in A, Pancoast tumor	Same as Klumpke palsy	Atrophy of intrinsic hand muscles; ischemia, pain, and edema due to vascular compression	C5 C6 C7 T1 *
Winged scapula	Lesion of long thoracic nerve, roots C5-C7 ("wings of heaven")	Axillary node dissection after mastectomy, stab wounds	Serratus anterior	Inability to anchor scapula to thoracic cage → cannot abduct arm above horizontal position B	B

FAS1\_2019\_11-Musculo.indd 448 11/7/19 5:23 PM

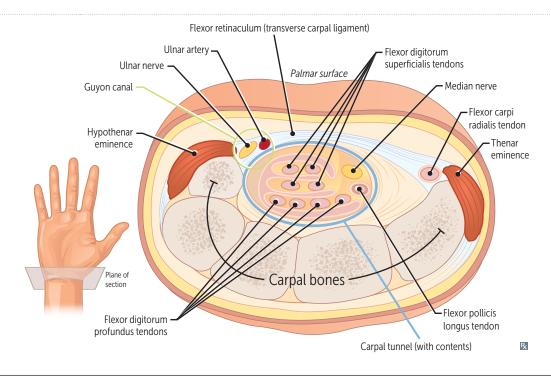
#### **Wrist region**



Scaphoid, Lunate, Triquetrum, Pisiform, Hamate, Capitate, Trapezoid, Trapezium A. (So Long To Pinky, Here Comes The Thumb) Scaphoid (palpable in anatomic snuff box B) is the most commonly fractured carpal bone, typically due to a fall on an outstretched hand. Complications of proximal scaphoid fractures include avascular necrosis and nonunion due to retrograde blood supply from a branch of the radial artery. Fracture not always seen on initial x-ray.

Dislocation of lunate may cause acute carpal tunnel syndrome.

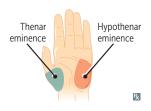




FAS1\_2019\_11-Musculo.indd 449 11/7/19 5:23 PM

#### MUSCULOSKELETAL, SKIN, AND CONNECTIVE TISSUE ► ANATOMY AND PHYSIOLOGY

#### **Hand muscles**



Thenar (median)—Opponens pollicis, Abductor pollicis brevis, Flexor pollicis brevis, superficial head (deep head by ulnar nerve).

Hypothenar (ulnar)—Opponens digiti minimi, Abductor digiti minimi, Flexor digiti minimi brevis.

Dorsal interossei (ulnar)—abduct the fingers. Palmar interossei (ulnar)—adduct the fingers. Lumbricals (lst/2nd, median; 3rd/4th, ulnar)—flex at the MCP joint, extend PIP and DIP joints.

Both groups perform the same functions: Oppose, Abduct, and Flex (OAF).

DAB = Dorsals ABduct. PAD = Palmars ADduct.

FAS1\_2019\_11-Musculo.indd 450 11/7/19 5:23 PM

**Distortions of the hand** At rest, a balance exists between the extrinsic flexors and extensors of the hand, as well as the intrinsic muscles of the hand-particularly the lumbrical muscles (flexion of MCP, extension of DIP and PIP joints).

> "Clawing"—seen best with distal lesions of median or ulnar nerves. Remaining extrinsic flexors of the digits exaggerate the loss of the lumbricals → fingers extend at MCP, flex at DIP and PIP

Deficits less pronounced in **proximal** lesions; deficits present during voluntary flexion of the digits.

SIGN	"Ulnar claw"	"Pope's blessing"	"Median claw"	"OK gesture"
PRESENTATION				
CONTEXT	Extending fingers/at rest	Making a fist	Extending fingers/at rest	Making a fist
LOCATION OF LESION	Distal ulnar nerve	Proximal median nerve	Distal median nerve	Proximal ulnar nerve

Note: Atrophy of the thenar eminence (unopposable thumb → "ape hand") can be seen in median nerve lesions, while atrophy of the hypothenar eminence can be seen in ulnar nerve lesions.

#### **Actions of hip muscles**

ACTION	MUSCLES
Abductors	Gluteus medius, gluteus minimus
Adductors	Adductor magnus, adductor longus, adductor brevis
Extensors	Gluteus maximus, semitendinosus, semimembranosus
Flexors	Iliopsoas, rectus femoris, tensor fascia lata, pectineus, sartorius
Internal rotation	Gluteus medius, gluteus minimus, tensor fascia latae
External rotation	Iliopsoas, gluteus maximus, piriformis, obturator

FAS1\_2019\_11-Musculo.indd 451 11/7/19 5:23 PM

#### **Lower extremity nerves**

NERVE	INNERVATION	CAUSE OF INJURY	PRESENTATION/COMMENTS
Iliohypogastric (T12-L1)	Sensory—suprapubic region Motor—transversus abdominis and internal oblique	Abdominal surgery	Burning or tingling pain in surgical incision site radiating to inguinal and suprapubic region
Genitofemoral nerve (L1-L2)	Sensory—scrotum/labia majora, medial thigh Motor—cremaster	Laparoscopic surgery	upper medial thigh and anterior thigh sensation beneath the inguinal ligament (lateral part of the femoral triangle); absent cremasteric reflex
Lateral femoral cutaneous (L2-L3)	Sensory—anterior and lateral thigh	Tight clothing, obesity, pregnancy, pelvic procedures	↓ thigh sensation (anterior and lateral)
Obturator (L2-L4)	Sensory—medial thigh Motor—obturator externus, adductor longus, adductor brevis, gracilis, pectineus, adductor magnus	Pelvic surgery	↓ thigh sensation (medial) and adduction
Femoral (L2-L4)	Sensory—anterior thigh, medial leg Motor—quadriceps, iliacus, pectineus, sartorius	Pelvic fracture	↓ leg extension (↓ patellar reflex)
Sciatic (L4-S3)	Motor—semitendinosus, semimembranosus, biceps femoris, adductor magnus	Herniated disc, posterior hip dislocation	Splits into common peroneal and tibial nerves

FAS1\_2019\_11-Musculo.indd 452 11/7/19 5:23 PM

#### Lower extremity nerves (continued)

NERVE	INNERVATION	CAUSE OF INJURY	PRESENTATION/COMMENTS
Common (fibular) peroneal (L4-S2)	Superficial peroneal nerve:  Sensory—dorsum of foot (except webspace between hallux and 2nd digit)  Motor—peroneus longus and brevis  Deep peroneal nerve:  Sensory—webspace between hallux and 2nd digit  Motor—tibialis anterior	Trauma or compression of lateral aspect of leg, fibular neck fracture	PED = Peroneal Everts and Dorsiflexes; if injured, foot dropPED Loss of sensation on dorsum of foot Foot drop—inverted and plantarflexed at rest, loss of eversion and dorsiflexion; "steppage gait"
Tibial (L4-S3)	Sensory—sole of foot Motor—biceps femoris (long head), triceps surae, plantaris, popliteus, flexor muscles of foot	Knee trauma, Baker cyst (proximal lesion); tarsal tunnel syndrome (distal lesion)	TIP = Tibial Inverts and Plantarflexes; if injured, can't stand on TIPtoes Inability to curl toes and loss of sensation on sole; in proximal lesions, foot everted at rest with loss of inversion and plantar flexion
Superior gluteal (L4-S1)  Trendelenburg sign	Motor—gluteus medius, gluteus minimus, tensor fascia latae	Iatrogenic injury during intramuscular injection to superomedial gluteal region (prevent by choosing superolateral quadrant, preferably anterolateral region)	Trendelenburg sign/gait— pelvis tilts because weight- bearing leg cannot maintain alignment of pelvis through hip abduction Lesion is contralateral to the side of the hip that drops, ipsilateral to extremity on which the patient stands
Inferior gluteal (L5-S2)	Motor—gluteus maximus	Posterior hip dislocation	Difficulty climbing stairs, rising from seated position; loss of hip extension
Pudendal (S2-S4)	Sensory—perineum Motor—external urethral and anal sphincters	Stretch injury during childbirth, prolonged cycling, horseback riding	sensation in perineum and genital area; can cause fecal and/or urinary incontinence Can be blocked with local anesthetic during childbirth using ischial spine as a landmark for injection

FAS1\_2019\_11-Musculo.indd 453 11/7/19 5:23 PM

#### **SECTION III**

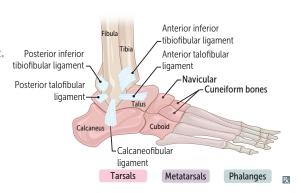
#### Lateral femoral condyle to anterior tibia: ACL. **Knee exam** Femur Medial femoral condyle to posterior tibia: PCL. LAMP. Lateral Medial condyle condyle ACL **PCL** MCL LCL Lateral Medial meniscus meniscus Fibula Tibia TEST PROCEDURE Bending knee at 90° angle, † anterior gliding of **Anterior drawer sign** tibia (relative to femur) due to ACL injury ACL tear Lachman test also tests ACL, but is more sensitive († anterior gliding of tibia [relative to femur] with knee bent at 30° angle) Ŗ Posterior drawer sign Bending knee at 90° angle, † posterior gliding of tibia due to PCL injury PCL tear Ŗ **Abnormal passive** Knee either extended or at $\sim 30^{\circ}$ angle, lateral abduction (valgus) force → medial space widening of Abduction (valgus) MCL tear tibia → MCL injury force Ŗ **Abnormal passive** Knee either extended or at $\sim 30^{\circ}$ angle, medial adduction (varus) force → lateral space widening of tibia Adduction LCL tear (varus) → LCL injury force Ŗ During flexion and extension of knee with McMurray test Internal Lateral rotation of tibia/foot (LIME): rotation meniscal Pain, "popping" on internal rotation and tear varus force and varus force → Lateral meniscal tear (Internal rotation stresses lateral meniscus) Pain, "popping" on external rotation and External Medial valgus force → Medial meniscal tear rotation meniscal tear (External rotation stresses medial meniscus) valgus force Ŗ

FAS1\_2019\_11-Musculo.indd 454 11/7/19 5:23 PM

#### **Ankle sprains**

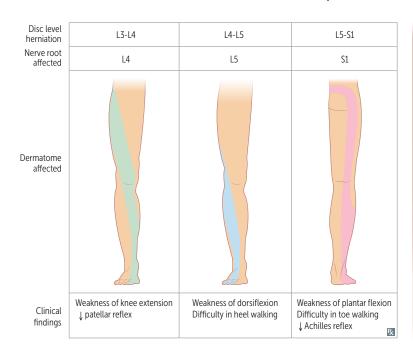
Anterior TaloFibular ligament—most common ankle sprain overall, classified as a low ankle sprain. Due to overinversion/supination of foot. Anterior inferior tibiofibular ligament—most common high ankle sprain.

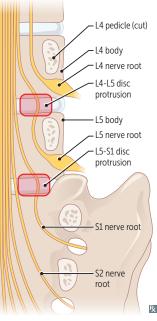
Always Tears First.



## Signs of lumbosacral radiculopathy

Paresthesia and weakness related to specific lumbosacral spinal nerves. Intervertebral disc (nucleus pulposus) herniates posterolaterally through annulus fibrosus (outer ring) into central canal due to thin posterior longitudinal ligament and thicker anterior longitudinal ligament along midline of vertebral bodies. Nerve affected is usually below the level of herniation.





#### **Neurovascular pairing**

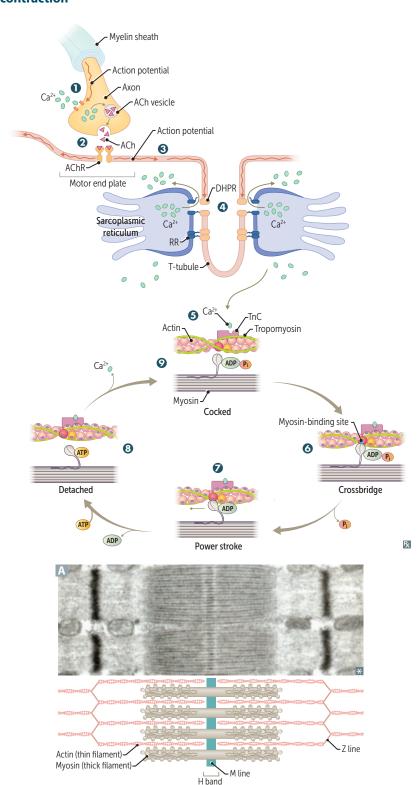
Nerves and arteries are frequently named together by the bones/regions with which they are associated. The following are exceptions to this naming convention.

LOCATION	NERVE	ARTERY
Axilla/lateral thorax	Long thoracic	Lateral thoracic
Surgical neck of humerus	Axillary	Posterior circumflex
Midshaft of humerus	Radial	Deep brachial
Distal humerus/cubital fossa	Median	Brachial
Popliteal fossa	Tibial	Popliteal
Posterior to medial malleolus	Tibial	Posterior tibial

FAS1\_2019\_11-Musculo.indd 455

## Motoneuron action potential to muscle contraction

T-tubules are extensions of plasma membrane in contact with the sarcoplasmic reticulum, allowing for coordinated contraction of striated muscles.



A band

Sarcomere (Z line to Z line)

- Action potential opens presynaptic voltagegated Ca<sup>2+</sup> channels, inducing acetylcholine (ACh) release.
- 2 Postsynaptic ACh binding leads to muscle cell depolarization at the motor end plate.
- 3 Depolarization travels over the entire muscle cell and deep into the muscle via the T-tubules.
- Membrane depolarization induces conformational changes in the voltage-sensitive dihydropyridine receptor (DHPR) and its mechanically coupled ryanodine receptor (RR) → Ca<sup>2+</sup> release from the sarcoplasmic reticulum into the cytoplasm.
- **5** Tropomyosin is blocking myosin-binding sites on the actin filament. Released Ca<sup>2+</sup> binds to troponin C (TnC), shifting tropomyosin to expose the myosin-binding sites.
- **6** The myosin head binds strongly to actin, forming a crossbridge. P<sub>i</sub> is then released, initiating the power stroke.
- During the power stroke, force is produced as myosin pulls on the thin filament A. Muscle shortening occurs, with shortening of H and I bands and between Z lines (HIZ shrinkage). The A band remains the same length (A band is Always the same length). ADP is released at the end of the power stroke.
- **3** Binding of new ATP molecule causes detachment of myosin head from actin filament. Ca<sup>2+</sup> is resequestered.
- ② ATP hydrolysis into ADP and P₁ results in myosin head returning to high-energy position (cocked). The myosin head can bind to a new site on actin to form a crossbridge if Ca²+ remains available.

FAS1\_2019\_11-Musculo.indd 456 11/7/19 5:23 PM

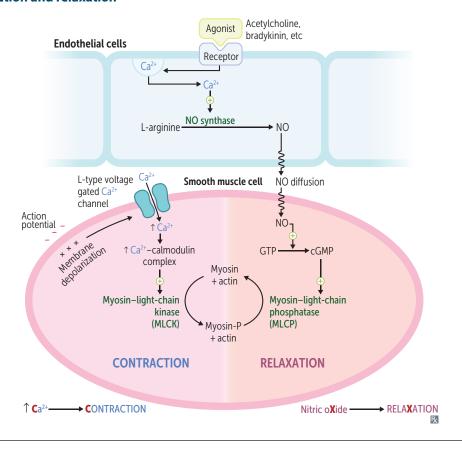
Ŗ

I band

#### **Types of muscle fibers**

	Type I	Type II
CONTRACTION VELOCITY	Slow	Fast
FIBER COLOR	Red	White
PREDOMINANT METABOLISM	Oxidative phosphorylation → sustained contraction	Anaerobic glycolysis
MITOCHONDRIA, MYOGLOBIN	t	↓
TYPE OF TRAINING	Endurance training	Weight/resistance training, sprinting
NOTES	Think "1 slow red ox"	

#### Vascular smooth muscle contraction and relaxation

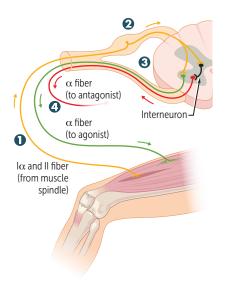


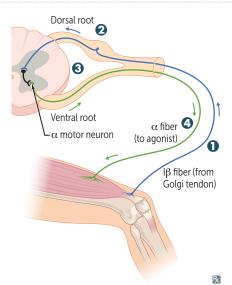
FAS1\_2019\_11-Musculo.indd 457 11/7/19 5:23 PM

**Bone formation** 

Muscle	proprioce	ptors S	Specialized	sensory	receptor	s that rela	y information	about muscle d	lynamics.
--------	-----------	---------	-------------	---------	----------	-------------	---------------	----------------	-----------

Golgi tendon organ  h → ② via  1 tension → ② via DRG → ③ activation of inhibitory interneuron → ④ inhibition of
α motor neuron agonist muscle (reduced tension within muscle and tendon)  ng) and activation  n).
sensory axons Tendons/type Ib sensory axons
↑ muscle force
1





Endochondral	Bones of axial skeleton, appendicular skeleton, and base of skull. Cartilaginous model of bone is
ossification	first made by chondrocytes. Osteoclasts and osteoblasts later replace with woven bone and then
	remodel to lamellar bone. In adults, woven bone occurs after fractures and in Paget disease.
	Defective in achondroplasia.

	Delective in actionaropiasia.
Membranous ossification	Bones of calvarium, facial bones, and clavicle. Woven bone formed directly without cartilage. Later remodeled to lamellar bone.
	, , , , , , , , , , , , , , , , , , , ,

FAS1\_2019\_11-Musculo.indd 458 11/7/19 5:23 PM

#### **Cell biology of bone**

Builds bone by secreting collagen and catalyzing mineralization in alkaline environment via ALP. Differentiates from mesenchymal stem cells in periosteum. Osteoblastic activity measured by bone ALP, osteocalcin, propeptides of type I procollagen.
Dissolves ("crushes") bone by secreting H <sup>+</sup> and collagenases. Differentiates from a fusion of monocyte/macrophage lineage precursors. RANK receptors on osteoclasts are stimulated by RANKL (RANK ligand, expressed on osteoblasts). OPG (osteoprotegerin, a RANKL decoy receptor) binds RANKL to prevent RANK-RANKL interaction → ↓ osteoclast activity.
At low, intermittent levels, exerts anabolic effects (building bone) on osteoblasts and osteoclasts (indirect). Chronically † PTH levels (1° hyperparathyroidism) cause catabolic effects (osteitis fibrosa cystica).
Inhibits apoptosis in bone-forming osteoblasts and induces apoptosis in bone-resorbing osteoclasts. Causes closure of epiphyseal plate during puberty. Estrogen deficiency (surgical or postmenopausal) → ↑ cycles of remodeling and bone resorption → ↑ risk of osteoporosis.

#### ► MUSCULOSKELETAL, SKIN, AND CONNECTIVE TISSUE—PATHOLOGY

#### Overuse injuries of the elbow

Medial epicondylitis (golfer's elbow)	Repetitive flexion (forehand shots) or idiopathic → pain near medial epicondyle.
Lateral epicondylitis (tennis elbow)	Repetitive extension (backhand shots) or idiopathic → pain near lateral epicondyle.

#### Wrist and hand injuries

## Metacarpal neck fracture



Also called boxer's fracture. Common fracture caused by direct blow with a closed fist (eg, from punching a wall). Most commonly seen in 4th and 5th metacarpals A.

## Carpal tunnel syndrome



Entrapment of median nerve in carpal tunnel (between transverse carpal ligament and carpal bones) → nerve compression → paresthesia, pain, and numbness in distribution of median nerve. Thenar eminence atrophies **B** but sensation spared, because palmar cutaneous branch enters hand external to carpal tunnel.

Suggested by ⊕ Tinel sign (percussion of wrist causes tingling) and Phalen maneuver (90° flexion of wrist causes tingling).

Associated with pregnancy (due to edema), rheumatoid arthritis, hypothyroidism, diabetes, acromegaly, dialysis-related amyloidosis; may

be associated with repetitive use.

## Guyon canal syndrome

Compression of ulnar nerve at wrist. Classically seen in cyclists due to pressure from handlebars.

FAS1\_2019\_11-Musculo.indd 459 11/7/19 5:23 PM

#### **Clavicle fractures**

Common in children and as birth trauma. Usually caused by a fall on outstretched hand or by direct trauma to shoulder. Weakest point at the junction of middle and lateral thirds; fractures at the middle third segment are most common. Presents as shoulder drop, shortened clavicle (lateral fragment is depressed due to arm weight and medially rotated by arm adductors [eg, pectoralis major]).

#### **Common hip and knee conditions**

#### "Unhappy triad"

Common injury in contact sports due to lateral force applied to a planted foot. Consists of damage to the ACL A, MCL, and medial meniscus (attached to MCL). However, lateral meniscus involvement is more common than medial meniscus involvement in conjunction with ACL and MCL injury. Presents with acute pain and signs of joint instability.



#### **Prepatellar bursitis**

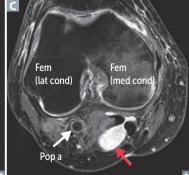
Inflammation of the prepatellar bursa in front of the kneecap (red arrow in **B**). Can be caused by repeated trauma or pressure from excessive kneeling (also called "housemaid's knee").

#### **Baker cyst**

Popliteal fluid collection (red arrow in c) in gastrocnemius-semimembranosus bursa commonly communicating with synovial space and related to chronic joint disease (eg, osteoarthritis, rheumatoid arthritis).







FAS1\_2019\_11-Musculo.indd 460 11/7/19 5:23 PM

#### **Common musculoskeletal conditions**

De Quervain tenosynovitis	Noninflammatory thickening of abductor pollicis longus and extensor pollicis brevis tendons  → pain or tenderness at radial styloid. ⊕ Finkelstein test (pain at radial styloid with active or passive stretch of thumb tendons). ↑ risk in new mothers, golfers, racquet sport players, "thumb" texters.
Ganglion cyst	Fluid-filled swelling overlying joint or tendon sheath, most commonly at dorsal side of wrist. Arises from herniation of dense connective tissue.
Iliotibial band syndrome	Overuse injury of lateral knee that occurs primarily in runners. Pain develops 2° to friction of iliotibial band against lateral femoral epicondyle.
Limb compartment syndrome	† pressure within fascial compartment of a limb → venous outflow obstruction and arteriolar collapse → anoxia and necrosis. Causes include significant long bone fractures, reperfusion injury, animal venoms. Presents with severe pain and tense, swollen compartments with passive stretch of muscles in the affected compartment. Motor deficits are late sign of irreversible muscle and nerve damage.
Medial tibial stress syndrome	Also called shin splints. Common cause of shin pain and diffuse tenderness in runners and military recruits. Caused by bone resorption that outpaces bone formation in tibial cortex.
Plantar fasciitis	Inflammation of plantar aponeurosis characterized by heel pain (worse with first steps in the morning or after period of inactivity) and tenderness.

#### **Childhood musculoskeletal conditions**

Developmental dysplasia of the hip	Abnormal acetabulum development in newborns. Major risk factor includes breech presentation. Results in hip instability/dislocation. Commonly tested with Ortolani and Barlow maneuvers (manipulation of newborn hip reveals a "clunk"). Confirmed via ultrasound (x-ray not used until ~4–6 months because cartilage is not ossified).
Legg-Calvé-Perthes disease	Idiopathic avascular necrosis of femoral head. Commonly presents between 5–7 years with insidious onset of hip pain that may cause child to limp. More common in males (4:1 ratio). Initial x-ray often normal.
Osgood-Schlatter disease	Also called traction apophysitis. Overuse injury caused by repetitive strain and chronic avulsion of the secondary ossification center of proximal tibial tubercle. Occurs in adolescents after growth spurt. Common in running and jumping athletes. Presents with progressive anterior knee pain.



Patellofemoral
syndrome
Overuse injury that commonly presents in young, female athletes as anterior knee pain.
Exacerbated by prolonged sitting or weight-bearing on a flexed knee. Treatment: NSAIDs, thigh muscle strengthening.

## Radial head subluxation

Also called nursemaid's elbow.

Common elbow injury in children < 5 years. Caused by a sudden pull on the arm → immature annular ligament slips over head of radius. Injured arm held in extended/slightly flexed and pronated position.

## Slipped capital femoral epiphysis

Classically presents in an obese young adolescent with hip/knee pain and altered gait. Increased axial force on femoral head → epiphysis displaces relative to femoral neck (like a scoop of ice cream slipping off a cone). Diagnosed via x-ray.

FAS1\_2019\_11-Musculo.indd 461 11/7/19 5:23 PM

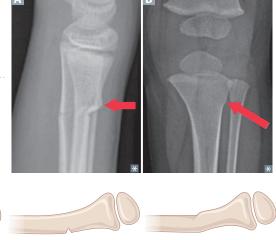
#### **Common pediatric fractures**

#### **Greenstick fracture**

Incomplete fracture extending partway through width of bone A following bending stress; bone fails on tension side; compression side intact (compare to torus fracture). Bone is bent like a green twig.

#### Torus (buckle) fracture

Axial force applied to immature bone → cortex buckles on compression (concave) side and fractures B. Tension (convex) side remains solid (intact).





Norma Complete fracture

Greenstick fracture

Torus fracture

#### **Achondroplasia**

Failure of longitudinal bone growth (endochondral ossification) → short limbs. Membranous ossification is not affected → large head relative to limbs. Constitutive activation of fibroblast growth factor receptor (FGFR3) actually inhibits chondrocyte proliferation. > 85% of mutations occur sporadically; autosomal dominant with full penetrance (homozygosity is lethal). Associated with † paternal age. Most common cause of short-limbed dwarfism.

#### Osteoporosis



Trabecular (spongy) and cortical bone lose mass Can lead to vertebral compression despite normal bone mineralization and lab values (serum Ca<sup>2+</sup> and PO<sub>4</sub><sup>3-</sup>).

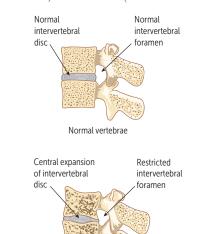
Most commonly due to † bone resorption related to ↓ estrogen levels and old age. Can be 2° to drugs (eg, steroids, alcohol, anticonvulsants, anticoagulants, thyroid replacement therapy) or other conditions (eg, hyperparathyroidism, hyperthyroidism, multiple myeloma, malabsorption syndromes, anorexia).

Diagnosed by bone mineral density measurement by DEXA (dual-energy X-ray absorptiometry) at the lumbar spine, total hip, and femoral neck, with a T-score of  $\leq -2.5$  or by a fragility fracture (eg, fall from standing height, minimal trauma) at hip or vertebra. One time screening recommended in women  $\geq$  65 years old.

Prophylaxis: regular weight-bearing exercise and adequate Ca<sup>2+</sup> and vitamin D intake throughout adulthood.

Treatment: bisphosphonates, teriparatide, SERMs, rarely calcitonin; denosumab (monoclonal antibody against RANKL).

fractures A — acute back pain, loss of height, kyphosis. Also can present with fractures of femoral neck, distal radius (Colles fracture).



Mild compression fracture

FAS1 2019 11-Musculo.indd 462 11/7/19 5:23 PM

#### Osteopetrosis



Failure of normal bone resorption due to defective osteoclasts → thickened, dense bones that are prone to fracture. Mutations (eg, carbonic anhydrase II) impair ability of osteoclast to generate acidic environment necessary for bone resorption. Overgrowth of cortical bone fills marrow space → pancytopenia, extramedullary hematopoiesis. Can result in cranial nerve impingement and palsies due to narrowed foramina.

X-rays show diffuse symmetric sclerosis (bone-in-bone, "stone bone" A). Bone marrow transplant is potentially curative as osteoclasts are derived from monocytes.

#### Osteomalacia/rickets



Defective mineralization of osteoid (osteomalacia) or cartilaginous growth plates (rickets, only in children). Most commonly due to vitamin D deficiency.

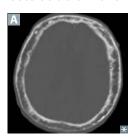
X-rays show osteopenia and "Looser zones" (pseudofractures) in osteomalacia, epiphyseal widening and metaphyseal cupping/fraying in rickets. Children with rickets have pathologic bow legs (genu varum A), bead-like costochondral junctions (rachitic rosary B), craniotabes (soft skull).

↓ vitamin D → ↓ serum Ca<sup>2+</sup> → ↑ PTH secretion
 → ↓ serum PO<sub>4</sub><sup>3-</sup>.

Hyperactivity of osteoblasts → ↑ ALP.



#### **Osteitis deformans**



Also called Paget disease of bone. Common, localized disorder of bone remodeling caused by † osteoclastic activity followed by † osteoblastic activity that forms poor-quality bone. Serum Ca<sup>2+</sup>, phosphorus, and PTH levels are normal. † ALP. Mosaic pattern of woven and lamellar bone (osteocytes within lacunae in chaotic juxtapositions); long bone chalk-stick fractures. † blood flow from † arteriovenous shunts may cause high-output heart failure. † risk of osteosarcoma.

Hat size can be increased due to skull thickening A; hearing loss is common due to auditory foramen narrowing.

Stages of Paget disease:

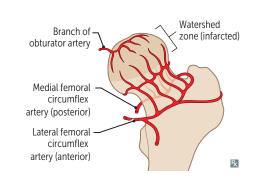
- Lytic—osteoclasts
- Mixed—osteoclasts + osteoblasts
- Sclerotic—osteoblasts
- Quiescent—minimal osteoclast/osteoblast activity

Treatment: bisphosphonates.

## Avascular necrosis of bone



Infarction of bone and marrow, usually very painful. Most common site is femoral head (watershed zone) A (due to insufficiency of medial circumflex femoral artery). Causes include Corticosteroids, Alcoholism, Sickle cell disease, Trauma, SLE, "the Bends" (caisson/decompression disease), LEgg-Calvé-Perthes disease (idiopathic), Gaucher disease, Slipped capital femoral epiphysis—CASTS Bend LEGS.



FAS1\_2019\_11-Musculo.indd 463 11/7/19 5:23 PM

#### Lab values in bone disorders

DISORDER	SERUM Ca <sup>2+</sup>	PO <sub>4</sub> 3-	ALP	PTH	COMMENTS
Osteoporosis	_	_	_	_	↓ bone mass
Osteopetrosis	/ <b>↓</b>	_	_	_	Dense, brittle bones. Ca²+ ↓ in severe, malignant disease
Paget disease of bone	_	_	†	_	Abnormal "mosaic" bone architecture
Osteitis fibrosa cystica					
Primary hyperparathyroidism	t	1	t	t	"Brown tumors" due to fibrous replacement of bone, subperiosteal thinning Idiopathic or parathyroid hyperplasia, adenoma, carcinoma
Secondary hyperparathyroidism	1	Ť	<b>†</b>	Ť	Often as compensation for CKD (\$\ddagger\$ PO <sub>4</sub> \$\dagger^3\$- excretion and production of activated vitamin D)
Osteomalacia/rickets	1	ţ	†	†	Soft bones; vitamin D deficiency also causes 2° hyperparathyroidism
Hypervitaminosis D	†	1	_	ţ	Caused by oversupplementation or granulomatous disease (eg, sarcoidosis)

 $↑ ↓ = 1^{\circ}$  change.

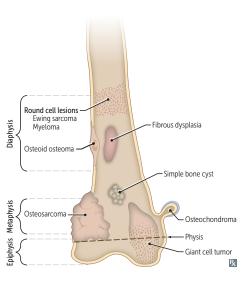
**Primary bone tumors** Metastatic disease is more common than 1° bone tumors. Benign bone tumors that start with O are more common in boys.

	more common in boys.		
TUMOR TYPE	EPIDEMIOLOGY	LOCATION	CHARACTERISTICS
Benign tumors			
Osteochondroma	Most common benign bone tumor Males < 25 years old	Metaphysis of long bones	Lateral bony projection of growth plate (continuous with marrow space) covered by cartilaginous cap A Rarely transforms to chondrosarcoma
Osteoma	Middle age	Surface of facial bones	Associated with Gardner syndrome
Osteoid osteoma	Adults < 25 years old Males > females	Cortex of long bones	Presents as bone pain (worse at night) that is relieved by NSAIDs Bony mass (< 2 cm) with radiolucent osteoid core     B
Osteoblastoma	Males > females	Vertebrae	Similar histology to osteoid osteoma Larger size (> 2 cm), pain unresponsive to NSAIDs
Chondroma		Medulla of small bones of hand and feet	Benign tumor of cartilage
Giant cell tumor	20–40 years old	Epiphysis of long bones (often in knee region)	Locally aggressive benign tumor Neoplastic mononuclear cells that express RANKL and reactive multinucleated giant (osteoclast-like) cells. "Osteoclastoma" "Soap bubble" appearance on x-ray

FAS1\_2019\_11-Musculo.indd 464 11/7/19 5:23 PM

#### **Primary bone tumors (continued)**

	Accounts for 20% of 1°	M. 1	
		M . 1 : (1 1	
	bone cancers. Peak incidence of 1° tumor in males < 20 years. Less common in elderly; usually 2° to predisposing factors, such as Paget disease of bone, bone infarcts, radiation, familial retinoblastoma, Li-Fraumeni syndrome.	Metaphysis of long bones (often in knee region).	Pleomorphic osteoid-producing cells (malignant osteoblasts).  Presents as painful enlarging mass or pathologic fractures.  Codman triangle (from elevation of periosteum) or sunburst pattern on x-ray (think of an osteocod (bone fish) swimming in the sun).  Aggressive. 1° usually responsive to treatment (surgery, chemotherapy), poor prognosis for 2°.
Chondrosarcoma		Medulla of pelvis, proximal femur and humerus.	Tumor of malignant chondrocytes.
	Most common in Caucasians. Generally boys < 15 years old.	Diaphysis of long bones (especially femur), pelvic flat bones.	Anaplastic small blue cells of neuroectodermal origin (resemble lymphocytes) .  Differentiate from conditions with similar morphology (eg, lymphoma, chronic osteomyelitis) by testing for t(11;22) (fusion protein EWS-FLII). "Onion skin" periosteal reaction in bone.  Aggressive with early metastases, but responsive to chemotherapy.  11 + 22 = 33 (Patrick Ewing's jersey number).



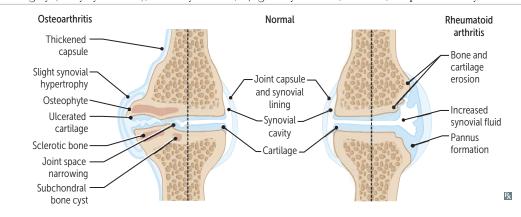


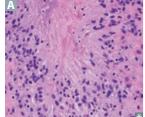
FAS1\_2019\_11-Musculo.indd 465 11/7/19 5:23 PM

#### Osteoarthritis vs rheumatoid arthritis

	Osteoarthritis	Rheumatoid arthritis
PATHOGENESIS	Mechanical—wear and tear destroys articular cartilage (degenerative joint disorder)  → inflammation with inadequate repair. Chondrocytes mediate degradation and inadequate repair.	Autoimmune—inflammation A induces formation of pannus (proliferative granulation tissue), which erodes articular cartilage and bone.
PREDISPOSING FACTORS	Age, female, obesity, joint trauma.	Female, HLA-DR4 (4-walled "rheum"), smoking. ⊕ rheumatoid factor (IgM antibody that targets IgG Fc region; in 80%), anti-cyclic citrullinated peptide antibody (more specific).
PRESENTATION	Pain in weight-bearing joints after use (eg, at the end of the day), improving with rest.  Asymmetric joint involvement. Knee cartilage loss begins medially ("bowlegged"). No systemic symptoms.	Pain, swelling, and morning stiffness lasting > 1 hour, improving with use. Symmetric joint involvement. Systemic symptoms (fever, fatigue, weight loss). Extraarticular manifestations common.*
JOINT FINDINGS	Osteophytes (bone spurs), joint space narrowing, subchondral sclerosis and cysts. Synovial fluid noninflammatory (WBC < 2000/mm³). Development of Heberden nodes <b>B</b> (at DIP) and Bouchard nodes <b>C</b> (at PIP), and 1st CMC; not MCP.	Erosions, juxta-articular osteopenia, soft tissue swelling, subchondral cysts, joint space narrowing. Deformities: cervical subluxation, ulnar finger deviation, swan neck D, boutonniere E. Involves MCP, PIP, wrist; not DIP or 1st CMC.
TREATMENT	Activity modification, acetaminophen, NSAIDs, intra-articular glucocorticoids.	NSAIDs, glucocorticoids, disease-modifying agents (eg, methotrexate, sulfasalazine), biologic agents (eg, TNF-α inhibitors).

<sup>\*</sup>Extraarticular manifestations include rheumatoid nodules (fibrinoid necrosis with palisading histiocytes) in subcutaneous tissue and lung (+ pneumoconiosis → Caplan syndrome), interstitial lung disease, pleuritis, pericarditis, anemia of chronic disease, neutropenia + splenomegaly (Felty syndrome), AA amyloidosis, Sjögren syndrome, scleritis, carpal tunnel syndrome.













FAS1\_2019\_11-Musculo.indd 466 11/7/19 5:23 PM

#### Gout

#### FINDINGS

Acute inflammatory monoarthritis caused by precipitation of monosodium urate crystals in joints A. Risk factors: male sex, hypertension, obesity, diabetes, dyslipidemia, alcohol use. Strongest risk factor is hyperuricemia, which can be caused by:

- Underexcretion of uric acid (90% of patients)—largely idiopathic, potentiated by renal failure; can be exacerbated by certain medications (eg, thiazide diuretics).
- Overproduction of uric acid (10% of patients)—Lesch-Nyhan syndrome, PRPP excess, † cell turnover (eg, tumor lysis syndrome), von Gierke disease.

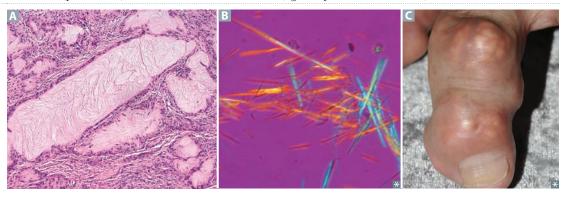
Crystals are needle shaped and ⊖ birefringent under polarized light (yellow under parallel light, blue under perpendicular light B). Serum uric acid levels may be normal during an acute attack.

SYMPTOMS

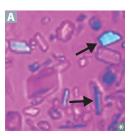
Asymmetric joint distribution. Joint is swollen, red, and painful. Classic manifestation is painful MTP joint of big toe (podagra). Tophus formation **()** (often on external ear, olecranon bursa, or Achilles tendon). Acute attack tends to occur after a large meal with foods rich in purines (eg, red meat, seafood), trauma, surgery, dehydration, diuresis, or alcohol consumption (alcohol metabolites compete for same excretion sites in kidney as uric acid → ↓ uric acid secretion and subsequent buildup in blood).

TREATMENT

Acute: NSAIDs (eg, indomethacin), glucocorticoids, colchicine. Chronic (preventive): xanthine oxidase inhibitors (eg, allopurinol, febuxostat).



#### Calcium pyrophosphate deposition disease



Previously called pseudogout. Deposition of calcium pyrophosphate crystals within the joint space. Occurs in patients > 50 years old; both sexes affected equally. Usually idiopathic, sometimes associated with hemochromatosis, hyperparathyroidism, joint trauma.

Pain and swelling with acute inflammation (pseudogout) and/or chronic degeneration (pseudo-osteoarthritis). Most commonly affected joint is the knee.

Chondrocalcinosis (cartilage calcification) on x-ray.

Crystals are rhomboid and weakly  $\oplus$  birefringent under polarized light (blue when parallel to light)  $\blacksquare$ .

Acute treatment: NSAIDs, colchicine, glucocorticoids.
Prophylaxis: colchicine.

birefringence, calcium Pyrophosphate, Pseudogout

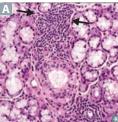
The blue P's—blue (when Parallel), Positive

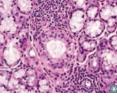
FAS1 2019 11-Musculo.indd 467

#### Systemic juvenile idiopathic arthritis

Systemic arthritis seen in < 16 year olds. Usually presents with daily spiking fevers, salmonpink macular rash, arthritis (commonly 2+ joints). Associated with anterior uveitis. Frequently presents with leukocytosis, thrombocytosis, anemia, † ESR, † CRP. Treatment: NSAIDs, steroids, methotrexate, TNF inhibitors.

#### Sjögren syndrome







Autoimmune disorder characterized by destruction of exocrine glands (especially lacrimal and salivary) by lymphocytic infiltrates A. Predominantly affects women 40-60 years old.

#### Findings:

- Inflammatory joint pain
- Keratoconjunctivitis sicca (↓ tear production and subsequent corneal damage)
- Xerostomia (↓ saliva production) → mucosal atrophy, fissuring of the tongue B
- Presence of antinuclear antibodies, rheumatoid factor (can be positive in the absence of rheumatoid arthritis), antiribonucleoprotein antibodies: SS-A (anti-Ro) and/or SS-B (anti-La)
- Bilateral parotid enlargement

Anti-SSA and anti-SSB may also be seen in SLE.

A common 1° disorder or a 2° syndrome associated with other autoimmune disorders (eg, rheumatoid arthritis, SLE, systemic sclerosis).

Complications: dental caries; mucosa-associated lymphoid tissue (MALT) lymphoma (may present as parotid enlargement).

Focal lymphocytic sialadenitis on labial salivary gland biopsy can confirm diagnosis.

#### **Septic arthritis**



S aureus, Streptococcus, and Neisseria gonorrhoeae are common causes. Affected joint is swollen A, red, and painful. Synovial fluid purulent (WBC > 50,000/mm<sup>3</sup>).

Gonococcal arthritis—STI that presents as either purulent arthritis (eg, knee) or triad of polyarthralgia, tenosynovitis (eg, hand), dermatitis (eg, pustules).

FAS1 2019 11-Musculo.indd 468 11/7/19 5:23 PM

Seronegative spondyloarthritis	Arthritis without rheumatoid factor (no anti-IgG antibody). Strong association with HLA-B27 (MHC class I serotype). Subtypes (PAIR) share variable occurrence of inflammatory back pain (associated with morning stiffness, improves with exercise), peripheral arthritis, enthesitis (inflamed insertion sites of tendons, eg, Achilles), dactylitis ("sausage fingers"), uveitis.			
Psoriatic arthritis	Associated with skin psoriasis and nail lesions. Asymmetric and patchy involvement A. Dactylitis and "pencil-in-cup" deformity of DIP on x-ray B.	Seen in fewer than <sup>1</sup> / <sub>3</sub> of patients with psoriasis.		
Ankylosing spondylitis	Symmetric involvement of spine and sacroiliac joints → ankylosis (joint fusion), uveitis, aortic regurgitation.	Bamboo spine (vertebral fusion) . Costovertebral and costosternal ankylosis may cause restrictive lung disease. Monitor degree of reduced chest wall expansion to assess disease severity. More common in males.		
Inflammatory bowel disease	Crohn disease and ulcerative colitis are often associated with spondyloarthritis.			
Reactive arthritis	Formerly called Reiter syndrome. Classic triad: Conjunctivitis Urethritis Arthritis	"Can't see, can't pee, can't bend my knee." Shigella, Yersinia, Chlamydia, Campylobacter, Salmonella (ShY ChiCS).		



FAS1\_2019\_11-Musculo.indd 469 11/7/19 5:23 PM

## Systemic lupus erythematosus

Systemic, remitting, and relapsing autoimmune disease. Organ damage primarily due to a type III hypersensitivity reaction and, to a lesser degree, a type II hypersensitivity reaction. Associated with deficiency of early complement proteins (eg, Clq, C4, C2) → ↓ clearance of immune complexes. Classic presentation: rash, joint pain, and fever in a female of reproductive age (especially of African-American or Hispanic descent).



Libman-Sacks Endocarditis—nonbacterial, verrucous thrombi usually on mitral or aortic valve and can be present on either surface of the valve (but usually on undersurface). LSE in SLE.

Lupus nephritis (glomerular deposition of DNA-anti-DNA immune complexes) can be nephritic or nephrotic (causing hematuria or proteinuria). Most common and severe type is diffuse proliferative.

Common causes of death in SLE: Renal disease (most common), Infections, Cardiovascular disease (accelerated CAD).

In an anti-SSA ⊕ pregnant woman, † risk of newborn developing neonatal lupus → congenital heart block, periorbital/diffuse rash, transaminitis, and cytopenias at birth.

#### **RASH OR PAIN:**

Rash (malar A or discoid B)

Arthritis (nonerosive)

Serositis (eg, pleuritis, pericarditis)

Hematologic disorders (eg, cytopenias)

Oral/nasopharyngeal ulcers (usually painless)

Renal disease

**P**hotosensitivity

Antinuclear antibodies

Immunologic disorder (anti-dsDNA, anti-Sm, antiphospholipid)

Neurologic disorders (eg, seizures, psychosis)

Lupus patients die with Redness In their Cheeks.

## Mixed connective tissue disease

Features of SLE, systemic sclerosis, and/or polymyositis. Associated with anti-U1 RNP antibodies (speckled ANA).

## Antiphospholipid syndrome

1° or 2° autoimmune disorder (most commonly in SLE).

Diagnosed based on clinical criteria including history of thrombosis (arterial or venous) or spontaneous abortion along with laboratory findings of lupus anticoagulant, anticardiolipin, anti- $\beta_2$  glycoprotein I antibodies.

Treatment: systemic anticoagulation.

Anticardiolipin antibodies can cause false-positive VDRL/RPR.

Lupus anticoagulant can cause prolonged PTT that is not corrected by the addition of normal platelet-free plasma.

#### Polymyalgia rheumatica

SYMPTOMS	Pain and stiffness in proximal muscles (eg, shoulders, hips), often with fever, malaise, weight loss. Does not cause muscular weakness. More common in women > 50 years old; associated with giant cell (temporal) arteritis.
FINDINGS	† ESR, † CRP, normal CK.
TREATMENT	Rapid response to low-dose corticosteroids.

FAS1\_2019\_11-Musculo.indd 470 11/7/19 5:23 PM

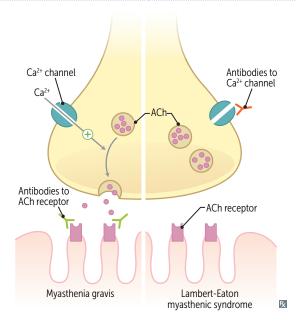
#### **Fibromyalgia** Most common in women 20-50 years old. Chronic, widespread musculoskeletal pain associated with "tender points," stiffness, paresthesias, poor sleep, fatigue, cognitive disturbance ("fibro fog"). Treatment: regular exercise, antidepressants (TCAs, SNRIs), neuropathic pain agents (eg, gabapentin). Polymyositis/ Nonspecific: ⊕ ANA, ↑ CK. Specific: ⊕ anti-Jo-l (histidyl-tRNA synthetase), ⊕ anti-SRP (signal dermatomyositis recognition particle), $\oplus$ anti-Mi-2 (helicase). **Polymyositis** Progressive symmetric proximal muscle weakness, characterized by endomysial inflammation with CD8+ T cells. Most often involves shoulders. **Dermatomyositis** Clinically similar to polymyositis, but also involves Gottron papules A, photodistributed facial erythema (eg, heliotrope [violaceous] edema of the eyelids **B**), "shawl and face" rash **C**, darkening and thickening of fingertips and sides resulting in irregular, "dirty"-appearing marks. † risk of occult malignancy. Perimysial inflammation and atrophy with CD4+ T cells.



FAS1\_2019\_11-Musculo.indd 471 11/7/19 5:23 PM

#### **Neuromuscular junction diseases**

	Myasthenia gravis	Lambert-Eaton myasthenic syndrome
FREQUENCY	Most common NMJ disorder	Uncommon
PATHOPHYSIOLOGY	Autoantibodies to postsynaptic ACh receptor	Autoantibodies to presynaptic Ca²+ channel  → ↓ ACh release
CLINICAL	Fatigable muscle weakness—ptosis; diplopia; proximal weakness; respiratory muscle involvement → dyspnea; bulbar muscle involvement → dysphagia, difficulty chewing	Proximal muscle weakness, autonomic symptoms (dry mouth, constipation, impotence)
	Spared reflexes	Hyporeflexia
	Worsens with muscle use	Improves with muscle use
ASSOCIATED WITH	Thymoma, thymic hyperplasia	Small cell lung cancer
ACHE INHIBITOR ADMINISTRATION	Reverses symptoms (pyridostigmine for treatment)	Minimal effect



#### Raynaud phenomenon



↓ blood flow to skin due to arteriolar (small vessel) vasospasm in response to cold or stress: color change from white (ischemia) to blue (hypoxia) to red (reperfusion). Most often in the fingers ⚠ and toes. Called Raynaud disease when 1° (idiopathic), Raynaud syndrome when 2° to a disease process such as mixed connective tissue disease, SLE, or CREST syndrome (limited form of systemic sclerosis). Digital ulceration (critical ischemia) seen in 2° Raynaud syndrome. Treat with calcium²+ channel blockers.

FAS1\_2019\_11-Musculo.indd 472 11/7/19 5:23 PM

#### Scleroderma

Systemic sclerosis. Triad of autoimmunity, noninflammatory vasculopathy, and collagen deposition with fibrosis. Commonly sclerosis of skin, manifesting as puffy, taut skin A without wrinkles, fingertip pitting B. Can involve other systems, eg, renal (scleroderma renal crisis; treat with ACE inhibitors), pulmonary (interstitial fibrosis, pulmonary HTN), GI (esophageal dysmotility and reflux), cardiovascular. 75% female. 2 major types:

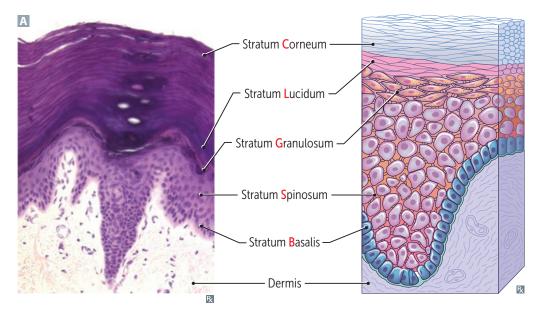
- **Diffuse scleroderma**—widespread skin involvement, rapid progression, early visceral involvement. Associated with anti-Scl-70 antibody (anti-DNA topoisomerase-I antibody) and anti-RNA polymerase III.
- Limited scleroderma—limited skin involvement confined to fingers and face. Also with CREST syndrome: Calcinosis cutis , anti-Centromere antibody, Raynaud phenomenon, Esophageal dysmotility, Sclerodactyly, and Telangiectasia. More benign clinical course.



#### ► MUSCULOSKELETAL, SKIN, AND CONNECTIVE TISSUE—DERMATOLOGY

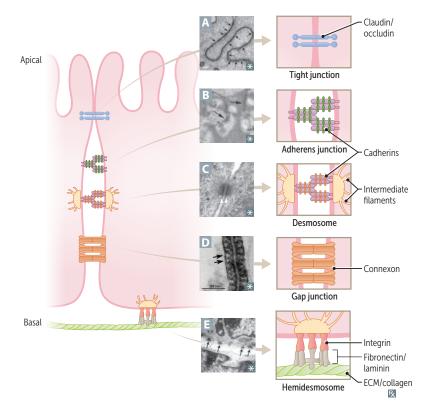
#### **Skin layers**

Skin has 3 layers: epidermis, dermis, subcutaneous fat (hypodermis, subcutis). Epidermal layers: Come, Let's Get Sun Burned.



FAS1\_2019\_11-Musculo.indd 473 11/7/19 5:24 PM

#### **Epithelial cell junctions**



Tight junctions (zonula occludens) A—prevents paracellular movement of solutes; composed of claudins and occludins.

Adherens junction (belt desmosome, zonula adherens) B—forms "belt" connecting actin cytoskeletons of adjacent cells with CADherins (Ca<sup>2+</sup>-dependent adhesion proteins). Loss of E-cadherin promotes metastasis.

Desmosome (spot desmosome, macula adherens)

C—structural support via intermediate filament interactions. Autoantibodies to desmoglein 1 and/or 3 → pemphigus vulgaris.

Gap junction —channel proteins called connexons permit electrical and chemical communication between cells.

Hemidesmosome E—connects keratin in basal cells to underlying basement membrane.
Autoantibodies → bullous pemphigoid.
(Hemidesmosomes are down "bullow.")

Integrins—membrane proteins that maintain integrity of basolateral membrane by binding to collagen, laminin, and fibronectin in basement membrane.

FAS1\_2019\_11-Musculo.indd 474 11/7/19 5:24 PM

#### **Dermatologic macroscopic terms**

CHARACTERISTICS	EXAMPLES
Flat lesion with well-circumscribed change in skin color < 1 cm	Freckle (ephelide), labial macule A
Macule > 1 cm	Large birthmark (congenital nevus)
Elevated solid skin lesion < 1 cm	Mole (nevus) 🕻, acne
Papule > 1 cm	Psoriasis D
Small fluid-containing blister < 1 cm	Chickenpox (varicella), shingles (zoster) 🗉
Large fluid-containing blister > 1 cm	Bullous pemphigoid <b>F</b>
Vesicle containing pus	Pustular psoriasis 🜀
Transient smooth papule or plaque	Hives (urticaria) H
Flaking off of stratum corneum	Eczema, psoriasis, SCC 👖
Dry exudate	Impetigo 🗾
	Flat lesion with well-circumscribed change in skin color < 1 cm  Macule > 1 cm  Elevated solid skin lesion < 1 cm  Papule > 1 cm  Small fluid-containing blister < 1 cm  Large fluid-containing blister > 1 cm  Vesicle containing pus  Transient smooth papule or plaque  Flaking off of stratum corneum



#### **Dermatologic microscopic terms**

LESION	CHARACTERISTICS	EXAMPLES
Hyperkeratosis	† thickness of stratum corneum	Psoriasis, calluses
Parakeratosis	Retention of nuclei in stratum corneum	Psoriasis, actinic keratosis
Hypergranulosis	† thickness of stratum granulosum	Lichen planus
Spongiosis	Epidermal accumulation of edematous fluid in intercellular spaces	Eczematous dermatitis
Acantholysis	Separation of epidermal cells	Pemphigus vulgaris
Acanthosis	Epidermal hyperplasia († spinosum)	Acanthosis nigricans, psoriasis

FAS1\_2019\_11-Musculo.indd 475 11/7/19 5:24 PM

#### **Pigmented skin disorders**

Albinism	Normal melanocyte number with ↓ melanin production ⚠ due to ↓ tyrosinase activity or defective tyrosine transport. ↑ risk of skin cancer.
Melasma (chloasma)	Acquired hyperpigmentation associated with pregnancy ("mask of pregnancy" <b>B</b> ) or OCP use. More common in women with darker complexions.
Vitiligo	Irregular patches of complete depigmentation <b>C</b> . Caused by destruction of melanocytes (believed to be autoimmune). Associated with other autoimmune disorders.



#### **Seborrheic dermatitis**



Erythematous, well-demarcated plaques A with greasy yellow scales in areas rich in sebaceous glands, such as scalp, face, and periocular region. Common in both infants (cradle cap) and adults, associated with Parkinson disease. Sebaceous glands are not inflamed, but play a role in disease development. Possibly associated with *Malassezia* spp. Treatment: topical antifungals and corticosteroids.

FAS1\_2019\_11-Musculo.indd 476 11/7/19 5:24 PM

#### **Common skin disorders**

Acne	Multifactorial etiology—† sebum/androgen production, abnormal keratinocyte desquamation, Cutibacterium acnes colonization of the pilosebaceous unit (comedones), and inflammation (papules/pustules A, nodules, cysts). Treatment: retinoids, benzoyl peroxide, and antibiotics.	
Atopic dermatitis (eczema)	Type I hypersensitivity reaction. Pruritic eruption, commonly on skin flexures. Associated with other atopic diseases (asthma, allergic rhinitis, food allergies); † serum IgE. Mutations in filaggrin gene predispose (via skin barrier dysfunction). Often appears on face in infancy B and then in antecubit fossa C in children and adults.	
Allergic contact dermatitis	Type IV hypersensitivity reaction secondary to contact allergen (eg, nickel <b>D</b> , poison ivy, neomycin <b>E</b> )	
Melanocytic nevus	Common mole. Benign, but melanoma can arise in congenital or atypical moles. Intradermal nevi are papular <b>[</b> ]. Junctional nevi are flat macules <b>[</b> ].	
Pseudofolliculitis barbae	Foreign body inflammatory facial skin disorder characterized by firm, hyperpigmented papules and pustules that are painful and pruritic. Located on cheeks, jawline, and neck. Commonly occurs as a result of shaving ("razor bumps"), primarily affects African-American males.	
Psoriasis	Papules and plaques with silvery scaling ℍ, especially on knees and elbows. Acanthosis with parakeratotic scaling (nuclei still in stratum corneum), Munro microabscesses. ↑ stratum spinosum, ↓ stratum granulosum. Auspitz sign (Ⅱ)—pinpoint bleeding spots from exposure of dermal papillae when scales are scraped off. Associated with nail pitting and psoriatic arthritis.	
Rosacea	Inflammatory facial skin disorder characterized by erythematous papules and pustules , but no comedones. May be associated with facial flushing in response to external stimuli (eg, alcohol, heat). Phymatous rosacea can cause rhinophyma (bulbous deformation of nose).	
Seborrheic keratosis	Flat, greasy, pigmented squamous epithelial proliferation of immature keratinocytes with keratin-filled cysts (horn cysts) K. Looks "stuck on." Lesions occur on head, trunk, and extremities.  Common benign neoplasm of older persons. Leser-Trélat sign —rapid onset of multiple seborrheic keratoses, indicates possible malignancy (eg, GI adenocarcinoma).	
Verrucae	Warts; caused by low-risk HPV strains. Soft, tan-colored, cauliflower-like papules M. Epidermal hyperplasia, hyperkeratosis, koilocytosis. Condyloma acuminatum on anus or genitals N.	
Urticaria	Hives. Pruritic wheals that form after mast cell degranulation . Characterized by superficial dermal edema and lymphatic channel dilation.	



FAS1\_2019\_11-Musculo.indd 477 11/7/19 5:24 PM

#### Vascular tumors of skin

Angiosarcoma	Rare blood vessel malignancy typically occurring in the head, neck, and breast areas. Usually in elderly, on sun-exposed areas. Associated with radiation therapy and chronic postmastectomy lymphedema. Hepatic angiosarcoma associated with vinyl chloride and arsenic exposures. Very aggressive and difficult to resect due to delay in diagnosis.	
Bacillary angiomatosis	Benign capillary skin papules A found in AIDS patients. Caused by <i>Bartonella</i> infections. Frequently mistaken for Kaposi sarcoma, but has neutrophilic infiltrate.	
Cherry hemangioma	Benign capillary hemangioma  commonly appearing in middle-aged adults. Does not regress. Frequency † with age.	
Glomus tumor	Benign, painful, red-blue tumor, commonly under fingernails . Arises from modified smooth muscle cells of the thermoregulatory glomus body.	
Kaposi sarcoma	Endothelial malignancy most commonly affecting the skin, mouth, GI tract, respiratory tract. Classically seen in older Eastern European males, patients with AIDS, and organ transplant patients. Associated with HHV-8 and HIV. Rarely mistaken for bacillary angiomatosis, but has lymphocytic infiltrate.	
Pyogenic granuloma	Polypoid lobulated capillary hemangioma D that can ulcerate and bleed. Associated with trauma and pregnancy.	
Strawberry hemangioma	Benign capillary hemangioma of infancy <b>E</b> . Appears in first few weeks of life (1/200 births); grows rapidly and regresses spontaneously by 5–8 years old.	











FAS1\_2019\_11-Musculo.indd 478 11/7/19 5:24 PM

Skin infections		
Bacterial infections		
Impetigo	Very superficial skin infection. Usually from <i>S aureus</i> or <i>S pyogenes</i> . Highly contagious. Honeycolored crusting A. Bullous impetigo B has bullae and is usually caused by <i>S aureus</i> .	
Erysipelas	Infection involving upper dermis and superficial lymphatics, usually from <i>S pyogenes</i> . Presents wit well-defined, raised demarcation between infected and normal skin <b>C</b> .	
Cellulitis	Acute, painful, spreading infection of deeper dermis and subcutaneous tissues. Usually from <i>S pyogenes</i> or <i>S aureus</i> . Often starts with a break in skin from trauma or another infection <b>D</b> .	
Abscess	Collection of pus from a walled-off infection within deeper layers of skin <b>E</b> . Offending organism is almost always <i>S aureus</i> .	
Necrotizing fasciitis	Deeper tissue injury, usually from anaerobic bacteria or <i>S pyogenes</i> . Pain may be out of proportion to exam findings. Results in crepitus from methane and CO <sub>2</sub> production. "Flesh-eating bacteria." Causes bullae and skin necrosis → violaceous color of bullae, surrounding skin <b>F</b> . Surgical emergency.	
Staphylococcal scalded skin syndrome	Exotoxin destroys keratinocyte attachments in stratum granulosum only (vs toxic epidermal necrolysis, which destroys epidermal-dermal junction). Characterized by fever and generalized erythematous rash with sloughing of the upper layers of the epidermis c that heals completely.   • Nikolsky sign (separation of epidermis upon manual stroking of skin). Commonly seen in newborns and children/adults with renal insufficiency.	
Viral infections		
Herpes	Herpes virus infections (HSV1 and HSV2) of skin can occur anywhere from mucosal surfaces to normal skin. These include herpes labialis, herpes genitalis, herpetic whitlow ℍ (finger).	
Molluscum contagiosum	Umbilicated papules  caused by a poxvirus. While frequently seen in children, it may be sexually transmitted in adults.	
Varicella zoster virus	Causes varicella (chickenpox) and zoster (shingles). Varicella presents with multiple crops of lesions in various stages from vesicles to crusts. Zoster is a reactivation of the virus in dermatomal distribution (unless it is disseminated).	
Hairy leukoplakia	Irregular, white, painless plaques on lateral tongue that cannot be scraped off <b>J</b> . EBV mediated. Occurs in HIV-positive patients, organ transplant recipients. Contrast with thrush (scrapable) and leukoplakia (precancerous).	
A	D E	



11/7/19 5:24 PM FAS1\_2019\_11-Musculo.indd 479

#### **Autoimmune blistering skin disorders**

	Pemphigus vulgaris	Bullous pemphigoid  Less severe than pemphigus vulgaris. Most commonly seen in older adults. Type II hypersensitivity reaction.  IgG antibodies against hemidesmosomes (epidermal basement membrane; antibodies are "bullow" the epidermis).  Tense blisters   containing eosinophils; oral mucosa spared. Nikolsky sign   .	
PATHOPHYSIOLOGY	Potentially fatal. Most commonly seen in older adults. Type II hypersensitivity reaction. IgG antibodies against desmoglein-1 and/or desmoglein-3 (component of desmosomes, which connect keratinocytes in the stratum spinosum).		
GROSS MORPHOLOGY	Flaccid intraepidermal bullae A caused by acantholysis (separation of keratinocytes, "row of tombstones" on H&E stain); oral mucosa is involved. Nikolsky sign ⊕.		
IMMUNOFLUORESCENCE	Reticular pattern around epidermal cells <b>B</b> .	Linear pattern at epidermal-dermal junction D.	
	A B	D RU	

FAS1\_2019\_11-Musculo.indd 480 11/7/19 5:24 PM

#### Other blistering skin disorders

Dermatitis herpetiformis	Pruritic papules, vesicles, and bullae (often found on elbows, knees, buttocks) A. Deposits of IgA at tips of dermal papillae. Associated with celiac disease. Treatment: dapsone, gluten-free diet.
Erythema multiforme	Associated with infections (eg, <i>Mycoplasma pneumoniae</i> , HSV), drugs (eg, sulfa drugs, β-lactams, phenytoin). Presents with multiple types of lesions—macules, papules, vesicles, target lesions (look like targets with multiple rings and dusky center showing epithelial disruption) <b>B</b> .
Stevens-Johnson syndrome	Characterized by fever, bullae formation and necrosis, sloughing of skin at dermal-epidermal junction ( $\oplus$ Nikolsky), high mortality rate. Typically mucous membranes are involved $\square$ . Targetoid skin lesions may appear, as seen in erythema multiforme. Usually associated with adverse drug reaction. Toxic epidermal necrolysis (TEN) $\square$ is more severe form of SJS involving > 30% body surface area. 10–30% involvement denotes SJS-TEN.



FAS1\_2019\_11-Musculo.indd 481 11/7/19 5:24 PM

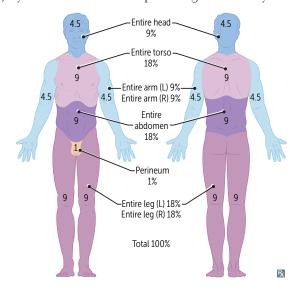
#### **Miscellaneous skin disorders**

Acanthosis nigricans	Epidermal hyperplasia causing symmetric, hyperpigmented thickening of skin, especially in axilla or on neck A B. Associated with insulin resistance (eg, diabetes, obesity, Cushing syndrome, PCOS), visceral malignancy (eg, gastric adenocarcinoma).		
Actinic keratosis	Premalignant lesions caused by sun exposure. Small, rough, erythematous or brownish papules or plaques  D. Risk of squamous cell carcinoma is proportional to degree of epithelial dysplasia.		
Erythema nodosum	Painful, raised inflammatory lesions of subcutaneous fat (panniculitis), usually on anterior shins. Often idiopathic, but can be associated with sarcoidosis, coccidioidomycosis, histoplasmosis, TB, streptococcal infections <b>E</b> , leprosy <b>F</b> , inflammatory bowel disease.		
Lichen Planus	Pruritic, Purple, Polygonal Planar Papules and Plaques are the 6 P's of lichen Planus GH.  Mucosal involvement manifests as Wickham striae (reticular white lines) and hypergranulosis.  Sawtooth infiltrate of lymphocytes at dermal-epidermal junction. Associated with hepatitis C.		
Pityriasis rosea	"Herald patch"  ☐ followed days later by other scaly erythematous plaques, often in a "Christmas tree" distribution on trunk ☐. Multiple pink plaques with collarette scale. Self-resolving in 6–8 weeks.		
Sunburn	Acute cutaneous inflammatory reaction due to excessive UV irradiation. Causes DNA mutations, inducing apoptosis of keratinocytes. UVB is dominant in sunBurn, UVA in tAnning and photoAging. Exposure to UVA and UVB † risk of skin cancer.		
A	B		

FAS1\_2019\_11-Musculo.indd 482 11/7/19 5:24 PM

#### Rule of 9's

The extent of a burn injury can be estimated as a percentage of the body surface area.



#### **Burn classification**

DEPTH	INVOLVEMENT	APPEARANCE	SENSATION
Superficial burn	Epidermis only	Similar to sunburn; localized, painful, dry, blanching redness with no blisters	Painful
Superficial partial- thickness	All of epidermis and some dermis	Blisters, blanches with pressure, swollen, warm	Painful to temperature and air
Deep partial- thickness burn	All of epidermis and some dermis	Blisters (easily unroofed), does not blanch with pressure	Painless; perception of pressure only
Full-thickness burn	All of skin (epidermis and dermis)	White, waxy, dry, inelastic, leathery, does not blanch with pressure	Painless; perception of deep pressure only
Deeper injury burn	All of skin and at least partial involvement of muscle and/or fascia	White, dry, inelastic, does not blanch with pressure	Painless; some perception of deep pressure

FAS1\_2019\_11-Musculo.indd 483 11/7/19 5:24 PM

#### Skin cancer

Basal cell carcinoma more common above upper lip Squamous cell carcinoma more common below lower lip Sun exposure strongly predisposes to skin cancer.



#### Basal cell carcinoma

Most common skin cancer. Found in sun-exposed areas of body (eg, face). Locally invasive, but rarely metastasizes. Waxy, pink, pearly nodules, commonly with telangiectasias, rolled borders A, central crusting or ulceration. BCCs also appear as nonhealing ulcers with infiltrating growth B or as a scaling plaque (superficial BCC) . Basal cell tumors have "palisading" (aligned) nuclei D.

#### Keratoacanthoma

Seen in middle-aged and elderly individuals. Rapidly growing, resembles squamous cell carcinoma. Presents as dome-shaped nodule with keratin-filled center. Grows rapidly (4-6 weeks) and may spontaneously regress **E**.

#### Melanoma

Common tumor with significant risk of metastasis. S-100 tumor marker. Associated with dysplastic nevi; fair-skinned persons are at † risk. Depth of tumor (Breslow thickness) correlates with risk of metastasis. Look for the ABCDEs: Asymmetry, Border irregularity, Color variation, Diameter > 6 mm, and Evolution over time. At least 4 different types of melanoma, including superficial spreading F, nodular G, lentigo maligna H, and acral lentiginous (highest prevalence in African-Americans and Asians) I. Often driven by activating mutation in BRAF kinase. Primary treatment is excision with appropriately wide margins. Metastatic or unresectable melanoma in patients with BRAF V600E mutation may benefit from vemurafenib, a BRAF kinase inhibitor.

## Squamous cell carcinoma

Second most common skin cancer. Associated with immunosuppression, chronic nonhealing wounds, and occasionally arsenic exposure. Commonly appears on face , lower lip , ears, hands. Locally invasive, may spread to lymph nodes, and will rarely metastasize. Ulcerative red lesions. Histopathology: keratin "pearls" .

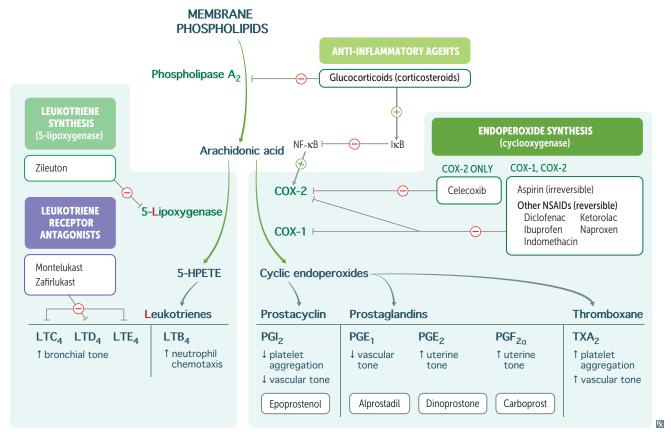
Actinic keratosis, a scaly plaque, is a precursor to squamous cell carcinoma.



FAS1\_2019\_11-Musculo.indd 484 11/7/19 5:24 PM

#### ► MUSCULOSKELETAL, SKIN, AND CONNECTIVE TISSUE—PHARMACOLOGY

#### **Arachidonic acid pathways**



LTB<sub>4</sub> is a **neutrophil** chemotactic agent. **PGI**<sub>2</sub> inhibits platelet aggregation and promotes vasodilation.

Neutrophils arrive "B4" others. Platelet-Gathering Inhibitor.

#### **Acetaminophen**

MECHANISM	Reversibly inhibits cyclooxygenase, mostly in CNS. Inactivated peripherally.
CLINICAL USE	Antipyretic, analgesic, but not anti-inflammatory. Used instead of aspirin to avoid Reye syndrome in children with viral infection.
ADVERSE EFFECTS	Overdose produces hepatic necrosis; acetaminophen metabolite (NAPQI) depletes glutathione and forms toxic tissue byproducts in liver. N-acetylcysteine is antidote—regenerates glutathione.

FAS1\_2019\_11-Musculo.indd 485 11/7/19 5:24 PM

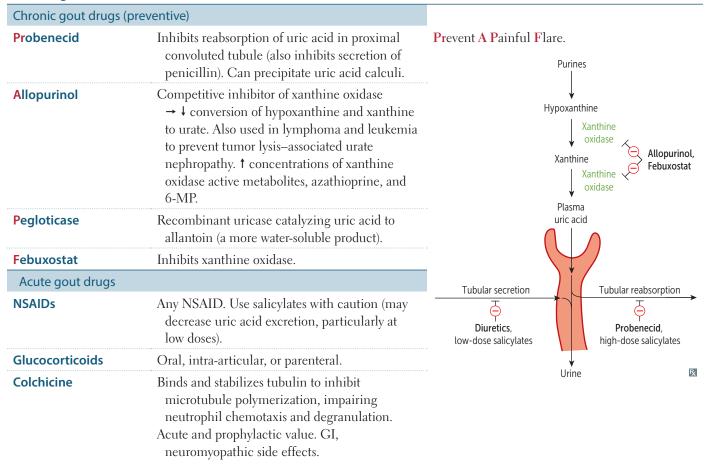
Aspirin		
MECHANISM	NSAID that irreversibly inhibits cyclooxygenase (both COX-1 and COX-2) by covalent acetylation → ↓ synthesis of TXA₂ and prostaglandins. ↑ bleeding time. No effect on PT, PTT. Effect lasts until new platelets are produced.	
CLINICAL USE	Low dose (< 300 mg/day): \$\daggregation\$ platelet aggregation. Intermediate dose (300–2400 mg/day): antipyre and analgesic. High dose (2400–4000 mg/day): anti-inflammatory.	
ADVERSE EFFECTS	Gastric ulceration, tinnitus (CN VIII), allergic reactions (especially in patients with asthma or nasal polyps). Chronic use can lead to acute kidney injury, interstitial nephritis, GI bleeding. Ris of Reye syndrome in children treated with aspirin for viral infection. Toxic doses cause respirato alkalosis early, but transitions to mixed metabolic acidosis-respiratory alkalosis. Treatment of overdose: NaHCO <sub>3</sub> .	
Celecoxib		
MECHANISM	Reversibly and <b>selectively</b> inhibits the cyclooxygenase ( <b>COX</b> ) isoform 2 (" <b>Selecoxib</b> "), which is found in inflammatory cells and vascular endothelium and mediates inflammation and pain; spares COX-1, which helps maintain gastric mucosa. Thus, does not have the corrosive effects of other NSAIDs on the GI lining. Spares platelet function as TXA <sub>2</sub> production is dependent on COX-1.	
CLINICAL USE	Rheumatoid arthritis, osteoarthritis.	
ADVERSE EFFECTS	† risk of thrombosis, sulfa allergy.	
Nonsteroidal anti-inflammatory drugs	Ibuprofen, naproxen, indomethacin, ketorolac, diclofenac, meloxicam, piroxicam.	
MECHANISM	Reversibly inhibit cyclooxygenase (both COX-1 and COX-2). Block prostaglandin synthesis.	
CLINICAL USE	Antipyretic, analgesic, anti-inflammatory. Indomethacin is used to close a PDA.	
ADVERSE EFFECTS	Interstitial nephritis, gastric ulcer (prostaglandins protect gastric mucosa), renal ischemia (prostaglandins vasodilate afferent arteriole), aplastic anemia.	
Leflunomide		
MECHANISM	Reversibly inhibits dihydroorotate dehydrogenase, preventing pyrimidine synthesis. Suppresses T-cell proliferation.	
CLINICAL USE	Rheumatoid arthritis, psoriatic arthritis.	
ADVERSE EFFECTS	Diarrhea, hypertension, hepatotoxicity, teratogenicity.	
Bisphosphonates	Alendronate, ibandronate, risedronate, zoledronate.	
MECHANISM	Pyrophosphate analogs; bind hydroxyapatite in bone, inhibiting osteoclast activity.	
CLINICAL USE	Osteoporosis, hypercalcemia, Paget disease of bone, metastatic bone disease, osteogenesis imperfecta.	
ADVERSE EFFECTS	Esophagitis (if taken orally, patients are advised to take with water and remain upright for 30 minutes), osteonecrosis of jaw, atypical femoral stress fractures.	

FAS1\_2019\_11-Musculo.indd 486 11/7/19 5:24 PM

#### **Teriparatide**

MECHANISM	Recombinant PTH analog. † osteoblastic activity when administered in pulsatile fashion.	
CLINICAL USE	Osteoporosis. Causes † bone growth compared to antiresorptive therapies (eg, bisphosphonates).	
ADVERSE EFFECTS	† risk of osteosarcoma (avoid use in patients with Paget disease of the bone or unexplained elevation of alkaline phosphatase). Avoid in patients who have had prior cancers or radiation therapy. Transient hypercalcemia.	

#### **Gout drugs**



#### $TNF-\alpha$ inhibitors

DRUG	MECHANISM	CLINICAL USE	ADVERSE EFFECTS
Etanercept	Fusion protein (decoy receptor for TNF-α + IgG <sub>1</sub> Fc), produced by recombinant DNA.  Etanercept intercepts TNF.	Rheumatoid arthritis, psoriasis, ankylosing spondylitis	Predisposition to infection, including reactivation of latent TB, since TNF is important in granuloma
Infliximab, adalimumab, certolizumab, golimumab	Anti-TNF-α monoclonal antibody.	Inflammatory bowel disease, rheumatoid arthritis, ankylosing spondylitis, psoriasis	formation and stabilization. Can also lead to drug-induced lupus.

FAS1\_2019\_11-Musculo.indd 487

488 SECTION II

MUSCULOSKELETAL, SKIN, AND CONNECTIVE TISSUE → PHARMACOLOGY

► NOTES	

FAS1\_2019\_11-Musculo.indd 488

#### HIGH-YIELD SYSTEMS

# Neurology and Special Senses

"We are all now connected by the Internet, like neurons in a giant brain."

—Stephen Hawking

"Anything's possible if you've got enough nerve."

—J.K. Rowling, Harry Potter and the Order of the Phoenix

"I like nonsense; it wakes up the brain cells."

-Dr. Seuss

"I believe in an open mind, but not so open that your brains fall out."

—Arthur Hays Sulzberger

"The chief function of the body is to carry the brain around."

—Thomas Edison

"Exactly how [the brain] operates remains one of the biggest unsolved mysteries, and it seems the more we probe its secrets, the more surprises we find."

—Neil deGrasse Tyson

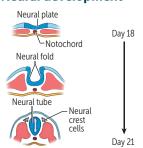
Understand the difference between upper motor neuron (UMN) and lower motor neuron (LMN) findings and the underlying anatomy. Know the major motor, sensory, cerebellar and visual pathways and their respective locations in the CNS. Connect key neurological associations with certain pathologies (eg, cerebellar lesions, stroke manifestations, Brown-Séquard syndrome). Recognize common findings on MRI/CT (eg, ischemic and hemorrhagic stroke) and on neuropathology (eg, neurofibrillary tangles and Lewy bodies). High-yield medications include those used to treat epilepsy, Parkinson disease, migraine, and pain (eg, opioids).

<b>▶</b> Embryology	490
Anatomy and Physiology	493
▶ Pathology	511
▶Otology	533
<b>▶</b> Ophthalmology	534
Pharmacology	544

FAS1\_2019\_12-Neurol.indd 489 11/8/19 7:39 AM

#### ► NEUROLOGY—EMBRYOLOGY

#### **Neural development**



Notochord induces overlying ectoderm to differentiate into neuroectoderm and form neural plate. Neural plate gives rise to neural tube and neural crest cells.

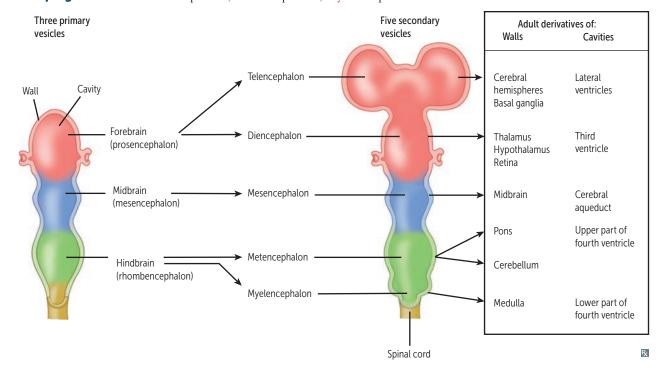
Notochord becomes nucleus pulposus of intervertebral disc in adults.

Alar plate (dorsal): sensory; regulated by TGF-β (including bone morphogenetic protein [*BMP*]) Basal plate (ventral): motor; regulated by sonic hedgehog gene (*SHH*)

Same orientation as spinal cord

## Regional specification of developing brain

Telencephalon is the 1st part. Diencephalon is the 2nd part. The rest are arranged alphabetically: mesencephalon, metencephalon, myelencephalon.



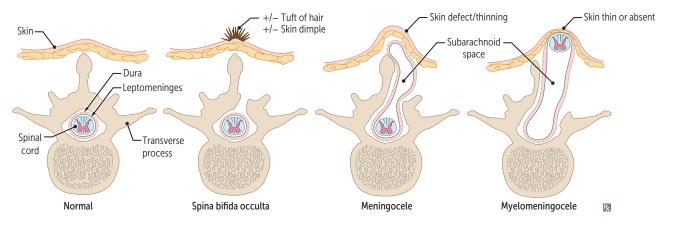
## Central and peripheral nervous systems origins

Neuroepithelia in neural tube—CNS neurons, ependymal cells (inner lining of ventricles, make CSF), oligodendrocytes, astrocytes.

Neural crest—PNS neurons, Schwann cells, glia, melanocytes, adrenal medulla. Mesoderm—Microglia (like Macrophages).

FAS1\_2019\_12-Neurol.indd 490 11/8/19 7:39 AM

Neural tube defects	Neuropores fail to fuse (4th week) → persistent connection between amniotic cavity and spinal canal. Associated with maternal diabetes and folate deficiency. ↑ α-fetoprotein (AFP) in amniotic fluid and maternal serum (except spina bifida occulta = normal AFP). ↑ acetylcholinesterase (AChE) in amniotic fluid is a helpful confirmatory test.
Spina bifida occulta	Failure of caudal neuropore to close, but no herniation. Usually seen at lower vertebral levels. Dura is intact. Associated with tuft of hair or skin dimple at level of bony defect.
Meningocele	Meninges (but no neural tissue) herniate through bony defect.
Myelomeningocele	Meninges and neural tissue (eg, cauda equina) herniate through bony defect.
Myeloschisis	Also called rachischisis. Exposed, unfused neural tissue without skin/meningeal covering.
Anencephaly	Failure of rostral neuropore to close → no forebrain, open calvarium. Clinical findings: polyhydramnios (no swallowing center in brain).



#### Holoprosencephaly



Failure of the embryonic forebrain (prosencephalon) to separate into 2 cerebral hemispheres; usually occurs during weeks 5–6. May be related to mutations in sonic hedgehog signaling pathway. Associated with other midline defects including cleft lip/palate (moderate form) and cyclopia (severe form). † risk for pituitary dysfunction (eg, diabetes insipidus). Can be seen with Patau syndrome (trisomy 13).

MRI reveals monoventricle **A** and fusion of basal ganglia (star in **A**).

#### Lissencephaly

Failure of neuronal migration resulting in a "smooth brain" that lacks sulci and gyri. May be associated with microcephaly, ventriculomegaly.

FAS1\_2019\_12-Neurol.indd 491 11/8/19 7:39 AM

#### **Posterior fossa malformations**

#### Chiari I malformation

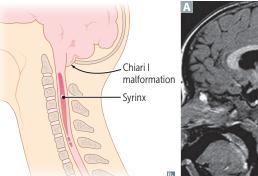
Ectopia of cerebellar **tonsils** inferior to foramen magnum (1 structure) A. Congenital, usually asymptomatic in childhood, manifests in adulthood with headaches and cerebellar symptoms. Associated with spinal cavitations (eg, syringomyelia).

#### **Chiari II malformation**

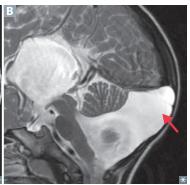
Herniation of cerebellar **vermis** and **tonsils** (2 structures) through foramen magnum with aqueductal stenosis → noncommunicating hydrocephalus. Usually associated with lumbosacral myelomeningocele (may present as paralysis/sensory loss at and below the level of the lesion). More severe than Chiari I, usually presents early in life.

## Dandy-Walker malformation

Agenesis of cerebellar vermis → cystic enlargement of 4th ventricle (arrow in **B**) that fills the enlarged posterior fossa. Associated with noncommunicating hydrocephalus, spina bifida.





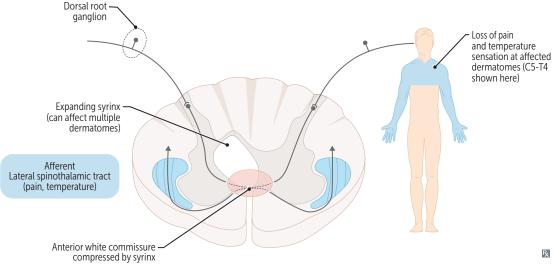


#### **Syringomyelia**



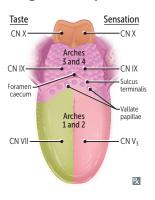
Cystic cavity (syrinx) within central canal of spinal cord (yellow arrows in A). Fibers crossing in anterior white commissure (spinothalamic tract) are typically damaged first. Results in a "capelike," bilateral, symmetrical loss of pain and temperature sensation in upper extremities (fine touch sensation is preserved).

Associated with Chiari I malformation (red arrow in A shows low-lying cerebellar tonsils), scoliosis and other congenital malformations; acquired causes include trauma and tumors. Most common location cervical > thoracic >> lumbar. Syrinx = tube, as in "syringe."



FAS1\_2019\_12-Neurol.indd 492 11/8/19 7:39 AM

#### **Tongue development**



1st and 2nd pharyngeal arches form anterior 2/3 (thus sensation via CN V<sub>3</sub>, taste via CN VII).
3rd and 4th pharyngeal arches form posterior 1/3(thus sensation and taste mainly via CN IX, extreme posterior via CN X).

Motor innervation is via CN XII to hyoglossus (retracts and depresses tongue), **geni**oglossus (**protrudes** tongue), and **styl**oglossus (draws sides of tongue upward to create a trough for swallowing).

Motor innervation is via CN X to palatoglossus (elevates posterior tongue during swallowing).

Taste—CN VII, IX, X (solitary nucleus). Pain—CN V<sub>3</sub>, IX, X. Motor—CN X, XII.

The Genie comes out of the lamp in style.

#### ► NEUROLOGY—ANATOMY AND PHYSIOLOGY

#### Neurons

Signal-transmitting cells of the nervous system. Permanent cells—do not divide in adulthood. Signal-relaying cells with dendrites (receive input), cell bodies, and axons (send output). Cell bodies and dendrites can be seen on Nissl staining (stains RER). RER is not present in the axon. Neuron markers: neurofilament protein, synaptophysin.

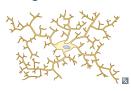
#### **Astrocytes**



Most common glial cell type in CNS. Physical support, repair, extracellular K<sup>+</sup> buffer, removal of excess neurotransmitter, component of blood-brain barrier, glycogen fuel reserve buffer. Reactive gliosis in response to neural injury.

Derived from neuroectoderm. Astrocyte marker: GFAP.

#### Microglia



Phagocytic scavenger cells of CNS (mesodermal, mononuclear origin). Activation in response to tissue damage → release of inflammatory mediators (eg, nitric oxide, glutamate). Not readily discernible by Nissl stain.

HIV-infected microglia fuse to form multinucleated giant cells in CNS seen in HIV-associated dementia.

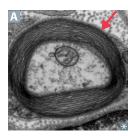
#### **Ependymal cells**

Ciliated simple columnar glial cells line the ventricles and central canal of spinal cord. Apical surfaces are covered in cilia (which circulate CSF) and microvilli (which help with CSF absorption). Specialized ependymal cells (choroid plexus) produce CSF.

FAS1\_2019\_12-Neurol.indd 493 11/8/19 7:39 AM

#### NEUROLOGY AND SPECIAL SENSES ► NEUROLOGY—ANATOMY AND PHYSIOLOGY

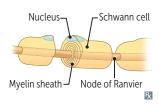
#### Myelin



† conduction velocity of signals transmitted down axons → saltatory conduction of action potential at the nodes of Ranvier, where there are high concentrations of Na<sup>+</sup> channels. In CNS (including CN II), myelin is synthesized by oligodendrocytes; in PNS (including CN III-XII), myelin is synthesized by Schwann cells. Wraps and insulates axons (arrow in A): † space constant and † conduction velocity.

COPS: CNS = Oligodendrocytes, PNS = Schwann cells.

#### **Schwann cells**

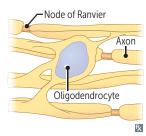


Promote axonal regeneration. Derived from neural crest.

Each "Schwone" cell myelinates only 1 PNS axon.

Injured in Guillain-Barré syndrome.

#### Oligodendrocytes



Myelinate axons of neurons in CNS. Each oligodendrocyte can myelinate many axons (~ 30). Predominant type of glial cell in white matter.

Derived from neuroectoderm.

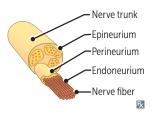
"Fried egg" appearance histologically.
Injured in multiple sclerosis, progressive multifocal leukoencephalopathy (PML), leukodystrophies.

#### **Sensory receptors**

RECEPTOR TYPE	SENSORY NEURON FIBER TYPE	LOCATION	SENSES		
Free nerve endings	Aδ—fast, myelinated fibers C—slow, unmyelinated A Delta plane is fast, but a taxC is slow	All skin, epidermis, some viscera	Pain, temperature		
Meissner corpuscles	Large, myelinated fibers; adapt quickly	Glabrous (hairless) skin	Dynamic, fine/light touch, position sense, low-frequency vibration		
Pacinian corpuscles	Large, myelinated fibers; adapt quickly	Deep skin layers, ligaments, joints	High-frequency vibration, pressure		
Merkel discs	Large, myelinated fibers; adapt slowly	Finger tips, superficial skin	Pressure, deep static touch (eg, shapes, edges), position sense		
Ruffini corpuscles	Dendritic endings with capsule; adapt slowly	Finger tips, joints	Pressure, slippage of objects along surface of skin, joint angle change		

FAS1\_2019\_12-Neurol.indd 494 11/8/19 7:39 AM

#### **Peripheral nerve**

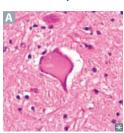


Endoneurium—thin, supportive connective tissue that ensheathes and supports individual myelinated nerve fibers.

Perineurium (blood-nerve Permeability barrier)—surrounds a fascicle of nerve fibers. Epineurium—dense connective tissue that surrounds entire nerve (fascicles and blood vessels).

Endo = inner Peri = around Epi = outer

#### **Chromatolysis**

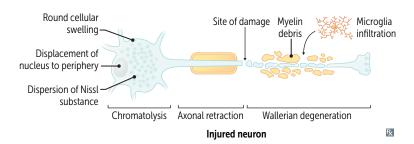


Reaction of neuronal cell body to axonal injury. Changes reflect † protein synthesis in effort to repair the damaged axon. Characterized by:

- Round cellular swelling A
- Displacement of the nucleus to the periphery
- Dispersion of Nissl substance throughout cytoplasm

Wallerian degeneration—disintegration of the axon and myelin sheath distal to site of axonal injury with macrophages removing debris.

Proximal to the injury, the axon retracts, and the cell body sprouts new protrusions that grow toward other neurons for potential reinnervation. Serves as a preparation for axonal regeneration and functional recovery.

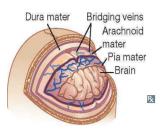


#### Neurotransmitter changes with disease

	LOCATION OF SYNTHESIS	ANXIETY	DEPRESSION	SCHIZOPHRENIA	ALZHEIMER DISEASE	HUNTINGTON DISEASE	PARKINSON DISEASE
Acetylcholine	Basal nucleus of Meynert				<b>†</b>	1	†
Dopamine	Ventral tegmentum, SNc		1	<b>†</b>		†	<b>†</b>
GABA	Nucleus accumbens	<b>†</b>				ţ	
Norepinephrine	Locus ceruleus (pons)	<b>†</b>	<b>†</b>				
Serotonin	Raphe nuclei (medulla, pons)	<b>†</b>	<b>†</b>				ţ

FAS1\_2019\_12-Neurol.indd 495 11/8/19 7:39 AM

#### **Meninges**



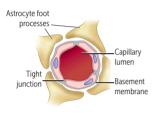
Three membranes that surround and protect the brain and spinal cord:

- Dura mater—thick outer layer closest to skull. Derived from mesoderm.
- Arachnoid mater—middle layer, contains web-like connections. Derived from neural crest
- Pia mater—thin, fibrous inner layer that firmly adheres to brain and spinal cord.
   Derived from neural crest.

CSF flows in the subarachnoid space, located between arachnoid and pia mater.

Epidural space—potential space between the dura mater and skull/vertebral column containing fat and blood vessels. Site of blood collection associated with middle meningeal artery injury.

#### **Blood-brain barrier**



Prevents circulating blood substances (eg, bacteria, drugs) from reaching the CSF/CNS. Formed by 3 structures:

- Tight junctions between nonfenestrated capillary endothelial cells
- Basement membrane
- Astrocyte foot processes

Glucose and amino acids cross slowly by carrier-mediated transport mechanisms.

Nonpolar/lipid-soluble substances cross rapidly via diffusion.

Circumventricular organs with fenestrated capillaries and no blood-brain barrier allow molecules in blood to affect brain function (eg, area postrema—vomiting after chemotherapy; OVLT [organum vasculosum lamina terminalis]—osmoreceptors) or neurosecretory products to enter circulation (eg, neurohypophysis—ADH release). Infarction and/or neoplasm destroys endothelial cell tight junctions → vasogenic edema. Hyperosmolar agents (eg, mannitol) can disrupt

the BBB  $\rightarrow$  † permeability of medications.

#### **Vomiting center**

Coordinated by nucleus tractus solitarius (NTS) in the medulla, which receives information from the chemoreceptor trigger zone (CTZ, located within area postrema in 4th ventricle), GI tract (via vagus nerve), vestibular system, and CNS.

CTZ and adjacent vomiting center nuclei receive input from 5 major receptors: muscarinic (M<sub>1</sub>), dopamine (D<sub>2</sub>), histamine (H<sub>1</sub>), serotonin (5-HT<sub>2</sub>), and neurokinin (NK-1) receptors.

- 5-HT<sub>3</sub>, D<sub>2</sub>, and NK-1 antagonists used to treat chemotherapy-induced vomiting.
- H<sub>1</sub> and M<sub>1</sub> antagonists treat motion sickness; H<sub>1</sub> antagonists treat hyperemesis gravidarum.

Sleep physiology	Sleep cycle is regulated by the circadian rhythm, which is driven by suprachiasmatic nucleus (SCN of the hypothalamus. Circadian rhythm controls nocturnal release of ACTH, prolactin, melatonin norepinephrine: SCN → norepinephrine release → pineal gland → ↑ melatonin. SCN is regulated by environment (eg, light).  Two stages: rapid-eye movement (REM) and non-REM.  Alcohol, benzodiazepines, and barbiturates are associated with ↓ REM sleep and N3 sleep; norepinephrine also ↓ REM sleep.  Benzodiazepines are useful for night terrors and sleepwalking by ↓ N3 and REM sleep.			
SLEEP STAGE (% OF TOTAL SLEEP TIME IN YOUNG ADULTS)	DESCRIPTION	EEG WAVEFORM AND NOTES		
Awake (eyes open)	Alert, active mental concentration.	Beta (highest frequency, lowest amplitude)		
Awake (eyes closed)		<b>A</b> lpha		
Non-REM sleep				
Stage N1 (5%)	Light sleep.	<b>T</b> heta		
Stage N <mark>2</mark> (45%)	Deeper sleep; when bruxism ("twoth" [tooth] grinding) occurs.	Sleep spindles and K complexes		
Stage N <mark>3</mark> (25%)	Deepest non-REM sleep (slow-wave sleep); sleepwalking, night terrors, and bedwetting occur (wee and flee in N3).	Delta (lowest frequency, highest amplitude)		
REM sleep (25%)	Loss of motor tone, † brain O <sub>2</sub> use, variable pulse/BP, † ACh. REM is when dreaming, nightmares, and penile/clitoral tumescence occur; may serve memory processing function. Extraocular movements due to activity of PPRF (paramedian pontine reticular formation/conjugate gaze center).  Occurs every 90 minutes, and duration † through the night.	Beta Changes in elderly: ↓ REM sleep time, ↓ N3. Changes in depression: ↑ REM sleep time, ↓ REM latency, ↓ N3, repeated nighttime awakenings, early morning awakening (terminal insomnia). Changes in narcolepsy: ↓ REM latency.  At night, BATS Drink Blood		

11/8/19 7:39 AM FAS1\_2019\_12-Neurol.indd 497

### NEUROLOGY AND SPECIAL SENSES ► NEUROLOGY—ANATOMY AND PHYSIOLOGY

Hypothalamus	(anterior pituitary) and Neurohypophysis (post	•
Lateral nucleus	Hunger. Destruction → anorexia, failure to thrive (infants). Stimulated by ghrelin, inhibited by leptin.	Lateral injury makes you Lean.
Ventromedial nucleus	Satiety. Destruction (eg, craniopharyngioma)  → hyperphagia. Stimulated by leptin.	VentroMedial injury makes you Very Massive.
Anterior nucleus	Cooling, parasympathetic.	A/C = Anterior Cooling.
Posterior nucleus	Heating, sympathetic.	Heating controlled by Posterior nucleus ("Hot Pot").
Suprachiasmatic nucleus	Circadian rhythm.	SCN is a Sun-Censing Nucleus.
Supraoptic and paraventricular nuclei	Synthesize ADH and oxytocin.	SAD POX: Supraoptic = ADH, Paraventricular = OXytocin  ADH and oxytocin are carried by neurophysins down axons to posterior pituitary, where these hormones are stored and released.
Preoptic nucleus	Thermoregulation, sexual behavior. Releases GnRH.	Failure of GnRH-producing neurons to migrate from olfactory pit → Kallmann syndrome.

NUCLEI	INPUT	SENSES	DESTINATION	MNEMONIC
Ventral Postero- Lateral nucleus	Spinothalamic and dorsal columns/medial lemniscus	Vibration, Pain, Pressure, Proprioception, Light touch, temperature	l° somatosensory cortex	
Ventral postero- Medial nucleus	Trigeminal and gustatory pathway	Face sensation, taste	l° somatosensory cortex	Makeup goes on the face
Lateral geniculate nucleus	CN II, optic chiasm, optic tract	Vision	l° visual cortex (calcarine sulcus)	Lateral = Light
Medial geniculate nucleus	Superior olive and inferior colliculus of tectum	Hearing	Auditory cortex of temporal lobe	Medial = Music
Ventral lateral nucleus	Cerebellum, basal ganglia	Motor	Motor cortex	

FAS1\_2019\_12-Neurol.indd 498 11/8/19 7:39 AM

#### **Limbic system**



Collection of neural structures involved in emotion, long-term memory, olfaction, behavior modulation, ANS function.

Consists of hippocampus (red arrows in A), amygdalae, mammillary bodies, anterior thalamic nuclei, cingulate gyrus (yellow arrows in A), entorhinal cortex. Responsible for Feeding, Fleeing, Fighting, Feeling, and Sex.

The famous **5 F**'s.

Dopaminergic pathways	Commonly altered by drugs (eg, antipsychotics) an	nd movement disorders (eg, Parkinson disease).
PATHWAY	SYMPTOMS OF ALTERED ACTIVITY	NOTES
Mesocortical	↓ activity → "negative" symptoms (eg, anergia, apathy, lack of spontaneity)	Antipsychotic drugs have limited effect
Mesolimbic	↑ activity → "positive" symptoms (eg, delusions, hallucinations)	1° therapeutic target of antipsychotic drugs  → ↓ positive symptoms (eg, in schizophrenia)
Nigrostriatal	<ul> <li>↓ activity → extrapyramidal symptoms (eg, dystonia, akathisia, parkinsonism, tardive dyskinesia)</li> </ul>	Major dopaminergic pathway in brain Significantly affected by movement disorders and antipsychotic drugs
Tuberoinfundibular	↓ activity → ↑ prolactin → ↓ libido, sexual dysfunction, galactorrhea, gynecomastia (in men)	

#### Cerebellum



Modulates movement; aids in coordination and balance A.

#### Input:

- Contralateral cortex via middle cerebellar peduncle
- Ipsilateral proprioceptive information via inferior cerebellar peduncle from spinal cord

#### Output:

- Deep nuclei (lateral → medial)—Dentate,
   Emboliform, Globose, Fastigial

**Lateral** lesions—affect voluntary movement of extremities (**lateral** structures); when injured, propensity to fall toward injured (ipsilateral) side.

Medial lesions (eg, vermis, fastigial nuclei, flocculonodular lobe)—truncal ataxia (widebased cerebellar gait), nystagmus, head tilting. Generally result in bilateral motor deficits affecting axial and proximal limb musculature (medial structures).

Don't Eat Greasy Foods

FAS1\_2019\_12-Neurol.indd 499 11/8/19 7:39 AM

#### NEUROLOGY AND SPECIAL SENSES ► NEUROLOGY—ANATOMY AND PHYSIOLOGY

#### **Basal ganglia**



Important in voluntary movements and adjusting posture A. Receives cortical input, provides negative feedback to cortex to modulate movement.

D<sub>1</sub> Receptor = D1Rect pathway. Indirect (D<sub>2</sub>) = Inhibitory.

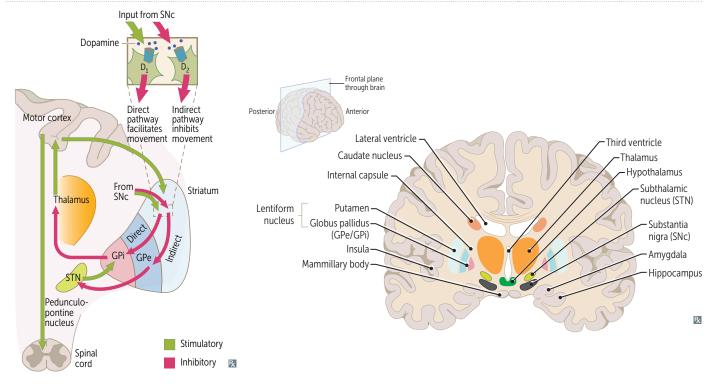
Striatum = putamen (motor) + Caudate (cognitive).

Lentiform = putamen + globus pallidus.

Direct (excitatory) pathway—SNc input to the striatum via the nigrostriatal dopaminergic pathway releases GABA, which inhibits GABA release from the GPi, disinhibiting the Thalamus via the GPi († motion).

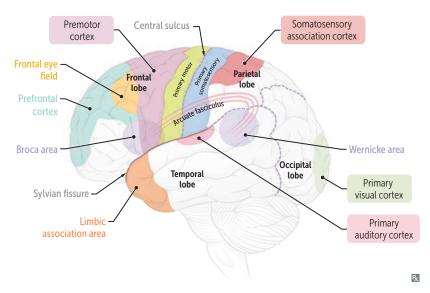
Indirect (inhibitory) pathway—SNc input to the striatum via the nigrostriatal dopaminergic pathway releases GABA that disinhibits STN via GPe inhibition, and STN stimulates GPi to inhibit the thalamus (‡ motion).

Dopamine binds to  $D_1$ , stimulating the excitatory pathway, and to  $D_2$ , inhibiting the inhibitory pathway  $\rightarrow \uparrow$  motion.



FAS1\_2019\_12-Neurol.indd 500 11/8/19 7:39 AM

#### **Cerebral cortex regions**



#### **Cerebral perfusion**

Relies on tight autoregulation. Primarily driven by Pco<sub>2</sub> (Po<sub>2</sub> also modulates perfusion in severe hypoxia).

Also relies on a pressure gradient between mean arterial pressure (MAP) and intracranial pressure (ICP). ↓ blood pressure or † ICP → ↓ cerebral perfusion pressure (CPP).

Therapeutic hyperventilation → ↓ Pco,

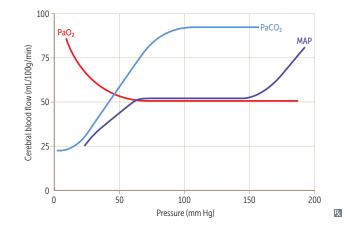
- → vasoconstriction → ↓ cerebral blood flow
- $\rightarrow$  ICP. May be used to treat acute cerebral edema (eg, 2° to stroke) unresponsive to other interventions.

CPP = MAP - ICP. If CPP = 0, there is no cerebral perfusion  $\rightarrow$  brain death.

Hypoxemia increases CPP only if Po<sub>2</sub>

< 50 mm Hg.

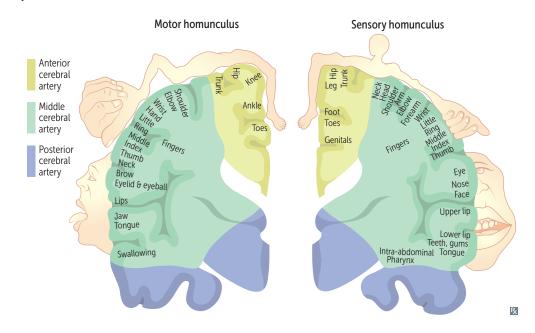
CPP is directly proportional to Pco<sub>2</sub> until Pco<sub>2</sub> > 90 mm Hg.



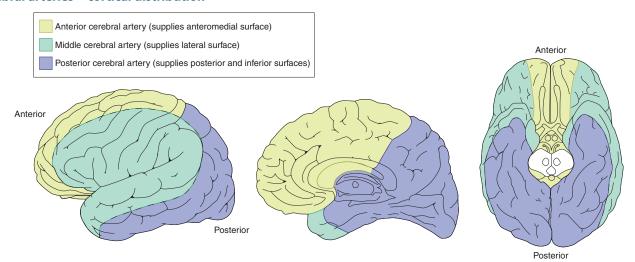
FAS1\_2019\_12-Neurol.indd 501 11/8/19 7:39 AM

#### **Homunculus**

Topographic representation of motor and sensory areas in the cerebral cortex. Distorted appearance is due to certain body regions being more richly innervated and thus having † cortical representation.



#### Cerebral arteries—cortical distribution



#### Watershed zones



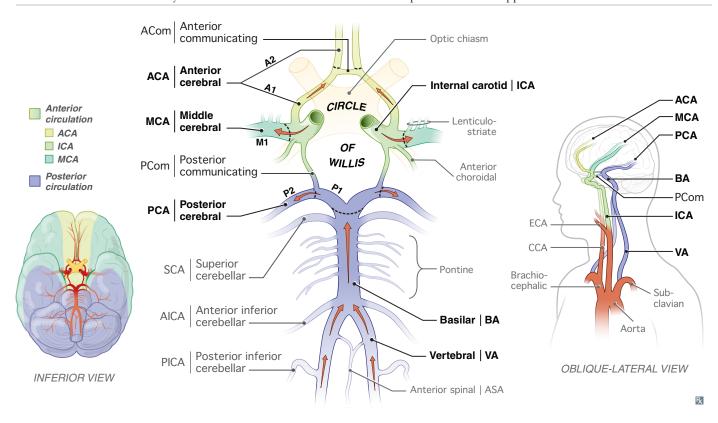
Cortical border zones occur between anterior and middle cerebral arteries and posterior and middle cerebral arteries (blue areas in A). Internal border zones occur between the superficial and deep vascular territories of the middle cerebral artery (red areas in A).

Infarct due to severe hypoperfusion → proximal upper and lower extremity weakness ("manin-the-barrel syndrome"), higher order visual dysfunction (if posterior cerebral/middle cerebral cortical border zone stroke).

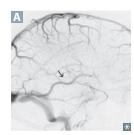
FAS1\_2019\_12-Neurol.indd 502 11/8/19 7:39 AM

#### **Circle of Willis**

System of anastomoses between anterior and posterior blood supplies to brain.

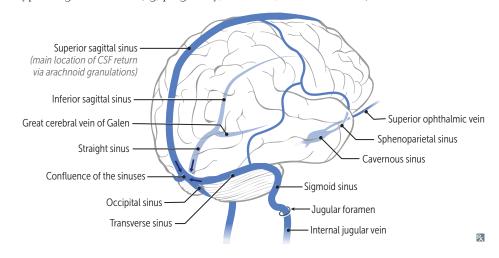


#### **Dural venous sinuses**



Large venous channels A that run through the periosteal and meningeal layers of the dura mater. Drain blood from cerebral veins (arrow) and receive CSF from arachnoid granulations. Empty into internal jugular vein.

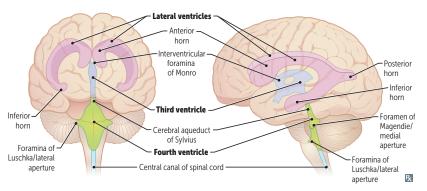
**Venous sinus thrombosis**—presents with signs/symptoms of † ICP (eg, headache, seizures, papilledema, focal neurologic deficits). May lead to venous hemorrhage. Associated with hypercoagulable states (eg, pregnancy, OCP use, factor V Leiden).



FAS1\_2019\_12-Neurol.indd 503 11/8/19 7:39 AM

#### NEUROLOGY AND SPECIAL SENSES ► NEUROLOGY—ANATOMY AND PHYSIOLOGY

#### **Ventricular system**



Lateral ventricles → 3rd ventricle via right and left interventricular foramina of Monro.

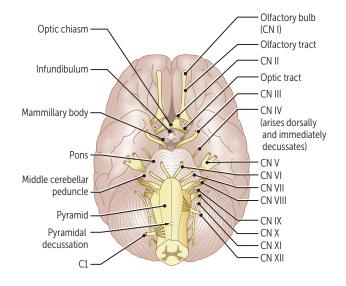
3rd ventricle → 4th ventricle via cerebral aqueduct of Sylvius.

4th ventricle → subarachnoid space via:

- Foramina of Luschka = Lateral.
- Foramen of Magendie = Medial.

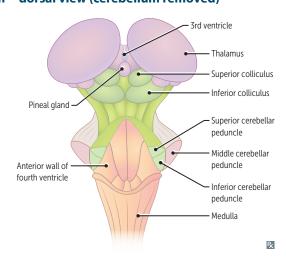
CSF made by choroid plexuses located in the lateral and fourth ventricles. Travels to subarachnoid space via foramina of Luschka and Magendie, is reabsorbed by arachnoid granulations, and then drains into dural venous sinuses.

#### **Brain stem—ventral view**



- 4 CN are above pons (I, II, III, IV).
- 4 CN exit the pons (V, VI, VII, VIII).
- 4 CN are in medulla (IX, X, XI, XII).
- 4 CN nuclei are medial (III, IV, VI, XII). "Factors of 12, except 1 and 2."

#### Brain stem—dorsal view (cerebellum removed)



Pineal gland—melatonin secretion, circadian rhythms.

Superior colliculi—direct eye movements to stimuli (noise/movements) or objects of interest.

Inferior colliculi—auditory.

Your eyes are **above** your ears, and the superior colliculus (visual) is **above** the inferior colliculus (auditory).

FAS1\_2019\_12-Neurol.indd 504 11/8/19 7:39 AM

#### **Cranial nerve nuclei**

Located in tegmentum portion of brain stem (between dorsal and ventral portions):

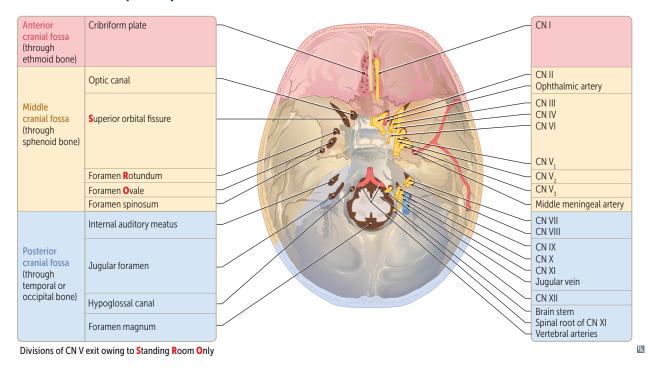
- Midbrain—nuclei of CN III, IV
- Pons—nuclei of CN V, VI, VII, VIII
- Medulla—nuclei of CN IX, X, XII
- Spinal cord—nucleus of CN XI

Lateral nuclei = sensory (aLar plate).

-Sulcus limitans-

Medial nuclei = Motor (basal plate).

#### **Cranial nerve and vessel pathways**



FAS1\_2019\_12-Neurol.indd 505 11/8/19 7:39 AM

#### **Cranial nerves**

NERVE	CN	FUNCTION	TYPE	MNEMONIC
Olfactory	I	Smell (only CN without thalamic relay to cortex)	Sensory	Some
Optic	II	Sight	Sensory	<b>S</b> ay
Oculomotor	III	Eye movement (SR, IR, MR, IO), pupillary constriction (sphincter pupillae: Edinger-Westphal nucleus, muscarinic receptors), accommodation, eyelid opening (levator palpebrae)	Motor	<b>M</b> arry
Trochlear	IV	Eye movement (SO)	Motor	Money
Trigeminal	V	Mastication, facial sensation (ophthalmic, maxillary, mandibular divisions), somatosensation from anterior 2/3 of tongue, dampening of loud noises (tensor tympani)	Both	But
Abducens	VI	Eye movement (LR)	Motor	<b>M</b> y
Facial	VII	Facial movement, taste from anterior 2/3 of tongue (chorda tympani), lacrimation, salivation (submandibular and sublingual glands are innervated by CN seven), eye closing (orbicularis oculi), auditory volume modulation (stapedius)	Both	Brother
Vestibulocochlear	VIII	Hearing, balance	Sensory	Says
Glossopharyngeal	IX	Taste and sensation from posterior 1/3 of tongue, swallowing, salivation (parotid gland), monitoring carotid body and sinus chemo- and baroreceptors, and elevation of pharynx/larynx (stylopharyngeus)	Both	Big
Vagus	X	Taste from supraglottic region, swallowing, soft palate elevation, midline uvula, talking, cough reflex, parasympathetics to thoracoabdominal viscera, monitoring aortic arch chemo- and baroreceptors	Both	Brains
Accessory	XI	Head turning, shoulder shrugging (SCM, trapezius)	Motor	Matter
Hypoglossal	XII	Tongue movement	Motor	Most

### Vagal nuclei

NUCLEUS	FUNCTION	CRANIAL NERVES
Nucleus tractus Solitarius	Visceral Sensory information (eg, taste, baroreceptors, gut distention)	VII, IX, X
Nucleus a <mark>M</mark> biguus	<b>M</b> otor innervation of pharynx, larynx, upper esophagus (eg, swallowing, palate elevation)	IX, X, XI (cranial portion)
Dorsal motor nucleus	Sends autonomic (parasympathetic) fibers to heart, lungs, upper GI	X

FAS1\_2019\_12-Neurol.indd 506 11/8/19 7:39 AM

#### **Cranial nerve reflexes**

REFLEX	AFFERENT	EFFERENT
Corneal	$V_1$ ophthalmic (nasociliary branch)	Bilateral VII (temporal branch—orbicularis oculi)
Lacrimation	${ m V_{_{1}}}$ (loss of reflex does not preclude emotional tears)	VII
Jaw jerk	V <sub>3</sub> (sensory—muscle spindle from masseter)	V <sub>3</sub> (motor—masseter)
Pupillary	II	III
Gag	IX	X
Cough	X	X
Mastication muscles	3 muscles close jaw: Masseter, teMporalis, Medial pterygoid. 1 opens: Lateral pterygoid.	M's Munch. Lateral Lowers (when speaking of pterygoids

All are innervated by trigeminal nerve  $(V_2)$ .

with respect to jaw motion).

"It takes more muscle to keep your mouth shut."

#### **Spinal nerves**

There are 31 pairs of spinal nerves: 8 cervical, 12 thoracic, 5 lumbar, 5 sacral, 1 coccygeal. Nerves C1–C7 exit above the corresponding vertebrae (eg, C3 exits above the 3rd cervical vertebra). C8 spinal nerve exits below C7 and above T1. All other nerves exit below (eg, L2 exits below the 2nd lumbar vertebra).

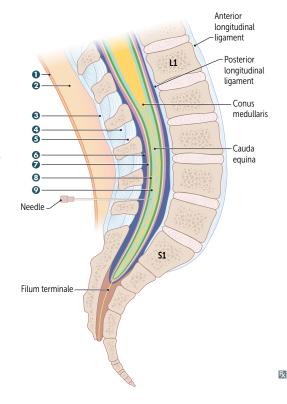
#### Spinal cord—lower extent

In adults, spinal cord ends at lower border of L1–L2 vertebrae. Subarachnoid Space (which contains the CSF) extends to lower border of \$2 vertebra. Lumbar puncture is usually performed between L3-L4 or L4-L5 (level of cauda equina).

Goal of lumbar puncture is to obtain sample of CSF without damaging spinal cord. To keep the cord alive, keep the spinal needle between **L3** and **L5**.

Needle passes through:

- skin
- 2 fascia and fat
- supraspinous ligament
- 4 interspinous ligament
- 6 ligamentum flavum
- 6 epidural space (epidural anesthesia needle stops here)
- dura mater
- arachnoid mater
- subarachnoid space (CSF collection occurs here)

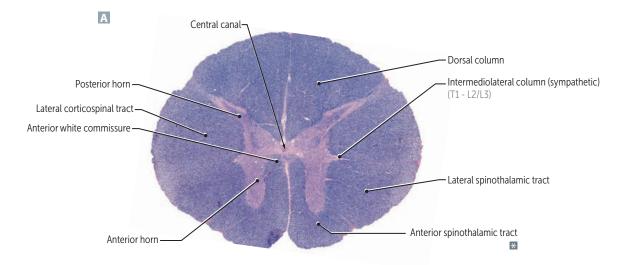


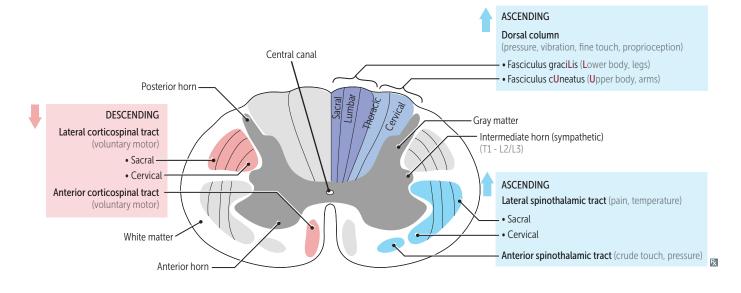
FAS1\_2019\_12-Neurol.indd 507 11/8/19 7:39 AM

# Spinal cord and associated tracts

Legs (Lumbosacral) are Lateral in Lateral corticospinal, spinothalamic tracts. Thoracic spinal cord section in A.

Dorsal columns are organized as you are, with hands at sides. "Arms outside, legs inside."





FAS1\_2019\_12-Neurol.indd 508 11/8/19 7:39 AM

# **Spinal tract anatomy** Ascending tracts synapse and then cross. **and functions**

TRACT	FUNCTION	1ST-ORDER NEURON	SYNAPSE 1	2ND-ORDER NEURON	SYNAPSE 2 + PROJECTIONS	
Ascending tracts						
Dorsal column	Pressure, vibration, fine touch, proprioception	Sensory nerve ending → bypasses pseudounipolar cell body in dorsal root ganglion → enters spinal cord → ascends ipsilaterally in dorsal columns	Nucleus gracilis, nucleus cuneatus (ipsilateral medulla)	Decussates in medulla  → ascends contralaterally as the medial lemniscus	VPL (thalamus) → sensory cortex	
Spinothalamic tract	Lateral: pain, temperature Anterior: crude touch, pressure	Sensory nerve ending (Aδ and C fibers) → bypasses pseudounipolar cell body in dorsal root ganglion → enters spinal cord	Ipsilateral gray matter (spinal cord)	Decussates in spinal cord as the anterior white commissure → ascends contralaterally	→ sensory cortex	
Descending tract						
Lateral corticospinal tract	Voluntary movement of contralateral limbs	UMN: cell body in 1° motor cortex → descends ipsilaterally (through posterior limb of internal capsule and cerebral peduncle), most fibers decussate at caudal medulla (pyramidal decussation) → descends contralaterally	Cell body of anterior horn (spinal cord)	LMN: leaves spinal cord	NMJ → muscle fibers	

FAS1\_2019\_12-Neurol.indd 509 11/8/19 7:39 AM

#### **Clinical reflexes**

C5, 6 C6, 7, 8 L2, 3, 4 S1, 2 Reflexes count up in order (main nerve root in **bold**):

Achilles reflex = S1, S2 ("buckle my shoe")

Patellar reflex = L2-L4 ("kick the door")

Biceps and brachioradialis reflexes = C5, C6

("pick up sticks") **Triceps reflex** = C6, **C**7, C8 ("lay them straight")

Additional reflexes:

**Cremasteric reflex** = L1, L2 ("testicles move") **Anal wink reflex** = S3, S4 ("winks galore")

Primitive reflexes	CNS reflexes that are present in a healthy infant, but are absent in a neurologically intact adult. Normally disappear within 1st year of life. These primitive reflexes are inhibited by a mature/ developing frontal lobe. They may reemerge in adults following frontal lobe lesions → loss of inhibition of these reflexes.
Moro reflex	"Hang on for life" reflex—abduct/extend arms when startled, and then draw together
Rooting reflex	Movement of head toward one side if cheek or mouth is stroked (nipple seeking)
Sucking reflex	Sucking response when roof of mouth is touched
Palmar reflex	Curling of fingers if palm is stroked
Plantar reflex	Dorsiflexion of large toe and fanning of other toes with plantar stimulation Babinski sign—presence of this reflex in an adult, which may signify a UMN lesion
Galant reflex	Stroking along one side of the spine while newborn is in ventral suspension (face down) causes lateral flexion of lower body toward stimulated side

#### **Landmark dermatomes**

DERMATOME	CHARACTERISTICS		
C2	Posterior half of skull	VI	
C3	High turtleneck shirt Diaphragm and gallbladder pain referred to the right shoulder via phrenic nerve C3, 4, 5 keeps the diaphragm alive	10 C2 C2 C3 C4 C4 C4 C4 C4 C4 C4 C4 C4 C4 C4 C4 C4	a a apparate the part of the p
C4	Low-collar shirt	75 16 77	C6 C8 T19 T19 T11
C6	Includes thumbs <b>Thumbs up</b> sign on left hand looks like a <mark>6</mark>	18 19 110 111 112 112	
T4	At the <mark>nipple</mark> T <b>4</b> at the teat <mark>pore</mark>	22.53	0/c3 (\$\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\
T7	At the xiphoid process 7 letters in xiphoid	L4	12
T10	At the umbilicus (belly but <mark>ten</mark> ) Point of referred pain in early appendicitis	LS	21   52
Ll	At the <b>I</b> nguinal <b>L</b> igament	51	L4 S1
L4	Includes the kneecaps Down on <b>ALL 4</b> 's	(J. L.S.	15-14
S2, S3, S4	Sensation of penile and anal zones S2, 3, 4 keep the penis off the floor		

FAS1\_2019\_12-Neurol.indd 510 11/8/19 7:39 AM

► NEUROLOGY—PATHOLOGY

AREA OF LESION	CONSEQUENCE	EXAMPLES/COMMENTS
Frontal lobe	Disinhibition and deficits in concentration, orientation, judgment; may have reemergence of primitive reflexes	
Frontal eye fields	Destructive lesions (eg, MCA stroke): eyes look toward brain lesion (ie, away from side of hemiplegia)	
Paramedian pontine reticular formation	Eyes look away from brain lesion (ie, toward side of hemiplegia)	
Medial longitudinal fasciculus	Internuclear ophthalmoplegia (impaired adduction of ipsilateral eye; nystagmus of contralateral eye with abduction)	Multiple sclerosis
Dominant parietal cortex	Agraphia, acalculia, finger agnosia, left-right disorientation	Gerstmann syndrome
Nondominant parietal cortex	Agnosia of the contralateral side of the world	Hemispatial neglect syndrome
Hippocampus (bilateral)	Anterograde amnesia—inability to make new memories	
Basal ganglia	May result in tremor at rest, chorea, athetosis	Parkinson disease, Huntington disease, Wilson disease
Subthalamic nucleus	Contralateral hemiballismus	
Mammillary bodies (bilateral)	Wernicke-Korsakoff syndrome—Confusion, Ataxia, Nystagmus, Ophthalmoplegia, memory loss (anterograde and retrograde amnesia), confabulation, personality changes	Wernicke problems come in a CAN O' beer and other conditions associated with thiamine deficiency
Amygdala (bilateral)	Klüver-Bucy syndrome—disinhibited behavior (eg, hyperphagia, hypersexuality, hyperorality)	HSV-1 encephalitis
Dorsal midbrain	Parinaud syndrome—vertical gaze palsy, pupillary light-near dissociation, lid retraction, convergence-retraction nystagmus	Stroke, hydrocephalus, pinealoma
Reticular activating system (midbrain)	Reduced levels of arousal and wakefulness	Coma
Cerebellar hemisphere	Intention tremor, limb ataxia, loss of balance; damage to cerebellum → ipsilateral deficits; fall toward side of lesion	Cerebellar hemispheres are laterally located—affect lateral limbs
Cerebellar vermis	Truncal ataxia (wide-based, "drunken sailor" gait), nystagmus	Vermis is <b>centrall</b> y located—affects <b>central</b> body Degeneration associated with chronic alcohol use
Red nucleus (midbrain)	Decorticate (flexor) posturing—lesion above red nucleus, presents with flexion of upper extremities and extension of lower extremities Decerebrate (extensor) posturing—lesion at or below red nucleus, presents with extension of upper and lower extremities	Worse prognosis with decerebrate posturing In decorticate posturing, your hands are near the cor (heart)

FAS1\_2019\_12-Neurol.indd 511 11/8/19 7:39 AM

### Ischemic brain disease/stroke

Irreversible neuronal injury begins after 5 minutes of hypoxia. Most vulnerable: hippocampus, neocortex, cerebellum (Purkinje cells), watershed areas ("vulnerable hippos need pure water"). Stroke imaging: noncontrast CT to exclude hemorrhage (before tPA can be given). CT detects ischemic changes in 6–24 hr. Diffusion-weighted MRI can detect ischemia within 3–30 min.

TIME SINCE ISCHEMIC EVENT	12-24 HOURS	24-72 HOURS	3-5 DAYS	1–2 WEEKS	> 2 WEEKS
Histologic features	Eosinophilic cytoplasm + pyknotic nuclei (red neurons)	Necrosis + neutrophils	Macrophages (microglia)	Reactive gliosis (astrocytes) + vascular proliferation	Glial scar

#### Ischemic stroke

Acute blockage of vessels → disruption of blood flow and subsequent ischemia → infarction → liquefactive necrosis.

#### 3 types:

- Thrombotic—due to a clot forming directly at site of infarction (commonly the MCA A), usually over a ruptured atherosclerotic plaque.
- Embolic—embolus from another part of the body obstructs vessel. Can affect multiple vascular territories. Examples: atrial fibrillation, carotid artery stenosis, DVT with patent foramen ovale, infective endocarditis.
- Hypoxic—due to hypoperfusion or hypoxemia. Common during cardiovascular surgeries, tends to affect watershed areas.

Treatment: tPA (if within 3–4.5 hr of onset and no hemorrhage/risk of hemorrhage) and/or thrombectomy (if large artery occlusion). Reduce risk with medical therapy (eg, aspirin, clopidogrel); optimum control of blood pressure, blood sugars, lipids; smoking cessation; and treat conditions that † risk (eg, atrial fibrillation, carotid artery stenosis).

### Transient ischemic attack

Brief, reversible episode of focal neurologic dysfunction without acute infarction (⊝ MRI), with the majority resolving in < 15 minutes; ischemia (eg, embolus, small vessel stenosis).

# Neonatal intraventricular hemorrhage



Bleeding into ventricles (arrow in coronal transcranial ultrasound A shows blood in right intraventricular space, extending into periventricular white matter). Increased risk in premature and low-birth-weight infants. Originates in germinal matrix, a highly vascularized layer within the subventricular zone. Due to reduced glial fiber support and impaired autoregulation of BP in premature infants. Can present with altered level of consciousness, bulging fontanelle, hypotension, seizures, coma.

FAS1\_2019\_12-Neurol.indd 512 11/8/19 7:39 AM

#### **Intracranial hemorrhage**

#### **Epidural hematoma**

Rupture of middle meningeal artery (branch of maxillary artery), often 2° to skull fracture (circle in ♠) involving the pterion (thinnest area of the lateral skull). Might present with transient loss of consciousness → recovery ("lucid interval") → rapid deterioration due to hematoma expansion.

Scalp hematoma (arrows in ♠) and rapid intracranial expansion (arrows in ♠) under systemic arterial pressure → transtentorial herniation, CN III palsy.

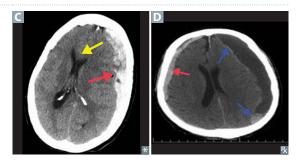
CT shows biconvex (lentiform), hyperdense blood collection **B** not crossing suture lines.



#### Subdural hematoma

Rupture of bridging veins. Can be acute (traumatic, high-energy impact → hyperdense on CT) or chronic (associated with mild trauma, cerebral atrophy, elderly, alcoholism → hypodense on CT). Also seen in shaken babies. Predisposing factors: brain atrophy, trauma

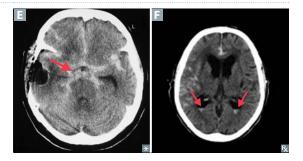
Crescent-shaped hemorrhage (red arrows in and b) that crosses suture lines. Can cause midline shift (yellow arrow in c), findings of "acute on chronic" hemorrhage (blue arrows in b).



### Subarachnoid hemorrhage

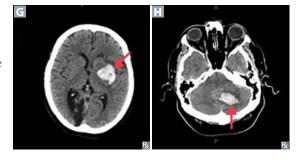
Bleeding **E f** due to trauma, or rupture of an aneurysm (such as a saccular aneurysm **E**) or arteriovenous malformation. Rapid time course. Patients complain of "worst headache of my life." Bloody or yellow (xanthochromic) lumbar puncture.

Vasospasm can occur due to blood breakdown or rebleed 3–10 days after hemorrhage → ischemic infarct; nimodipine used to prevent/reduce vasospasm. ↑ risk of developing communicating and/or obstructive hydrocephalus.



# Intraparenchymal hemorrhage

Most commonly caused by systemic hypertension. Also seen with amyloid angiopathy (recurrent lobar hemorrhagic stroke in elderly), vasculitis, neoplasm. May be 2° to reperfusion injury in ischemic stroke. Hypertensive hemorrhages (Charcot-Bouchard microaneurysm) most often occur in putamen of basal ganglia (lenticulostriate vessels ), followed by thalamus, pons, and cerebellum .



FAS1\_2019\_12-Neurol.indd 513 11/8/19 7:39 AM

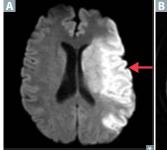
### **Effects of strokes**

ARTERY	AREA OF LESION	SYMPTOMS	NOTES
Anterior circula	ation		
Middle cerebral artery	Motor and sensory cortices A—upper limb and face. Temporal lobe (Wernicke area); frontal lobe (Broca area).	Contralateral paralysis and sensory loss—face and upper limb.  Aphasia if in dominant (usually left) hemisphere. Hemineglect if lesion affects nondominant (usually right) hemisphere.	Wernicke aphasia is associated with right superior quadrant visual field defect due to temporal lobe involvement.
Anterior cerebral artery	Motor and sensory cortices—lower limb.	Contralateral paralysis and sensory loss—lower limb, urinary incontinence.	
Lenticulo- striate artery	Striatum, internal capsule.	Contralateral paralysis. Absence of cortical signs (eg, neglect, aphasia, visual field loss).	Pure motor stroke. Common location of lacunar infarcts <b>B</b> , due to hyaline arteriosclerosis (lipohyalinosis) 2° to unmanaged hypertension.
Posterior circul	ation		
Anterior spinal artery	Corticospinal tract.  Medial lemniscus.  Caudal medulla—hypoglossal nerve.	Contralateral paralysis—upper and lower limbs.  ↓ contralateral proprioception. Ipsilateral hypoglossal dysfunction (tongue deviates ipsilaterally).	Medial medullary syndrome—caused by infarct of paramedian branches of ASA and/or vertebral arteries.
Posterior inferior cerebellar artery	Lateral medulla: Nucleus ambiguus (CN IX, X, XI)  Vestibular nuclei Lateral spinothalamic tract, spinal trigeminal nucleus  Sympathetic fibers Inferior cerebellar peduncle	Dysphagia, hoarseness, ↓ gag reflex, hiccups.  Vomiting, vertigo, nystagmus ↓ pain and temperature sensation from contralateral body, ipsilateral face.  Ipsilateral Horner syndrome.  Ipsilateral ataxia, dysmetria.	syndrome.  Nucleus ambiguus effects are specific to PICA lesions C.  "Don't pick a (PICA) horse (hoarseness) that can't eat (dysphagia)."  Also supplies inferior cerebellar peduncle (part of cerebellum).
Anterior inferior cerebellar artery	Lateral pons: Facial nucleus  Vestibular nuclei Spinothalamic tract, spinal trigeminal nucleus  Sympathetic fibers Middle and inferior cerebellar peduncles Labyrinthine artery	Paralysis of face (LMN lesion vs UMN lesion in cortical stroke), ↓ lacrimation, ↓ salivation, ↓ taste from anterior 2/3 of tongue. Vomiting, vertigo, nystagmus ↓ pain and temperature sensation from contralateral body, ipsilateral face. Ipsilateral Horner syndrome. Ipsilateral ataxia, dysmetria.  Ipsilateral sensorineural deafness, vertigo.	Lateral pontine syndrome. Facial nucleus effects are specific to AICA lesions.  "Facial droop means AICA's pooped." Also supplies middle and inferior cerebellar peduncles (part of cerebellum).

FAS1\_2019\_12-Neurol.indd 514 11/8/19 7:39 AM

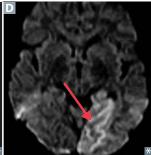
#### **Effects of strokes (continued)**

ARTERY	AREA OF LESION	SYMPTOMS	NOTES
Basilar artery	Pons, medulla, lower midbrain.	If RAS spared, consciousness is preserved.	Locked-in syndrome (locked in the basement).
	Corticospinal and corticobulbar tracts.	Quadriplegia; loss of voluntary facial, mouth, and tongue movements.	
	Ocular cranial nerve nuclei, paramedian pontine reticular formation.	Loss of horizontal, but not vertical, eye movements.	
Posterior cerebral artery	Occipital lobe D.	Contralateral hemianopia with macular sparing; alexia without agraphia (dominant hemisphere).	
	Δ	4.0	





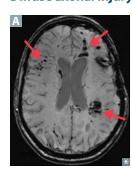




# Central poststroke pain syndrome

Neuropathic pain due to thalamic lesions. Initial paresthesias followed in weeks to months by allodynia (ordinarily painless stimuli cause pain) and dysesthesia (altered sensation) on the contralateral side. Occurs in 10% of stroke patients.

#### Diffuse axonal injury



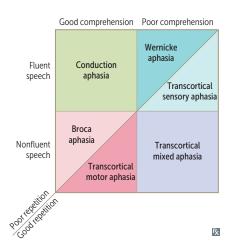
Caused by traumatic shearing forces during rapid acceleration and/or deceleration of the brain (eg, motor vehicle accident). Usually results in devastating neurologic injury, often causing coma or persistent vegetative state. MRI A shows multiple lesions (punctate hemorrhages) involving the white matter tracts.

FAS1\_2019\_12-Neurol.indd 515 11/8/19 7:39 AM

#### **Aphasia**

Aphasia—higher-order language deficit (inability to understand/produce/use language appropriately); caused by pathology in dominant cerebral hemisphere (usually left).

Dysarthria—motor inability to produce speech (movement deficit).



TYPE	COMMENTS
Broca (expressive)	Broca area in inferior frontal gyrus of frontal lobe. Patient appears frustrated, insight intact.  Broca = Broken Boca ( <i>boca</i> = mouth in Spanish).
Wernicke (receptive)	Wernicke area in superior temporal gyrus of temporal lobe. Patients do not have insight. Wernicke is a Word salad and makes no sense.
Conduction	Can be caused by damage to ar Cuate fasciculus.
Global	Broca and Wernicke areas affected.
Transcortical motor	Affects frontal lobe around Broca area, but Broca area is spared.
Transcortical sensory	Affects temporal lobe around Wernicke area, but Wernicke area is spared.
Transcortical mixed	Broca and Wernicke areas and arcuate fasciculus remain intact; surrounding watershed areas affected.

#### **Aneurysms**

Abnormal dilation of an artery due to weakening of vessel wall.

#### Saccular aneurysm



Also called berry aneurysm A. Occurs at bifurcations in the circle of Willis. Most common site is junction of ACom and ACA. Associated with ADPKD, Ehlers-Danlos syndrome. Other risk factors: advanced age, hypertension, smoking, race († risk in African-Americans).

Usually clinically silent until rupture (most common complication) → subarachnoid hemorrhage ("worst headache of my life" or "thunderclap headache") → focal neurologic deficits. Can also cause symptoms via direct compression of surrounding structures by growing aneurysm.

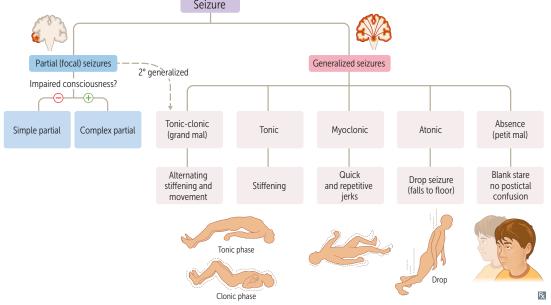
- ACom—compression → bitemporal hemianopia (compression of optic chiasm); visual acuity deficits; rupture → ischemia in ACA distribution → contralateral lower extremity hemiparesis, sensory deficits.
- MCA—rupture → ischemia in MCA distribution → contralateral upper extremity and lower facial hemiparesis, sensory deficits.
- PCom—compression → ipsilateral CN III palsy → mydriasis ("blown pupil"); may also see ptosis, "down and out" eye.

# Charcot-Bouchard microaneurysm

Common, associated with chronic hypertension; affects small vessels (eg, lenticulostriate arteries in basal ganglia, thalamus) and can cause hemorrhagic intraparenchymal strokes. Not visible on angiography.

FAS1\_2019\_12-Neurol.indd 516 11/8/19 7:39 AM

Seizures	Characterized by synchronized, high-frequency neuronal firing. Variety of form			
Partial (focal) seizures	Affect single area of the brain. Most commonly originate in medial temporal lobe. Types:  Simple partial (consciousness intact)— motor, sensory, autonomic, psychic  Complex partial (impaired consciousness, automatisms)	Epilepsy—disorder of recurrent, unprovoked seizures (febrile seizures are not epilepsy).  Status epilepticus—continuous (≥ 5 min) or recurring seizures that may result in brain injury.  Causes of seizures by age:		
Generalized seizures	Diffuse. Types:  Absence (petit mal)—3 Hz spike-and-wave discharges, no postictal confusion, blank stare  Myoclonic—quick, repetitive jerks  Tonic-clonic (grand mal)—alternating stiffening and movement, postictal confusion, urinary incontinence, tongue biting  Tonic—stiffening  Atonic—"drop" seizures (falls to floor); commonly mistaken for fainting	<ul> <li>Children—genetic, infection (febrile), trauma, congenital, metabolic</li> <li>Adults—tumor, trauma, stroke, infection</li> <li>Elderly—stroke, tumor, trauma, metabolic, infection</li> </ul>		
	Seizure	-		



#### Fever vs heat stroke

	Fever	Heat stroke
PATHOPHYSIOLOGY	Cytokine activation during inflammation (eg, infection)	Inability of body to dissipate heat (eg, exertion)
TEMPERATURE	Usually < 40 °C	Usually > 40 °C
COMPLICATIONS	Febrile seizure (benign, usually self-limiting)	CNS dysfunction (eg, confusion), end-organ damage, acute respiratory distress syndrome, rhabdomyolysis
MANAGEMENT	Acetaminophen or ibuprofen for comfort (does not prevent future febrile seizures), antibiotic therapy if indicated	Rapid external cooling, rehydration and electrolyte correction

FAS1\_2019\_12-Neurol.indd 517 11/8/19 7:39 AM

#### **Headaches**

Pain due to irritation of structures such as the dura, cranial nerves, or extracranial structures. More common in females, except cluster headaches.

CLASSIFICATION	LOCALIZATION	DURATION	DESCRIPTION	TREATMENT
Clustera	Unilateral	15 min–3 hr; repetitive	Excruciating periorbital pain ("suicide headache") with lacrimation and rhinorrhea. May present with Horner syndrome. More common in males.	Acute: sumatriptan, 100% O <sub>2</sub> . Prophylaxis: verapamil.
Migraine	Unilateral	4–72 hr	Pulsating pain with nausea, photophobia, or phonophobia. May have "aura." Due to irritation of CN V, meninges, or blood vessels (release of vasoactive neuropeptides [eg, substance P, calcitonin gene-related peptide]).	Acute: NSAIDs, triptans, dihydroergotamine. Prophylaxis: lifestyle changes (eg, sleep, exercise, diet), β-blockers, amitriptyline, topiramate, valproate, botulinum toxin, anti-CGRP monoclonal antibodies. POUND-Pulsatile, One-day duration, Unilateral, Nausea, Disabling.
Tension	Bilateral	> 30 min (typically 4–6 hr); constant	Steady, "band-like" pain. No photophobia or phonophobia. No aura.	Acute: analgesics, NSAIDs, acetaminophen. Prophylaxis: TCAs (eg, amitriptyline), behavioral therapy.

Other causes of headache include subarachnoid hemorrhage ("worst headache of my life"), meningitis, hydrocephalus, neoplasia, giant cell (temporal) arteritis.

<sup>a</sup>Compare with **trigeminal neuralgia**, which produces repetitive, unilateral, shooting/shock-like pain in the distribution of CN V. Triggered by chewing, talking, touching certain parts of the face. Lasts (typically) for seconds to minutes, but episodes often increase in intensity and frequency over time. First-line therapy: carbamazepine.

FAS1\_2019\_12-Neurol.indd 518 11/8/19 7:39 AM

#### **Movement disorders**

DISORDER	PRESENTATION	CHARACTERISTIC LESION	NOTES
Akathisia	Restlessness and intense urge to move.		Can be seen with neuroleptic use or as a side effect of Parkinson treatment.
Asterixis	Extension of wrists causes "flapping" motion.		Associated with hepatic encephalopathy, Wilson disease, and other metabolic derangements.
Athetosis	Slow, snake-like, writhing movements; especially seen in the fingers.	Basal ganglia.	Seen in Huntington disease.
Chorea	Sudden, jerky, purposeless movements.	Basal ganglia.	Chorea = dancing. Seen in Huntington disease and in acute rheumatic fever (Sydenham chorea).
Dystonia	Sustained, involuntary muscle contractions.		Writer's cramp, blepharospasm, torticollis. Treatment: botulinum toxin injection.
Essential tremor	High-frequency tremor with sustained posture (eg, outstretched arms), worsened with movement or when anxious.		Often familial. Patients often self-medicate with alcohol, which ↓ tremor amplitude. Treatment: nonselective β-blockers (eg, propranolol), primidone.
Intention tremor	Slow, zigzag motion when pointing/extending toward a target.	Cerebellar dysfunction.	
Resting tremor	Uncontrolled movement of distal appendages (most noticeable in hands); tremor alleviated by intentional movement.	Substantia nigra ( <b>Park</b> inson disease).	Occurs at rest; "pill-rolling tremor" of Parkinson disease. When you park your car, it is at rest.
Hemiballismus	Sudden, wild flailing of one side of the body.	Contralateral subthalamic nucleus (eg, lacunar stroke).	Pronounce "Half-of-body ballistic."
Myoclonus	Sudden, brief, uncontrolled muscle contraction.		Jerks; hiccups; common in metabolic abnormalities such as renal and liver failure.
Restless legs syndrome	Worse at rest/nighttime. Relieved by movement.		Associated with iron deficiency, CKD.
			Treatment: dopamine agonists (pramipexole, ropinirole).

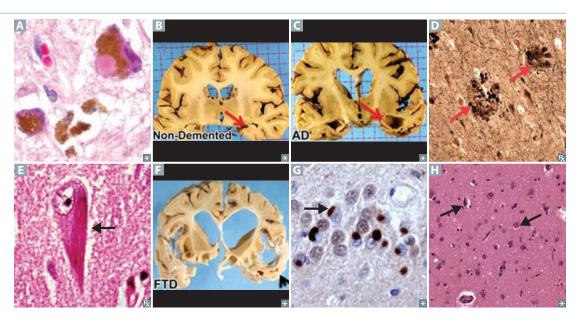
FAS1\_2019\_12-Neurol.indd 519 11/8/19 7:39 AM

Neurodegenerative disorders	↓ in cognitive ability, memory, or function with intact consciousness. Must rule out depression as cause of dementia (called pseudodementia). Other reversible causes of dementia: hypothyroidism, vitamin B <sub>12</sub> deficiency, neurosyphilis, normal pressure hydrocephalus.		
DISEASE	DESCRIPTION	HISTOLOGIC/GROSS FINDINGS	
Parkinson disease	Parkinson TRAPSS your body: Tremor (pill-rolling tremor at rest) Rigidity (cogwheel) Akinesia (or bradykinesia) Postural instability Shuffling gait Small handwriting (micrographia) MPTP, a contaminant in illegal drugs, is metabolized to MPP+, which is toxic to substantia nigra.	Loss of dopaminergic neurons (ie, depigmentation) of substantia nigra pars compacta.  Lewy bodies: composed of α-synuclein (intracellular eosinophilic inclusions A).	
Huntington disease	Autosomal dominant trinucleotide (CAG) <sub>n</sub> repeat expansion in the <b>hunt</b> ingtin ( <i>HTT</i> ) gene on chromosome <b>4</b> ( <b>4 letters</b> ). Symptoms manifest between ages 20 and 50: chorea, athetosis, aggression, depression, dementia (sometimes initially mistaken for substance abuse).  Anticipation results from expansion of <b>CAG</b> repeats. Caudate loses <b>ACh</b> and <b>GABA</b> .	Atrophy of caudate and putamen with ex vacuo ventriculomegaly.  † dopamine, ↓ GABA, ↓ ACh in brain. Neuronal death via NMDA-R binding and glutamate excitotoxicity.	
Alzheimer disease	Most common cause of dementia in elderly.  Down syndrome patients have ↑ risk of developing Alzheimer disease, as APP is located on chromosome 21.  ↓ ACh.  Associated with the following altered proteins:  ■ ApoE-2: ↓ risk of sporadic form  ■ ApoE-4: ↑ risk of sporadic form  ■ APP, presenilin-1, presenilin-2: familial forms (10%) with earlier onset	Widespread cortical atrophy (normal cortex <b>B</b> ; cortex in Alzheimer disease <b>C</b> ), especially hippocampus (arrows in <b>B</b> and <b>C</b> ). Narrowing of gyri and widening of sulci.  Senile plaques <b>D</b> in gray matter: extracellular β-amyloid core; may cause amyloid angiopathy → intracranial hemorrhage; Aβ (amyloid-β) synthesized by cleaving amyloid precursor protein (APP).  Neurofibrillary tangles <b>E</b> : intracellular, hyperphosphorylated tau protein = insoluble cytoskeletal elements; number of tangles correlates with degree of dementia.  Hirano bodies—intracellular eosinophilic proteinaceous rods in hippocampus.	
Frontotemporal dementia	Formerly called Pick disease. Early changes in personality and behavior (behavioral variant), or aphasia (primary progressive aphasia). May have associated movement disorders.	Frontotemporal lobe degeneration <b>F</b> . Inclusions of hyperphosphorylated tau (round Pick bodies <b>G</b> ) or ubiquitinated TDP-43.	

11/8/19 7:39 AM FAS1\_2019\_12-Neurol.indd 520

#### **Neurodegenerative disorders (continued)**

DISEASE	DESCRIPTION	HISTOLOGIC/GROSS FINDINGS
Lewy body dementia	Visual hallucinations ("haLewycinations"), dementia with fluctuating cognition/ alertness, REM sleep behavior disorder, and parkinsonism. Called Lewy body dementia if cognitive and motor symptom onset < 1 year apart, otherwise considered dementia 2° to Parkinson disease.	Intracellular Lewy bodies A primarily in cortex.
Vascular dementia	Result of multiple arterial infarcts and/or chronic ischemia.  Step-wise decline in cognitive ability with lateonset memory impairment. 2nd most common cause of dementia in elderly.	MRI or CT shows multiple cortical and/or subcortical infarcts.
Creutzfeldt-Jakob disease	Rapidly progressive (weeks to months) dementia with myoclonus ("startle myoclonus") and ataxia. Commonly see periodic sharp waves on EEG and † 14-3-3 protein in CSF.	Spongiform cortex (vacuolization without inflammation).  Prions (PrP <sup>c</sup> → PrP <sup>sc</sup> sheet [β-pleated sheet resistant to proteases]) <b>H</b> .



# Idiopathic intracranial hypertension

Also called pseudotumor cerebri. ↑ ICP with no obvious findings on imaging. Risk factors include **female** sex, Tetracyclines, Obesity, vitamin A excess, Danazol (**female TOAD**). Associated with cerebral venous sinus stenosis. Findings: headache, tinnitus, diplopia (usually from CN VI palsy), no change in mental status. Impaired optic nerve axoplasmic flow → papilledema. Visual field testing shows enlarged blind spot and peripheral constriction. Lumbar puncture reveals ↑ opening pressure and provides temporary headache relief.

Treatment: weight loss, acetazolamide, invasive procedures for refractory cases (eg, CSF shunt placement, optic nerve sheath fenestration surgery for visual loss).

FAS1\_2019\_12-Neurol.indd 521 11/8/19 7:39 AM

### SECTION III NEUROLOGY AND SPECIAL SENSES → NEUROLOGY—PATHOLOGY

Hydrocephalus	↑ CSF volume → ventricular dilation +/- ↑ ICP.		
Communicating			
Communicating hydrocephalus	↓ CSF absorption by arachnoid granulations (eg, arachnoid scarring post-meningitis) → ↑ ICP, papilledema, herniation.		
Normal pressure hydrocephalus	Affects the elderly; idiopathic; CSF pressure elevated only episodically; does not result in increased subarachnoid space volume. Expansion of ventricles ⚠ distorts the fibers of the corona radiata → triad of urinary incontinence, gait apraxia (magnetic gait), and cognitive dysfunction. "Wet, wobbly, and wacky." Symptoms potentially reversible with CSF drainage via lumbar puncture or shunt placement.		
Noncommunicating (ok	ostructive)		
Noncommunicating hydrocephalus	Caused by structural blockage of CSF circulation within ventricular system (eg, stenosis of aqueduct of Sylvius, colloid cyst blocking foramen of Monro, tumor <b>B</b> ).		
Hydrocephalus mimics			
Ex vacuo ventriculomegaly	Appearance of ↑ CSF on imaging , but is actually due to ↓ brain tissue and neuronal atrophy (eg, Alzheimer disease, advanced HIV, Pick disease, Huntington disease). ICP is normal; NPH triad is not seen.		
	A C		

FAS1\_2019\_12-Neurol.indd 522 11/8/19 7:39 AM

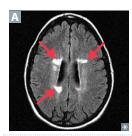
#### **Multiple sclerosis**

Autoimmune inflammation and demyelination of CNS (brain and spinal cord) with subsequent axonal damage. Can present with:

- Acute optic neuritis (painful unilateral visual loss associated with Marcus Gunn pupil)
- Brain stem/cerebellar syndromes (eg, diplopia, ataxia, scanning speech, intention tremor, nystagmus/INO [bilateral > unilateral])
- Pyramidal tract demyelination (eg, weakness, spasticity)
- Spinal cord syndromes (eg, electric shock-like sensation along cervical spine on neck flexion, neurogenic bladder, paraparesis, sensory manifestations affecting the trunk or one or more extremity)

Symptoms may exacerbate with increased body temperature (eg, hot bath, exercise). Relapsing and remitting is most common clinical course. Most often affects women in their 20s and 30s; more common in individuals living farther from equator and with low serum vitamin D levels.

#### **FINDINGS**



† IgG level and myelin basic protein in CSF. Oligoclonal bands are diagnostic. MRI is gold standard. Periventricular plaques A (areas of oligodendrocyte loss and reactive gliosis). Multiple white matter lesions disseminated in space and time.

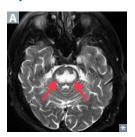
TREATMENT

Stop relapses and halt/slow progression with disease-modifying therapies (eg,  $\beta$ -interferon, glatiramer, natalizumab). Treat acute flares with IV steroids. Symptomatic treatment for neurogenic bladder (catheterization, muscarinic antagonists), spasticity (baclofen, GABA\_B receptor agonists), pain (TCAs, anticonvulsants).

FAS1\_2019\_12-Neurol.indd 523 11/8/19 7:39 AM

#### Other demyelinating and dysmyelinating disorders

### syndrome



Osmotic demyelination Also called central pontine myelinolysis. Massive axonal demyelination in pontine white matter A 2° to rapid osmotic changes, most commonly iatrogenic correction of hyponatremia but also rapid shifts of other osmolytes (eg, glucose). Acute paralysis, dysarthria, dysphagia, diplopia, loss of consciousness. Can cause "locked-in syndrome."

Correcting serum Na+ too fast:

- "From low to high, your pons will die" (osmotic demyelination syndrome)
- "From high to low, your brains will blow" (cerebral edema/herniation)

#### **Acute inflammatory** demyelinating polyradiculopathy

Most common subtype of Guillain-Barré syndrome.

Autoimmune condition that destroys Schwann cells via inflammation and demyelination of motor fibers, sensory fibers, peripheral nerves (including CN III-XII). Likely facilitated by molecular mimicry and triggered by inoculations or stress. Despite association with infections (eg, Campylobacter jejuni, viruses [eg, Zika]), no definitive causal link to any pathogen.

Results in symmetric ascending muscle weakness/paralysis and depressed/absent DTRs beginning in lower extremities. Facial paralysis (usually bilateral) and respiratory failure are common. May see autonomic dysregulation (eg, cardiac irregularities, hypertension, hypotension) or sensory abnormalities. Almost all patients survive: majority recover completely after weeks to months. † CSF protein with normal cell count (albuminocytologic dissociation).

Respiratory support is critical until recovery. Disease-modifying treatment: plasmapheresis or IV immunoglobulins. No role for steroids.

#### **Acute disseminated** (postinfectious) encephalomyelitis

Multifocal inflammation and demyelination after infection or vaccination. Presents with rapidly progressive multifocal neurologic symptoms, altered mental status.

#### **Charcot-Marie-Tooth** disease

Also called hereditary motor and sensory neuropathy. Group of progressive hereditary nerve disorders related to the defective production of proteins involved in the structure and function of peripheral nerves or the myelin sheath. Typically autosomal dominant and associated with foot deformities (eg, pes cavus, hammer toe), lower extremity weakness (eg, foot drop), and sensory deficits. Most common type, CMT1A, is caused by PMP22 gene duplication.

#### **Progressive multifocal** leukoencephalopathy



Demyelination of CNS B due to destruction of oligodendrocytes (2° to reactivation of latent JC virus infection). Seen in 2–4% of patients with AIDS. Rapidly progressive, usually fatal. Predominantly involves parietal and occipital areas; visual symptoms are common. † risk associated with natalizumab.

Other disorders

Krabbe disease, metachromatic leukodystrophy, adrenoleukodystrophy.

FAS1 2019 12-Neurol.indd 524 11/8/19 7:39 AM

#### **Neurocutaneous disorders**

DISORDER	GENETICS	PRESENTATION	NOTES
Sturge-Weber syndrome	Congenital nonhereditary anomaly of neural crest derivatives. Somatic mosaicism of an activating mutation in one copy of the GNAQ gene.	Capillary vascular malformation → portwine stain A (nevus flammeus or nonneoplastic birthmark) in CN V <sub>1</sub> /V <sub>2</sub> distribution; ipsilateral leptomeningeal angioma B → seizures/epilepsy; intellectual disability; episcleral hemangioma → † IOP → early-onset glaucoma.	Also called encephalotrigeminal angiomatosis.  SSTURGGE-Weber: Sporadic, port-wine Stain, Tram track calcifications (opposing gyri), Unilateral, intellectual disability (Retardation), Glaucoma, GNAQ gene, Epilepsy.
Tuberous sclerosis	AD, variable expression.  Mutation in tumor suppressor genes TSC1 on chromosome 9 (hamartin), TSC2 on chromosome 16 (tuberin).	Hamartomas in CNS and skin, Angiofibromas C, Mitral regurgitation, Ash-leaf spots D, cardiac Rhabdomyoma, (Tuberous sclerosis), autosomal dOminant; Mental retardation (intellectual disability), renal Angiomyolipoma E, Seizures, Shagreen patches.	HAMARTOMASS.  † incidence of Subependymal giant cell astrocytomas and ungual fibromas.
Neurofibromatosis type I	AD, 100% penetrance. Mutation in <i>NF1</i> tumor suppressor gene on chromosome 17 (encodes neurofibromin, a negative RAS regulator).	Café-au-lait spots <b>F</b> , Intellectual disability, Cutaneous neurofibromas <b>G</b> , Lisch nodules (pigmented iris hamartomas <b>H</b> ), Optic gliomas, Pheochromocytomas, Seizures/focal neurologic Signs (often from meningioma), bone lesions (eg, sphenoid dysplasia).	Also called von Recklinghausen disease.  17 letters in "von Recklinghausen."  CICLOPSS.
Neurofibromatosis type II	AD. Mutation in <i>NF2</i> tumor suppressor gene (merlin) on chromosome 22.	Bilateral vestibular schwannomas, juvenile cataracts, meningiomas, ependymomas.	NF2 affects 2 ears, 2 eyes.
von Hippel-Lindau disease	AD. Deletion of VHL gene on chromosome  3p. pVHL ubiquitinates hypoxia-inducible factor 1a.	Hemangioblastomas (high vascularity with hyperchromatic nuclei 1) in retina, brain stem, cerebellum, spine 1; Angiomatosis; bilateral Renal cell carcinomas; Pheochromocytomas.	Numerous tumors, benign and malignant. VHL = 3 letters. HARP.
F	B G	C D D	

FAS1\_2019\_12-Neurol.indd 525 11/8/19 7:39 AM

### **Adult primary brain tumors**

TUMOR	DESCRIPTION	HISTOLOGY
Glioblastoma multiforme	Grade IV astrocytoma. Common, highly malignant 1° brain tumor with ~ 1-year median survival. Found in cerebral hemispheres. Can cross corpus callosum ("butterfly glioma" A).	Astrocyte origin, GFAP ⊕. "Pseudopalisading" pleomorphic tumor cells <b>B</b> border central areas of necrosis, hemorrhage, and/or microvascular proliferation.
Oligodendroglioma	Relatively rare, slow growing. Most often in frontal lobes <b>C</b> . Often calcified.	Oligodendrocyte origin. "Fried egg" cells—round nuclei with clear cytoplasm <b>D</b> . "Chicken-wire" capillary pattern.
Meningioma	Common, typically benign. Females > males. Most often occurs near surfaces of brain and in parasagittal region. Extra-axial (external to brain parenchyma) and may have a dural attachment ("tail" <b>E</b> ). Often asymptomatic; may present with seizures or focal neurologic signs. Resection and/or radiosurgery.	Arachnoid cell origin. Spindle cells concentrically arranged in a whorled pattern <b>F</b> ; psammoma bodies (laminated calcifications).
Hemangioblastoma	Most often cerebellar <b>G</b> . Associated with von Hippel-Lindau syndrome when found with retinal angiomas. Can produce erythropoietin → 2° polycythemia.	Blood vessel origin. Closely arranged, thinwalled capillaries with minimal intervening parenchyma H.

FAS1\_2019\_12-Neurol.indd 526 11/8/19 7:39 AM

### Adult primary brain tumors (continued)

TUMOR	DESCRIPTION	HISTOLOGY	
Pituitary adenoma	May be nonfunctioning (silent) or hyperfunctioning (hormone-producing).  Nonfunctional tumors present with mass effect (eg, bitemporal hemianopia [due to pressure on optic chiasm ]). Pituitary apoplexy → hyperor hypopituitarism.  Prolactinoma classically presents as galactorrhea, amenorrhea, ↓ bone density due to suppression of estrogen in women and as ↓ libido, infertility in men.  Treatment: dopamine agonists (eg, bromocriptine, cabergoline), transsphenoidal resection.	Hyperplasia of only one type of endocrine cells found in pituitary. Most commonly from lactotrophs (prolactin)  → hyperprolactinemia. Less commonly, from somatotrophs (GH) → acromegaly, gigantism; corticotrophs (ACTH) → Cushing disease. Rarely, from thyrotrophs (TSH), gonadotrophs (FSH, LH).	
Schwannoma	Classically at the cerebellopontine angle K, benign, involving CNs V, VII, and VIII, but can be along any peripheral nerve. Often localized to CN VIII in internal acoustic meatus → vestibular schwannoma (can present as hearing loss and tinnitus). Bilateral vestibular schwannomas found in NF-2. Resection or stereotactic radiosurgery.	Schwann cell origin, S-100 ⊕. Biphasic, dense, hypercellular areas containing spindle cells alternating with hypocellular, myxoid areas L.	
	Patient		

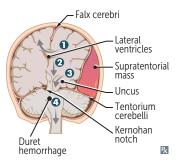
FAS1\_2019\_12-Neurol.indd 527 11/8/19 7:39 AM

#### **Childhood primary brain tumors**

TUMOR	DESCRIPTION	HISTOLOGY
Pilocytic astrocytoma	Low-grade astrocytoma. Most common 1° brain tumor in childhood. Usually well circumscribed. In children, most often found in posterior fossa A (eg, cerebellum). May be supratentorial. Benign; good prognosis.	Astrocyte origin, GFAP ⊕. Rosenthal fibers—eosinophilic, corkscrew fibers ■. Cystic + solid (gross).
Medulloblastoma	Most common malignant brain tumor in childhood. Commonly involves cerebellum  C. Can compress 4th ventricle, causing noncommunicating hydrocephalus  → headaches, papilledema. Can involve the cerebellar vermis → truncal ataxia. Can send "drop metastases" to spinal cord.	Form of primitive neuroectodermal tumor (PNET). Homer-Wright rosettes, small blue cells □. Synaptophysin ⊕.
Ependymoma	Most commonly found in 4th ventricle <b>E</b> . Can cause hydrocephalus. Poor prognosis.	Ependymal cell origin. Characteristic perivascular pseudorosettes <b>F</b> . Rod-shaped blepharoplasts (basal ciliary bodies) found near the nucleus.
Craniopharyngioma	Most common childhood supratentorial tumor. May be confused with pituitary adenoma (both cause bitemporal hemianopia).	Derived from remnants of Rathke pouch (ectoderm). Calcification is common GH. Cholesterol crystals found in "motor oil"-like fluid within tumor.
Pinealoma	Tumor of pineal gland. Can cause Parinaud syndrome (compression of tectum → vertical gaze palsy); obstructive hydrocephalus (compression of cerebral aqueduct); precocious puberty in males (hCG production).	Similar to germ cell tumors (eg, testicular seminoma).
	E F	

FAS1\_2019\_12-Neurol.indd 528 11/8/19 7:39 AM

#### **Herniation syndromes**



Cingulate (subfalcine) herniation under falx cerebri

Can compress anterior cerebral artery.

**2** Central/downward transtentorial herniation

Caudal displacement of brain stem → rupture of paramedian basilar artery branches → Duret hemorrhages. Usually fatal.

**3** Uncal transtentorial herniation

Uncus = medial temporal lobe. Early herniation → ipsilateral blown pupil (unilateral CN III compression), contralateral hemiparesis. Late herniation → coma, Kernohan phenomenon (misleading contralateral blown pupil and ipsilateral hemiparesis due to contralateral compression against Kernohan notch).

4 Cerebellar tonsillar herniation into the foramen magnum

Coma and death result when these herniations compress the brain stem.

#### **Motor neuron signs**

SIGN	UMN LESION	LMN LESION	COMMENTS
Weakness	+	+	Lower motor neuron = everything lowered  (less muscle mass, ↓ muscle tone, ↓ reflexes downgoing toes)  Upper motor neuron = everything up (tone, DTRs, toes)  Fasciculations = muscle twitching Positive Babinski is normal in infants
Atrophy	_	+	
Fasciculations	_	+	
Reflexes	<b>†</b>	ţ	
Tone	<b>†</b>	ţ	
Babinski	+	_	
Spastic paresis	+	_	
Flaccid paralysis	_	+	
Clasp knife spasticity	+	_	

FAS1\_2019\_12-Neurol.indd 529 11/8/19 7:39 AM

#### **Spinal lesions**

AREA AFFECTED	DISEASE	CHARACTERISTICS
	Spinal muscular atrophy	Congenital degeneration of anterior horns of spinal cord. LMN symptoms only, symmetric weakness. "Floppy baby" with marked hypotonia (Flaccid paralysis) and tongue Fasciculations. Autosomal recessive mutation in SMN1 → defective snRNP assembly.  SMA type 1 is called Werdnig-Hoffmann disease.
	Amyotrophic lateral sclerosis	Also called Lou Gehrig disease. Combined UMN (corticobulbar/corticospinal) and LMN (medullary and spinal cord) degeneration. No sensory or bowel/bladder deficits.  Can be caused by defect in superoxide dismutase 1.  LMN deficits: flaccid limb weakness, fasciculations, atrophy, bulbar palsy (dysarthria, dysphagia, tongue atrophy). UMN deficits: spastic limb weakness, hyperreflexia, clonus, pseudobulbar palsy (dysarthria, dysphagia, emotional lability). Fatal.  Treatment: "riLouzole".
Posterior spinal arteries  Anterior spinal artery	Complete occlusion of anterior spinal artery	Spares dorsal columns and Lissauer tract; midthoracic ASA territory is watershed area, as artery of Adamkiewicz supplies ASA below T8. Can be caused by aortic aneurysm repair. Presents with UMN deficit below the lesion (corticospinal tract), LMN deficit at the level of the lesion (anterior horn), and loss of pain and temperature sensation below the lesion (spinothalamic tract).
	Tabes dorsalis	Caused by 3° syphilis. Results from degeneration/ demyelination of dorsal columns and roots  → progressive sensory ataxia (impaired proprioception → poor coordination).  ⊕ Romberg sign and absent DTRs.  Associated with Charcot joints, shooting pain, Argyll Robertson pupils.
	Syringo myelia	Syrinx expands and damages anterior white commissure of spinothalamic tract (2nd-order neurons) → bilateral symmetric loss of pain and temperature sensation in cape-like distribution. Seen with Chiari I malformation. Can affect other tracts.
	Vitamin B <sub>12</sub> deficiency	Subacute combined degeneration (SCD)— demyelination of Spinocerebellar tracts, lateral Corticospinal tracts, and Dorsal columns. Ataxic gait, paresthesia, impaired position/vibration sense, UMN symptoms.
Compressed cauda equina	Cauda equina syndrome	Compression of spinal roots L2 and below, often due to intervertebral disc herniation or tumor. Radicular pain, absent knee and ankle reflexes, loss of bladder and anal sphineter control, saddle anesthesia.

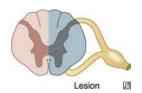
FAS1\_2019\_12-Neurol.indd 530 11/8/19 7:39 AM

#### **Poliomyelitis**

Caused by poliovirus (fecal-oral transmission). Replicates in oropharynx and small intestine before spreading via bloodstream to CNS. Infection causes destruction of cells in anterior horn of spinal cord (LMN death).

Signs of LMN lesion: asymmetric weakness (vs symmetric weakness in spinal muscular atrophy), hypotonia, flaccid paralysis, fasciculations, hyporeflexia, muscle atrophy. Respiratory muscle involvement leads to respiratory failure. Signs of infection: malaise, headache, fever, nausea, etc. CSF shows † WBCs (lymphocytic pleocytosis) and slight † of protein (with no change in CSF glucose). Virus recovered from stool or throat.

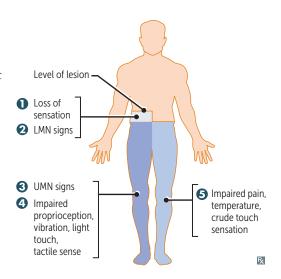
### Brown-Séquard syndrome



Hemisection of spinal cord. Findings:

- Ipsilateral loss of all sensation at level of lesion
- 2 Ipsilateral LMN signs (eg, flaccid paralysis) at level of lesion
- **3** Ipsilateral UMN signs **below** level of lesion (due to corticospinal tract damage)
- ② Ipsilateral loss of proprioception, vibration, light (2-point discrimination) touch, and tactile sense below level of lesion (due to dorsal column damage)
- **5** Contralateral loss of pain, temperature, and crude (non-discriminative) touch **below** level of lesion (due to spinothalamic tract damage) If lesion occurs above Tl, patient may present with ipsilateral Horner syndrome due to

damage of oculosympathetic pathway.



#### Friedreich ataxia

Autosomal recessive trinucleotide repeat disorder (GAA)<sub>n</sub> on chromosome 9 in gene that encodes frataxin (iron-binding protein). Leads to impairment in mitochondrial functioning. Degeneration of lateral corticospinal tract (spastic paralysis), spinocerebellar tract (ataxia), dorsal columns (\darkspace vibratory sense, proprioception), and dorsal root ganglia (loss of DTRs). Staggering gait, frequent falling, nystagmus, dysarthria, pes cavus, hammer toes, diabetes mellitus, hypertrophic cardiomyopathy (cause of death). Presents in childhood with kyphoscoliosis A B.

Friedreich is Fratastic (frataxin): he's your favorite frat brother, always staggering and falling but has a sweet, big heart.

Ataxic GAAit.





FAS1\_2019\_12-Neurol.indd 531 11/8/19 7:39 AM

#### **Common cranial nerve lesions**

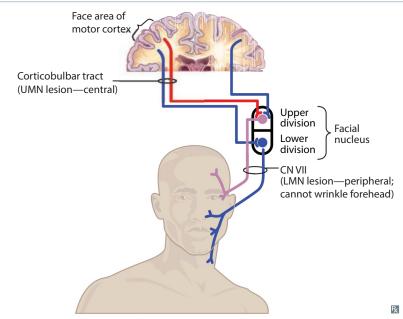
CN V motor lesion	Jaw deviates toward side of lesion due to unopposed force from the opposite pterygoid muscle.	
CN X lesion	Uvula deviates <b>away</b> from side of lesion. Weak side collapses and uvula points away.	
CN XI lesion	Weakness turning head to contralateral side of lesion (SCM). Shoulder droop on side of lesion (trapezius).  The left SCM contracts to help turn the head to the right.	
CN XII lesion LMN lesion. Tongue deviates toward side of lesion ("lick your wounds") due to weak muscles on affected side.		

#### **Facial nerve lesions**



**Bell palsy** is the most common cause of peripheral facial palsy A. Usually develops after HSV reactivation. Treatment: corticosteroids +/– acyclovir. Most patients gradually recover function, but aberrant regeneration can occur. Other causes of peripheral facial palsy include Lyme disease, herpes zoster (Ramsay Hunt syndrome), sarcoidosis, tumors (eg, parotid gland), diabetes mellitus.

	Upper motor neuron lesion	Lower motor neuron lesion	
LESION LOCATION	Motor cortex, connection from motor cortex to facial nucleus in pons	Facial nucleus, anywhere along CN VII	
AFFECTED SIDE	Contralateral	Ipsilateral	
MUSCLES INVOLVED	Lower muscles of facial expression	Upper and lower muscles of facial expression	
FOREHEAD INVOLVED?	Spared, due to bilateral UMN innervation	Affected	
OTHER SYMPTOMS	None	Incomplete eye closure (dry eyes, corneal ulceration), hyperacusis, loss of taste sensation to anterior tongue	



FAS1\_2019\_12-Neurol.indd 532 11/8/19 7:39 AM

### ▶ NEUROLOGY—OTOLOGY **Auditory physiology Outer ear** Visible portion of ear (pinna), includes auditory canal and tympanic membrane. Transfers sound waves via vibration of tympanic membrane. Middle ear Air-filled space with three bones called the ossicles (malleus, incus, stapes). Ossicles conduct and amplify sound from tympanic membrane to inner ear. Inner ear Snail-shaped, fluid-filled cochlea. Contains basilar membrane that vibrates 2° to sound waves. Vibration transduced via specialized hair cells → auditory nerve signaling → brain stem. Each frequency leads to vibration at specific location on basilar membrane (tonotopy): Low frequency heard at apex near helicotrema (wide and flexible). High frequency heard best at base of cochlea (thin and rigid).

# **Diagnosing hearing loss**

	Normal	Conductive	Sensorineural
Weber test Tuning fork on vertex of skull			
	No localization	Localizes to affected ear	Localizes to unaffected ear
Rinne test Tuning fork in front of ear (air conduction, AC), Tuning fork on mastoid process (bone conduction, BC)	AC > BC	BC > AC	AC > BC

Types	of	hearing	loss
· ypcs	•	iicui iiig	1033

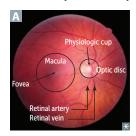
Types of hearing loss	3
Noise-induced hearing loss	Damage to stereociliated cells in organ of Corti. Loss of high-frequency hearing first. Sudden extremely loud noises can produce hearing loss due to tympanic membrane rupture.
Presbycusis	<b>Aging</b> -related progressive bilateral/symmetric sensorineural hearing loss (often of higher frequencies) due to destruction of hair cells at the cochlear base (preserved low-frequency hearing at apex).
Cholesteatoma	Overgrowth of desquamated keratin debris within the middle ear space (A, arrows); may erode ossicles, mastoid air cells → conductive hearing loss. Often presents with painless otorrhea.

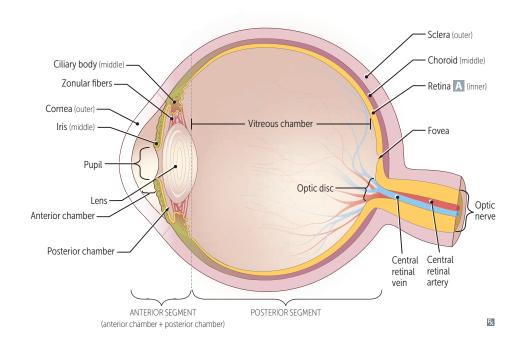
FAS1\_2019\_12-Neurol.indd 533 11/8/19 7:39 AM

Vertigo	Sensation of spinning while actually stationary. Subtype of "dizziness," but distinct from "lightheadedness."
Peripheral vertigo	More common. Inner ear etiology (eg, semicircular canal debris, vestibular nerve infection, Ménière disease [triad: sensorineural hearing loss, vertigo, tinnitus; endolymphatic hydrops → ↑ endolymph within the inner ear], benign paroxysmal positional vertigo [BPPV]). Treatment: antihistamines, anticholinergics, antiemetics (symptomatic relief); low-salt diet +/− diuretics (Ménière disease); Epley maneuver (BPPV).
Central vertigo	Brain stem or cerebellar lesion (eg, stroke affecting vestibular nuclei, demyelinating disease, or posterior fossa tumor). Findings: directional or purely vertical nystagmus, skew deviation (vertical misalignment of the eyes), diplopia, dysmetria. Focal neurologic findings.

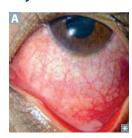
# ▶ NEUROLOGY—OPHTHALMOLOGY

### Normal eye anatomy





### **Conjunctivitis**



Inflammation of the conjunctiva  $\rightarrow$  red eye A.

Allergic—itchy eyes, bilateral.

Bacterial—pus; treat with antibiotics.

Viral—most common, often adenovirus; sparse mucous discharge, swollen preauricular node, † lacrimation; self-resolving.

FAS1\_2019\_12-Neurol.indd 534 11/8/19 7:39 AM

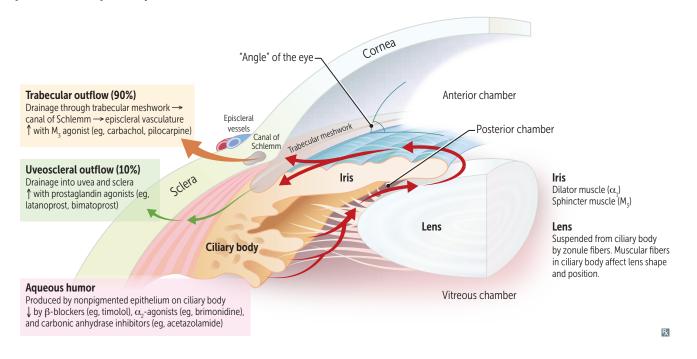
Refractive errors	Common cause of impaired vision, correctable with glasses.		
Hyperopia	Also called "farsightedness." Eye too short for refractive power of cornea and lens → light focused behind retina. Correct with convex (converging) lenses.		
Myopia Also called "nearsightedness." Eye too long for refractive power of cornea and lens in front of retina. Correct with concave (diverging) lens.			
Astigmatism	Abnormal curvature of cornea → different refractive power at different axes. Correct with cylindrical lens.		
Presbyopia	Aging-related impaired accommodation (focusing on near objects), primarily due to ↓ lens elasticity, changes in lens curvature, ↓ strength of the ciliary muscle. Patients often need "reading glasses" (magnifiers).		

#### **Cataract**



Painless, often bilateral, opacification of lens ⚠, often resulting in glare and ↓ vision, especially at night. Acquired risk factors: ↑ age, smoking, excessive alcohol use, excessive sunlight, prolonged corticosteroid use, diabetes mellitus, trauma, infection. Congenital risk factors: classic galactosemia, galactokinase deficiency, trisomies (13, 18, 21), TORCH infections (eg, rubella), Marfan syndrome, Alport syndrome, myotonic dystrophy, neurofibromatosis 2.

#### **Aqueous humor pathway**



FAS1\_2019\_12-Neurol.indd 535 11/8/19 7:39 AM

#### Glaucoma

Optic disc atrophy with characteristic cupping (normal A versus thinning of outer rim of optic nerve head B), usually with elevated intraocular pressure (IOP) and progressive peripheral visual field loss if untreated. Treatment is through pharmacologic or surgical lowering of IOP.

#### Open-angle glaucoma

Associated with † age, African-American race, family history. Painless, more common in US. Primary—cause unclear.

Secondary—blocked trabecular meshwork from WBCs (eg, uveitis), RBCs (eg, vitreous hemorrhage), retinal elements (eg, retinal detachment).

## Closed- or narrowangle glaucoma

Primary—enlargement or anterior movement of lens against central iris (pupil margin)

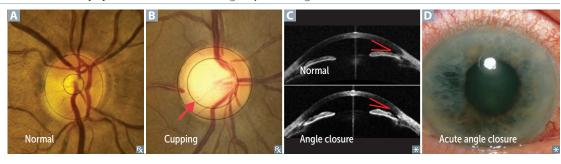
→ obstruction of normal aqueous flow through pupil → fluid builds up behind iris, pushing peripheral iris against cornea and impeding flow through trabecular meshwork.

Secondary—hypoxia from retinal disease (eg, diabetes mellitus, vein occlusion) induces vasoproliferation in iris that contracts angle.

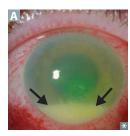
Chronic closure—often asymptomatic with damage to optic nerve and peripheral vision.

Acute closure—true ophthalmic emergency. ↑ IOP pushes iris forward → angle closes abruptly.

Very painful, red eye □, sudden vision loss, halos around lights, frontal headache, fixed and mid-dilated pupil, nausea and vomiting. Mydriatic agents contraindicated.

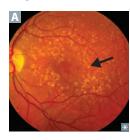


### **Uveitis**



Inflammation of uvea; specific name based on location within affected eye. Anterior uveitis: iritis; posterior uveitis: choroiditis and/or retinitis. May have hypopyon (accumulation of pus in anterior chamber A) or conjunctival redness. Associated with systemic inflammatory disorders (eg, sarcoidosis, rheumatoid arthritis, juvenile idiopathic arthritis, HLA-B27–associated conditions).

# Age-related macular degeneration



Degeneration of macula (central area of retina). Causes distortion (metamorphopsia) and eventual loss of central vision (scotomas).

- Dry (nonexudative, > 80%)—Deposition of yellowish extracellular material ("Drusen") in between Bruch membrane and retinal pigment epithelium ▲ with gradual ↓ in vision. Prevent progression with multivitamin and antioxidant supplements.
- Wet (exudative, 10–15%)—rapid loss of vision due to bleeding 2° to choroidal neovascularization. Treat with anti-VEGF (vascular endothelial growth factor) injections (eg, bevacizumab, ranibizumab).

FAS1\_2019\_12-Neurol.indd 536 11/8/19 7:39 AM

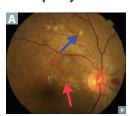
#### **Diabetic retinopathy**



Retinal damage due to chronic hyperglycemia. Two types:

- Nonproliferative—damaged capillaries leak blood → lipids and fluid seep into retina
   → hemorrhages (arrows in A) and macular edema. Treatment: blood sugar control.
- Proliferative—chronic hypoxia results in new blood vessel formation with resultant traction on retina → retinal detachment. Treatment: anti-VEGF injections, peripheral retinal photocoagulation, surgery.

# Hypertensive retinopathy



Retinal damage due to chronic uncontrolled HTN.

Flame-shaped retinal hemorrhages, arteriovenous nicking, microaneurysms, macular star (exudate, red arrow in A), cotton-wool spots (blue arrow in A). Presence of papilledema requires immediate lowering of BP.

Associated with † risk of stroke, CAD, kidney disease.

#### **Retinal vein occlusion**



Blockage of central or branch retinal vein due to compression from nearby arterial atherosclerosis. Retinal hemorrhage and venous engorgement ("blood and thunder appearance"; arrows in A), edema in affected area.

#### **Retinal detachment**



Separation of neurosensory layer of retina (photoreceptor layer with rods and cones) from outermost pigmented epithelium (normally shields excess light, supports retina) → degeneration of photoreceptors → vision loss. May be 2° to retinal breaks, diabetic traction, inflammatory effusions. Visualized on fundoscopy as crinkling of retinal tissue A and changes in vessel direction.

Breaks more common in patients with high myopia and/or history of head trauma. Often preceded by posterior vitreous detachment ("flashes" and "floaters") and eventual monocular loss of vision like a "curtain drawn down." Surgical emergency.

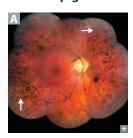
FAS1\_2019\_12-Neurol.indd 537 11/8/19 7:39 AM

# Central retinal artery occlusion



Acute, painless monocular vision loss. Retina cloudy with attenuated vessels and "cherry-red" spot at fovea (center of macula) A. Evaluate for embolic source (eg, carotid artery atherosclerosis, cardiac vegetations, patent foramen ovale).

### **Retinitis pigmentosa**



Inherited progressive retinal degeneration. Nyctalopia (night blindness) → peripheral vision loss. Bone spicule-shaped deposits A.

### **Papilledema**



Optic disc swelling (usually bilateral) due to † ICP (eg, 2° to mass effect). Enlarged blind spot and elevated optic disc with blurred margins A.

#### Leukocoria



Loss (whitening) of the red reflex. Important causes in children include retinoblastoma A, congenital cataract, toxocariasis.

FAS1\_2019\_12-Neurol.indd 538 11/8/19 7:39 AM

#### **Pupillary control**

#### Miosis

Constriction, parasympathetic:

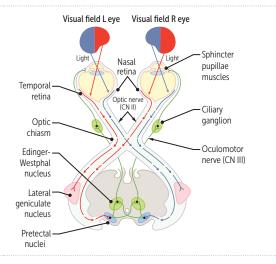
- 1st neuron: Edinger-Westphal nucleus to ciliary ganglion via CN III
- 2nd neuron: short ciliary nerves to sphincter pupillae muscles

Short ciliary nerves shorten the pupil diameter.

#### **Pupillary light reflex**

Light in either retina sends a signal via CN II to pretectal nuclei (dashed lines in image) in midbrain that activates bilateral Edinger-Westphal nuclei; pupils constrict bilaterally (direct and consensual reflex).

Result: illumination of 1 eye results in bilateral pupillary constriction.



#### Mydriasis

Dilation, sympathetic:

- 1st neuron: hypothalamus to ciliospinal center of Budge (C8–T2)
- 2nd neuron: exit at T1 to superior cervical ganglion (travels along cervical sympathetic chain near lung apex, subclavian vessels)
- 3rd neuron: plexus along internal carotid, through cavernous sinus; enters orbit as long ciliary nerve to pupillary dilator muscles. Sympathetic fibers also innervate smooth muscle of eyelids (minor retractors) and sweat glands of forehead and face.

Long ciliary nerves make the pupil diameter longer.

#### **Marcus Gunn pupil**

Also called relative afferent pupillary defect (RAPD). When the light shines into a normal eye, constriction of the ipsilateral (direct reflex) and contralateral eye (consensual reflex) is observed. When the light is then swung to the affected eye, both pupils dilate instead of constrict due to impaired conduction of light signal along the injured optic nerve. Associated with optic neuritis, early multiple sclerosis.

FAS1\_2019\_12-Neurol.indd 539 11/8/19 7:39 AM

### NEUROLOGY AND SPECIAL SENSES → NEUROLOGY—OPHTHALMOLOGY

#### **Horner syndrome**

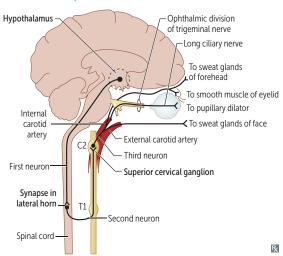
Sympathetic denervation of face →:

- Ptosis (slight drooping of eyelid: superior tarsal muscle)
- Anhidrosis (absence of sweating) and flushing of affected side of face
- Miosis (pupil constriction)

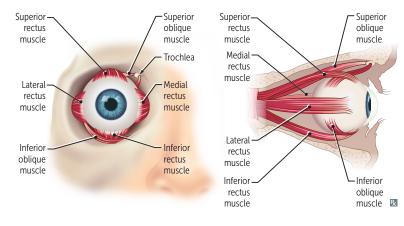
Associated with lesions along the sympathetic chain:

- Ist neuron: pontine hemorrhage, lateral medullary syndrome, spinal cord lesion above T1 (eg, Brown-Séquard syndrome, late-stage syringomyelia)
- 2nd neuron: stellate ganglion compression by Pancoast tumor
- 3rd neuron: carotid dissection (painful)

### PAM is horny (Horner).



### **Ocular motility**

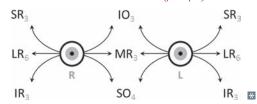


CN VI innervates the Lateral Rectus.

CN IV innervates the Superior Oblique.

CN III innervates the Rest.

The "chemical formula" LR<sub>6</sub>SO<sub>4</sub>R<sub>3</sub>.



Obliques go Opposite (left SO and IO tested with patient looking right).

IOU: IO tested looking Up.

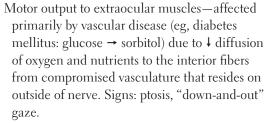
FAS1\_2019\_12-Neurol.indd 540 11/8/19 7:39 AM

### CN III, IV, VI palsies

#### **CN III damage**

CN III has both motor (central) and parasympathetic (peripheral) components. Common causes include:

- Ischemia → pupil sparing (motor fibers affected more than parasympathetic fibers)
- Uncal herniation → coma
- PCom aneurysm → sudden-onset headache
- Cavernous sinus thrombosis → proptosis, involvement of CNs IV, V<sub>1</sub>/V<sub>2</sub>, VI
- Midbrain stroke → contralateral hemiplegia



Parasympathetic output—fibers on the periphery are first affected by compression (eg, PCom aneurysm, uncal herniation). Signs: diminished or absent pupillary light reflex, "blown pupil" often with "down-and-out" gaze A.



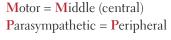
# **CN IV damage**

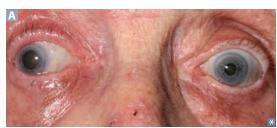
Characteristic head tilt to contralateral/ unaffected side to compensate for lack of intorsion in affected eye.

Can't see the floor with CN IV damage (eg, difficulty going down stairs, reading).



Affected eye unable to abduct and is displaced medially in primary position of gaze C.







FAS1\_2019\_12-Neurol.indd 541 11/8/19 7:39 AM

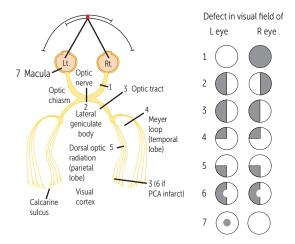
### NEUROLOGY AND SPECIAL SENSES → NEUROLOGY—OPHTHALMOLOGY

#### **Visual field defects**

- 1. Right anopia (monocular vision loss)
- 2. Bitemporal hemianopia (pituitary lesion, chiasm)
- 3. Left homonymous hemianopia
- 4. Left upper quadrantanopia (right temporal lesion, MCA)
- 5. Left lower quadrantanopia (right parietal lesion, MCA)
- 6. Left hemianopia with macular sparing (right occipital lesion, PCA)
- 7. Central scotoma (eg, macular degeneration)

Meyer Loop—Lower retina; Loops around inferior horn of Lateral ventricle.

Dorsal optic radiation—superior retina; takes shortest path via internal capsule.



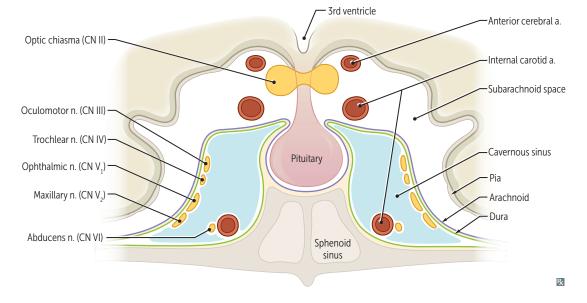
Note: When an image hits  $1^{\circ}$  visual cortex, it is upside down and left-right reversed.

#### **Cavernous sinus**

Collection of venous sinuses on either side of pituitary. Blood from eye and superficial cortex → cavernous sinus → internal jugular vein.

CNs III, IV,  $V_1$ ,  $V_2$ , and VI plus postganglionic sympathetic pupillary fibers en route to orbit all pass through cavernous sinus. Cavernous portion of internal carotid artery is also here.

Cavernous sinus syndrome—presents with variable ophthalmoplegia, ↓ corneal sensation, Horner syndrome and occasional decreased maxillary sensation. 2° to pituitary tumor mass effect, carotid-cavernous fistula, or cavernous sinus thrombosis related to infection.

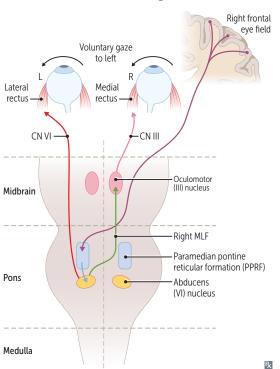


FAS1\_2019\_12-Neurol.indd 542 11/8/19 7:39 AM

# Internuclear ophthalmoplegia

Medial longitudinal fasciculus (MLF): pair of tracts that allows for crosstalk between CN VI and CN III nuclei. Coordinates both eyes to move in same horizontal direction. Highly myelinated (must communicate quickly so eyes move at same time). Lesions may be unilateral or bilateral (latter classically seen in multiple sclerosis, stroke).

Lesion in MLF = internuclear ophthalmoplegia (INO), a conjugate horizontal gaze palsy. Lack of communication such that when CN VI nucleus activates ipsilateral lateral rectus, contralateral CN III nucleus does not stimulate medial rectus to contract. Abducting eye displays nystagmus (CN VI overfires to stimulate CN III). Convergence normal.

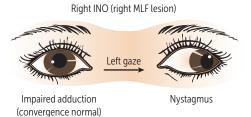


#### MLF in MS.

When looking left, the left nucleus of CN VI fires, which contracts the left lateral rectus and stimulates the contralateral (right) nucleus of CN III via the right MLF to contract the right medial rectus.

Directional term (eg, right INO, left INO) refers to the eye that is unable to adduct.

INO = Ipsilateral adduction failure, Nystagmus Opposite.



FAS1\_2019\_12-Neurol.indd 543 11/8/19 7:39 AM

# ► NEUROLOGY—PHARMACOLOGY

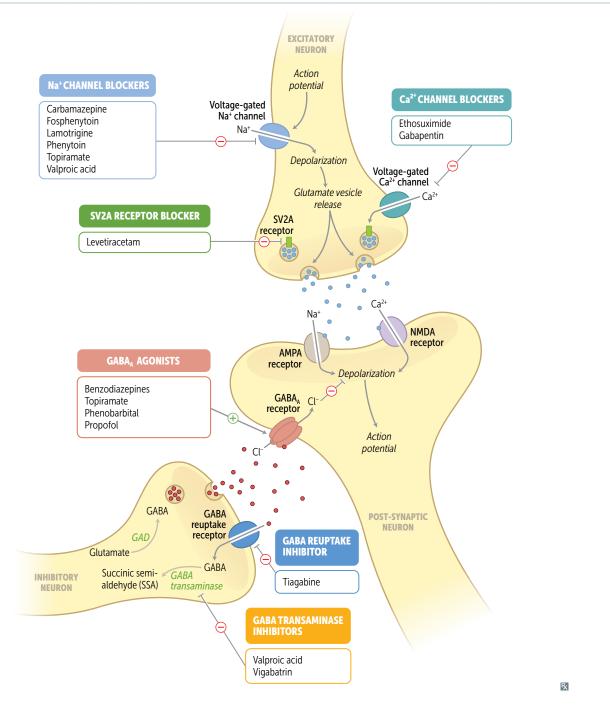
### **Epilepsy therapy**

	GENERALIZED		LIZED				
	PARTIAL (FOCAL)	TONIC-CLONIC	ABSENCE	STATUS EPILEPTICUS	MECHANISM	SIDE EFFECTS	NOTES
Benzodiazepines	_			**	↑ GABA <sub>A</sub> action	Sedation, tolerance, dependence, respiratory depression	Also for eclampsia seizures (1st line is MgSO <sub>4</sub> )
Carbamazepine	*  ✓	✓			Blocks Na+ channels	Diplopia, ataxia, blood dyscrasias (agranulocytosis, aplastic anemia), liver toxicity, teratogenesis (cleft lip/palate, spina bifida), induction of cytochrome P-450, SIADH, SJS	lst line for trigeminal neuralgia
Ethosuximide			* /		Blocks thalamic T-type Ca <sup>2+</sup> channels	EFGHIJ—Ethosuximide causes Fatigue, GI distress, Headache, Itching (and urticaria), SJS	Sucks to have Silent (absence) Seizures
Gabapentin	1				Primarily inhibits high-voltage- activated Ca <sup>2+</sup> channels; designed as GABA analog	Sedation, ataxia	Also used for peripheral neuropathy, postherpetic neuralgia
Lamotrigine	✓	<b>✓</b>	✓		Blocks voltage-gated Na <sup>+</sup> channels, inhibits the release of glutamate	SJS (must be titrated slowly), hemophagocytic lymphohistiocytosis (black box warning)	
Levetiracetam	✓	✓			SV2A receptor blocker; may modulate GABA and glutamate release, inhibit voltage-gated Ca <sup>2+</sup> channels	Neuropsychiatric symptoms (eg, personality change), fatigue, drowsiness, headache	
Phenobarbital	1	1		1	↑ GABA <sub>A</sub> action	Sedation, tolerance, dependence, induction of cytochrome P-450, cardiorespiratory depression	lst line in <mark>neonates</mark> ("pheno <mark>baby</mark> tal")
Phenytoin, fosphenytoin	✓	*		***	Blocks Na+ channels; zero- order kinetics	the channels; zero- PHENYTOIN: cytochrome P-450 induction, Hirsutism,	
Topiramate	✓	✓			Blocks Na+ channels, † GABA action	Sedation, slow cognition, kidney stones, skinny (weight loss), sight threatened (glaucoma), speech (word- finding) difficulties	Also used for migraine prophylaxis
Valproic acid	<b>√</b>	* ✓	<b>✓</b>		↑ Na+ channel inactivation, ↑ GABA concentration by inhibiting GABA transaminase	GI distress, rare but fatal hepatotoxicity (measure LFTs), pancreatitis, neural tube defects, tremor, weight gain, contraindicated in pregnancy	Also used for myoclonic seizures, bipolar disorder, migraine prophylaxis
Vigabatrin	1				† GABA. Irreversible GABA transaminase inhibitor  * = 1st line for recurrent seizure	Permanent visual loss (black box warning)	Vision gone all bad with Vigabatrin

<sup>\* =</sup> Common use, \*\* = 1st line for acute, \*\*\* = 1st line for recurrent seizure prophylaxis.

FAS1\_2019\_12-Neurol.indd 544 11/8/19 7:39 AM

## **Epilepsy therapy (continued)**



FAS1\_2019\_12-Neurol.indd 545 11/8/19 7:39 AM

# NEUROLOGY AND SPECIAL SENSES ► NEUROLOGY—PHARMACOLOGY

Barbiturates	Phenobarbital, pentobarbital, thiopental, secobarbital.			
MECHANISM	Facilitate GABA <sub>A</sub> action by ↑ duration of Cl <sup>-</sup> channel opening, thus ↓ neuron firing (barbidurates ↑ duration).			
CLINICAL USE	Sedative for anxiety, seizures, insomnia, induction of anesthesia (thiopental).			
Respiratory and cardiovascular depression (can be fatal); CNS depression (can be example alcohol use); dependence; drug interactions (induces cytochrome P-450).  Overdose treatment is supportive (assist respiration and maintain BP).  Contraindicated in porphyria.				
Benzodiazepines	Diazepam, lorazepam, triazolam, temazepam, oxazepam, midazolam, chlordiazepoxide, alprazolam.			
MECHANISM	Facilitate GABA <sub>A</sub> action by ↑ frequency of Cl <sup>-</sup> channel opening ("frenzodiazepines" ↑ frequency ↓ REM sleep. Most have long half-lives and active metabolites (exceptions [ATOM]: Alprazolam Triazolam, Oxazepam, and Midazolam are short acting → higher addictive potential).			
CLINICAL USE	Anxiety, panic disorder, spasticity, status epilepticus (lorazepam, diazepam, midazolam), eclamp detoxification (especially alcohol withdrawal—DTs), night terrors, sleepwalking, general anesth (amnesia, muscle relaxation), hypnotic (insomnia). Lorazepam, Oxazepam, and Temazepam c be used for those with liver disease who drink a LOT due to minimal first-pass metabolism.			
ADVERSE EFFECTS	Dependence, additive CNS depression effects with alcohol and barbiturates (all bind the $GABA_A$ receptor). Less risk of respiratory depression and coma than with barbiturates. Treat overdose with flumazenil (competitive antagonist at GABA benzodiazepine receptor). Can precipitate seizures by causing acute benzodiazepine withdrawal.			
Nonbenzodiazepine hypnotics	Zolpidem, Zaleplon, esZopiclone. "These ZZZs put you to sleep."			
MECHANISM	Act via the BZ <sub>1</sub> subtype of the GABA receptor. Effects reversed by flumazenil. Sleep cycle less affected as compared with benzodiazepine hypnotics.			
CLINICAL USE	Insomnia.			
ADVERSE EFFECTS	Ataxia, headaches, confusion. Short duration because of rapid metabolism by liver enzymes. Unlik older sedative-hypnotics, cause only modest day-after psychomotor depression and few amnestic effects. ↓ dependence risk than benzodiazepines.			

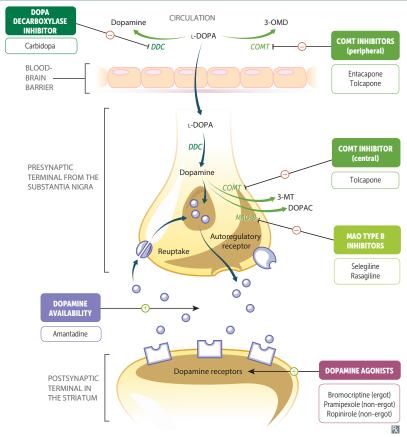
FAS1\_2019\_12-Neurol.indd 546 11/8/19 7:39 AM

Suvorexant				
MECHANISM	Orexin (hypocretin) receptor antagonist.	Suvorexant is an orexin antagonist.		
CLINICAL USE	Insomnia.			
ADVERSE EFFECTS	CNS depression (somnolence), headache, abnormal sleep-related activities. Contraindications: narcolepsy, combination with strong CYP3A4 inhibitors. Not recommended in patients with liver disease. Limited physical dependence or abuse potential.			
Ramelteon				
Melatonin receptor agonist; binds MT1 and MT2 in suprachiasmatic nucleus.		Ramelteon is a melatonin receptor agonist.		
CLINICAL USE	Insomnia.			
ADVERSE EFFECTS	Dizziness, nausea, fatigue, headache. No dependence (not a controlled substance).			
Triptans	Sumatriptan			
MECHANISM	5-HT <sub>IB/ID</sub> agonists. Inhibit trigeminal nerve activation, prevent vasoactive peptide release, induce vasoconstriction.	A sumo wrestler trips and falls on his head.		
CLINICAL USE	Acute migraine, cluster <mark>head</mark> ache attacks.			
ADVERSE EFFECTS	Coronary vasospasm (contraindicated in patients with CAD or vasospastic angina), mild paresthesia, serotonin syndrome (in combination with other 5-HT agonists).			

FAS1\_2019\_12-Neurol.indd 547 11/8/19 7:39 AM

# NEUROLOGY AND SPECIAL SENSES → NEUROLOGY—PHARMACOLOGY

<b>Parkinson disease</b> Parkinsonism is due to loss of dopaminergic neurons and excess cholinergic activity				
therapy	Bromocriptine, Amantadine, Levodopa (with carbidopa), Selegiline (and COMT inhibitors), Antimuscarinics (BALSA).			
STRATEGY	AGENTS			
Dopamine agonists	Ergot—Bromocriptine.  Non-ergot (preferred)—pramipexole, ropinirole; toxicity includes nausea, impulse control disorder (eg, gambling), postural hypotension, hallucinations, confusion.			
† dopamine availability	Amantadine († dopamine release and ↓ dopamine reuptake); toxicity = peripheral edema, livedo reticularis, ataxia.			
↑ L-DOPA availability	Agents prevent peripheral (pre-BBB) L-DOPA degradation → ↑ L-DOPA entering CNS → ↑ central L-DOPA available for conversion to dopamine.  Levodopa (L-DOPA)/carbidopa—carbidopa blocks peripheral conversion of L-DOPA to dopamine by inhibiting DOPA decarboxylase. Also reduces side effects of peripheral L-DOPA conversion into dopamine (eg, nausea, vomiting).  Entacapone and tolcapone prevent peripheral L-DOPA degradation to 3-O-methyldopa (3-OMD) by inhibiting COMT. Used in conjunction with levodopa.			
Prevent dopamine breakdown	Agents act centrally (post-BBB) to inhibit breakdown of dopamine.  Selegiline, rasagiline—block conversion of dopamine into DOPAC by selectively inhibiting MAO-B.  Tolcapone—crosses BBB and blocks conversion of dopamine to 3-methoxytyramine (3-MT) in the brain by inhibiting central COMT.			
Curb excess cholinergic activity	Benztropine, trihexyphenidyl (Antimuscarinic; improves tremor and rigidity but has little effect on bradykinesia in Parkinson disease). Park your Mercedes-Benz.			



FAS1\_2019\_12-Neurol.indd 548 11/8/19 7:40 AM

#### Carbidopa/levodopa

MECHANISM	† dopamine in brain. Unlike dopamine, L-DOPA can cross blood-brain barrier and is converted by dopa decarboxylase in the CNS to dopamine. Carbidopa, a peripheral DOPA decarboxylase inhibitor, is given with L-DOPA to † bioavailability of L-DOPA in the brain and to limit peripheral side effects.
CLINICAL USE	Parkinson disease.
ADVERSE EFFECTS	Nausea, hallucinations, postural hypotension. With progressive disease, L-DOPA can lead to "on-off" phenomenon with improved mobility during "on" periods, then impaired motor function during "off" periods when patient responds poorly to L-DOPA or medication wears off.

### Selegiline, rasagiline

J	
MECHANISM	Selectively inhibit MAO-B (metabolize dopamine) → ↑ dopamine availability.  Selegiline selectively inhibits MAO-B and is more commonly found in the Brain than in the periphery.
CLINICAL USE	Adjunctive agent to L-DOPA in treatment of Parkinson disease.
ADVERSE EFFECTS	May enhance adverse effects of L-DOPA.

### **Neurodegenerative disease therapy**

DISEASE	AGENT	MECHANISM	NOTES
Alzheimer disease	Donepezil, rivastigmine, galantamine	AChE inhibitor	lst-line treatment Adverse effects: nausea, dizziness, insomnia Dona Riva dances at the gala
	Memantine	NMDA receptor antagonist; helps prevent excitotoxicity (mediated by Ca <sup>2+</sup> )	Used for moderate to advanced dementia Adverse effects: dizziness, confusion, hallucinations
Amyotrophic lateral sclerosis	Riluzole	↓ neuron glutamate excitotoxicity	† survival Treat Lou Gehrig disease with rilouzole
Huntington disease	Tetrabenazine	Inhibit vesicular monoamine transporter (VMAT) → ↓ dopamine vesicle packaging and release	May be used for Huntington chorea and tardive dyskinesia

### **Anesthetics—general** principles

CNS drugs must be lipid soluble (cross the blood-brain barrier) or be actively transported. Drugs with ↓ solubility in blood = rapid induction and recovery times.

Drugs with  $\uparrow$  solubility in lipids =  $\uparrow$  potency =  $\frac{1}{MAC}$ 

MAC = Minimum Alveolar Concentration (of inhaled anesthetic) required to prevent 50% of subjects from moving in response to noxious stimulus (eg, skin incision).

Examples: nitrous oxide (N₂O) has ↓ blood and lipid solubility, and thus fast induction and low potency. Halothane has † lipid and blood solubility, and thus high potency and slow induction.

FAS1\_2019\_12-Neurol.indd 549 11/8/19 7:40 AM

# 550 SECTION III

# NEUROLOGY AND SPECIAL SENSES ► NEUROLOGY—PHARMACOLOGY

Inhaled anesthetics	Desflur <mark>ane</mark> , haloth <mark>ane</mark> , enflur <mark>an</mark>	e, isoflurane, sevoflurane, metho	oxyflur <mark>ane</mark> , N <sub>2</sub> O.	
MECHANISM	Mechanism unknown.			
EFFECTS	Myocardial depression, respiratory depression, postoperative nausea/vomiting, ↑ cerebral blood flow ↓ cerebral metabolic demand.			
ADVERSE EFFECTS	Hepatotoxicity (halothane), nephrotoxicity (methoxyflurane), proconvulsant (enflurane, epileptogenic), expansion of trapped gas in a body cavity (N,O).			
	inherited as autosomal domina	muscle contractions and hyperth nt with variable penetrance. Mu e) cause † Ca²+ release from sarco	ermia. Susceptibility is often tations in voltage-sensitive	
ntravenous anestheti	CS MECHANISM	ANESTHESIA USE	NOTES	
Thiopental	Facilitates GABA <sub>A</sub> (barbiturate)	Anesthesia induction, short surgical procedures	<ul> <li>↓ cerebral blood flow. High lipid solubility</li> <li>Effect terminated by rapid redistribution into tissue, fat</li> </ul>	

AGENT	MECHANISM	ANESTHESIA USE	NOTES
Thiopental	Facilitates GABA <sub>A</sub> (barbiturate)	Anesthesia induction, short surgical procedures	↓ cerebral blood flow. High lipid solubility Effect terminated by rapid redistribution into tissue, fat
Midazolam	Facilitates GABA <sub>A</sub> (benzodiazepine)	Procedural sedation (eg, endoscopy), anesthesia induction	May cause severe postoperative respiratory depression, ↓ BP, anterograde amnesia
Propofol	Potentiates GABA <sub>A</sub>	Rapid anesthesia induction, short procedures, ICU sedation	May cause respiratory depression, hypotension
Ketamine	NMDA receptor antagonist	Dissociative anesthesia Sympathomimetic	† cerebral blood flow Emergence reaction possible with disorientation, hallucination, vivid dreams

Local anesthetics	Esters—procaine, tetracaine, benzocaine, chloroprocaine. Amides—lIdocaIne, mepIvacaIne, bupIvacaIne, ropIvacaIne (amIdes have 2 I's in name).	
MECHANISM	Block Na <sup>+</sup> channels by binding to specific receptors on inner portion of channel. Most effective in rapidly firing neurons. 3° amine local anesthetics penetrate membrane in uncharged form, then bind to ion channels as charged form.  Can be given with vasoconstrictors (usually epinephrine) to enhance local action—↓ bleeding,  ↑ anesthesia by ↓ systemic concentration.  In infected (acidic) tissue, alkaline anesthetics are charged and cannot penetrate membrane effectively → need more anesthetic.	
	Order of nerve blockade: small-diameter fibers > large diameter. Myelinated fibers > unmyelinated fibers. Overall, size factor predominates over myelination such that small myelinated fibers > small unmyelinated fibers > large myelinated fibers > large unmyelinated fibers. Order of loss: (1) pain, (2) temperature, (3) touch, (4) pressure.	
CLINICAL USE	Minor surgical procedures, spinal anesthesia. If allergic to esters, give amides.	
ADVERSE EFFECTS	CNS excitation, severe cardiovascular toxicity (bupivacaine), hypertension, hypotension, arrhythmias (cocaine), methemoglobinemia (benzocaine).	

FAS1\_2019\_12-Neurol.indd 550 11/8/19 7:40 AM

Neuromuscular blocking drugs	Muscle paralysis in surgery or mechanical ventilation. Selective for Nm nicotinic receptors at neuromuscular junction but not autonomic Nn receptors.	
Depolarizing neuromuscular blocking drugs	Succinylcholine—strong ACh receptor agonist; produces sustained depolarization and prevents muscle contraction.  Reversal of blockade:  Phase I (prolonged depolarization)—no antidote. Block potentiated by cholinesterase inhibitors.  Phase II (repolarized but blocked; ACh receptors are available, but desensitized)—may be reversed with cholinesterase inhibitors.  Complications include hypercalcemia, hyperkalemia, malignant hyperthermia.	
Nondepolarizing neuromuscular blocking drugs	Atracurium, cisatracurium, pancuronium, rocuronium, tubocurarine, vecuronium—competitive ACh antagonist.  Reversal of blockade—cholinesterase inhibitors (eg, neostigmine, edrophonium) are given with anticholinergics (eg, atrophine, glycopyrrolate) to prevent muscarinic effects, such as bradycardia.	

# Spasmolytics, antispasmodics

DRUG	MECHANISM	CLINICAL USE	NOTES
Baclofen	$GABA_{B}$ receptor agonist in spinal cord.	Muscle spasticity, dystonia, multiple sclerosis.	Acts on the back (spinal cord).
Cyclobenzaprine	Acts within CNS, mainly at the brain stem.	Muscle spasticity.	Centrally acting. Structurally related to TCAs. May cause anticholinergic side effects, sedation.
Dantrolene	Prevents release of Ca <sup>2+</sup> from sarcoplasmic reticulum of skeletal muscle by inhibiting the ryanodine receptor.	Malignant hyperthermia (toxicity of inhaled anesthetics and succinylcholine) and neuroleptic malignant syndrome (toxicity of antipsychotic drugs).	Acts Directly on muscle.
Tizanidine	$\alpha_{_{\! 2}}$ agonist, acts centrally.	Muscle spasticity, multiple sclerosis, ALS, cerebral palsy.	

# Opioid analgesics

MECHANISM	Act as agonists at opioid receptors ( $\mu = \beta$ -endorphin, $\delta$ = enkephalin, $\kappa$ = dynorphin) to modulate synaptic transmission—close presynaptic Ca <sup>2+</sup> channels, open postsynaptic K <sup>+</sup> channels $\rightarrow$ \$\display\$ synaptic transmission. Inhibit release of ACh, norepinephrine, 5-HT, glutamate, substance P
EFFICACY	Full agonist: morphine, heroin, meperidine, methadone, codeine, fentanyl. Partial agonist: buprenorphine. Mixed agonist/antagonist: nalbuphine, pentazocine, butorphanol. Antagonist: naloxone, naltrexone, methylnaltrexone.
CLINICAL USE	Moderate to severe or refractory pain, diarrhea (loperamide, diphenoxylate), acute pulmonary edema, maintenance programs for heroin addicts (methadone, buprenorphine + naloxone).
ADVERSE EFFECTS	Nausea, vomiting, pruritus, addiction, respiratory depression, constipation, sphincter of Oddi spasm, miosis (except meperidine → mydriasis), additive CNS depression with other drugs. Tolerance does not develop to miosis and constipation. Treat toxicity with naloxone (competitive opioid receptor antagonist) and prevent relapse with naltrexone once detoxified.

FAS1\_2019\_12-Neurol.indd 551 11/8/19 7:40 AM

# Mixed agonist and antagonist opioid analgesics

DRUG	MECHANISM	CLINICAL USE		NOTES	
Pentazocine	κ-opioid receptor agonist and μ-opioid receptor weak antagonist or partial agonist.	Analgesia for moderate to severe pain.		Can cause opioid withdrawal symptoms if patient is also taking full opioid agonist (due to competition for opioid receptors).	
Butorphanol	κ-opioid receptor agonist and μ-opioid receptor partial agonist.	Severe pain (eg, migraine, labor).		Causes less respiratory depression than full opioid agonists. Use with full opioid agonist can precipitate withdrawal. Not easily reversed with naloxone.	
<b>Framadol</b>					
MECHANISM	Very weak opioid agonist; also in reuptake of norepinephrine an			light opioid agonist, and a norepinephrine reuptake	
CLINICAL USE	Chronic pain.			used for Stubborn pain, but	
ADVERSE EFFECTS	Similar to opioids; decreases sei serotonin syndrome.	zure threshold;	Serotonin Syn	zure threshold, and may cause drome.	
Glaucoma therapy	↓ IOP via ↓ amount of aqueous  BAD humor may not be Politic	ally Correct.	nthesis/secretion o		
DRUG CLASS	EXAMPLES TO THE PROPERTY OF TH	MECHANISM	.1 .	ADVERSE EFFECTS	
β-blockers	Timolol, betaxolol, carteolol	↓ aqueous hum	•	No pupillary or vision changes	
α-agonists	Epinephrine $(\alpha_1)$ , apraclonidine, brimonidine $(\alpha_2)$	<ul> <li>↓ aqueous humor synthesis via vasoconstriction (epinephrine)</li> <li>↓ aqueous humor synthesis (apraclonidine, brimonidine)</li> </ul>		Mydriasis (α <sub>1</sub> ); do not use in closed-angle glaucoma Blurry vision, ocular hyperemia, foreign body sensation, ocular allergic reactions, ocular pruritus	
Diuretics	Acetazolamide	↓ aqueous humor synthesis     via inhibition of carbonic     anhydrase		No pupillary or vision changes	
Prostaglandins	Bimatoprost, latanoprost $(PGF_{2\alpha})$	↑ outflow of aqueous humor via ↓ resistance of flow through uveoscleral pathway		Darkens color of iris (browning), eyelash growth	
Cholinomimetics (M <sub>3</sub> )	Direct: pilocarpine, carbachol Indirect: physostigmine, echothiophate	contraction of and opening o meshwork Use pilocarpine closure glauco	in acute angle ma—very ening meshwork	Miosis (contraction of pupillary sphincter muscles) and cyclospasm (contraction of ciliary muscle)	

FAS1\_2019\_12-Neurol.indd 552 11/8/19 7:40 AM

# HIGH-YIELD PRINCIPLES IN

# **Psychiatry**

"Words of comfort, skillfully administered, are the oldest therapy known to man."

—Louis Nizer

"All men should strive to learn before they die what they are running from, and to, and why."

-James Thurber

"The sorrow which has no vent in tears may make other organs weep."

—Henry Maudsley

"It's no use going back to yesterday, because I was a different person then."

—Lewis Carroll, Alice in Wonderland

This chapter encompasses overlapping areas in psychiatry, psychology, sociology, and psychopharmacology. High-yield topics include schizophrenia, mood disorders, eating disorders, personality disorders, somatic symptom disorders, substance abuse, and antipsychotic agents. Know the DSM-5 criteria for diagnosing common psychiatric disorders.

▶ Psychology 554

▶ Pathology 556

▶ Pharmacology 572

553

FAS1\_2019\_13-Psych.indd 553 11/7/19 5:28 PM

▶ PS	YCH	IATRY-	—PSY	CH0	LOGY

	Learning in which a natural response (salivation) is elicited by a conditioned, or learned, stimulus (bell) that previously was presented in conjunction with an unconditioned stimulus (food).	Pavlov's o	elicits <b>involuntary</b> classical experiment the bell provoked	nts with dogs—
Operant conditioning	Learning in which a particular action is elicited b Usually elicits <b>voluntary</b> responses.	pecause it p	oroduces a punishr	ment or reward.
Reinforcement	Target behavior (response) is followed by desired reward (positive reinforcement) or removal of aversive stimulus (negative reinforcement).	Skin	ner operant condit	tioning quadrants:  Decrease behavior
Punishment	Repeated application of aversive stimulus (positive punishment) or removal of desired reward (negative punishment) to extinguish unwanted behavior.	ve a Add a ilus stimulus	Positive reinforcement  Negative	Positive punishment  Negative
Extinction	Discontinuation of reinforcement (positive or negative) eventually eliminates behavior. Can occur in operant or classical conditioning.	프 reinforcement punishmen		punishment
Transference and counton	Patient projects feelings about formative or other	important	persons onto physi	cian (eg, psychiatrist
Countertransference	is seen as parent).  Doctor projects feelings about formative or other reminds physician of younger sibling).	important	persons onto patie	nt (eg, patient
Ego defenses	Thoughts and behaviors (voluntary or involuntary feelings (eg, anxiety, depression).	y) used to re	esolve conflict and	prevent undesirable
Ego defenses  IMMATURE DEFENSES		y) used to re	esolve conflict and	prevent undesirable
	feelings (eg, anxiety, depression).	EXAMPLE A patient		ointments after deep
IMMATURE DEFENSES	feelings (eg, anxiety, depression).  DESCRIPTION  Subconsciously coping with stressors or emotional conflict using actions rather than	A patient discom  A patient schedul	skips therapy app fort from dealing v	ointments after deep with his past. s a full-time work arned of significant
IMMATURE DEFENSES  Acting out	feelings (eg, anxiety, depression).  DESCRIPTION  Subconsciously coping with stressors or emotional conflict using actions rather than reflections or feelings.	A patient discom  A patient schedul fatigue  After bei frustrat her hus	skips therapy app fort from dealing v with cancer plans de despite being wa during chemother ng reprimanded by ed teacher returns	ointments after deep with his past. s a full-time work arned of significant capy.

11/7/19 5:28 PM FAS1\_2019\_13-Psych.indd 554

# **Ego defenses** (continued)

Partially remaining at a more childish level of development (vs regression).  Expressing extremely positive thoughts of self and others while ignoring negative thoughts.  Largely unconscious assumption of the characteristics, qualities, or traits of another person or group.  Using facts and logic to emotionally distance oneself from a stressful situation.  Separating feelings from ideas and events.	A surgeon throws a tantrum in the operating room because the last case ran very late.  A patient boasts about his physician and his accomplishments while ignoring any flaws.  A resident starts putting his stethoscope in his pocket like his favorite attending, instead of wearing it around his neck like before.  A patient diagnosed with cancer discusses the pathophysiology of the disease.  Describing murder in graphic detail with no
and others while ignoring negative thoughts.  Largely unconscious assumption of the characteristics, qualities, or traits of another person or group.  Using facts and logic to emotionally distance oneself from a stressful situation.	accomplishments while ignoring any flaws.  A resident starts putting his stethoscope in his pocket like his favorite attending, instead of wearing it around his neck like before.  A patient diagnosed with cancer discusses the pathophysiology of the disease.
characteristics, qualities, or traits of another person or group.  Jsing facts and logic to emotionally distance oneself from a stressful situation.	pocket like his favorite attending, instead of wearing it around his neck like before.  A patient diagnosed with cancer discusses the pathophysiology of the disease.
oneself from a stressful situation.	pathophysiology of the disease.
separating feelings from ideas and events.	Describing murder in graphic detail with no
	emotional response.
Demonstrating hostile feelings in a nonconfrontational manner; showing indirect opposition.	A disgruntled employee is repeatedly late to work, but won't admit it is a way to get back at the manager.
attributing an unacceptable internal impulse to an external source (vs displacement).	A man who wants to cheat on his wife accuses his wife of being unfaithful.
asserting plausible explanations for events that actually occurred for other reasons, usually to avoid self-blame.	A man who was recently fired claims that the job was not important anyway.
Replacing a warded-off idea or feeling with an emphasis on its opposite (vs sublimation).	A stepmother treats a child she resents with excessive nurturing and overprotection.
nvoluntarily turning back the maturational clock to behaviors previously demonstrated under stress (vs fixation).	A previously toilet-trained child begins bedwetting again following the birth of a sibling.
nvoluntarily withholding an idea or feeling from conscious awareness (vs suppression).	A 20-year-old does not remember going to counseling during his parents' divorce 10 years earlier.
Believing that people are either all good or all bad at different times due to intolerance of ambiguity. Common in borderline personality disorder.	A patient says that all the nurses are cold and insensitive, but the doctors are warm and friendly.
Replacing an unacceptable wish with a course of action that is similar to the wish but socially acceptable (vs reaction formation).	A teenager's aggression toward his parents because of their high expectations is channeled into excelling in sports.
alleviating negative feelings via unsolicited generosity, which provides gratification (vs reaction formation).	A mafia boss makes a large donation to charity.
ntentionally withholding an idea or feeling from conscious awareness (vs repression); temporary.	An athlete focuses on other tasks to prevent worrying about an important upcoming match.
ightheartedly expressing uncomfortable feelings to shift the internal focus away from the distress.	A nervous medical student jokes about the boards.
	opposition.  Attributing an unacceptable internal impulse to an external source (vs displacement).  Asserting plausible explanations for events that actually occurred for other reasons, usually to avoid self-blame.  Replacing a warded-off idea or feeling with an emphasis on its opposite (vs sublimation).  Involuntarily turning back the maturational clock to behaviors previously demonstrated under stress (vs fixation).  Involuntarily withholding an idea or feeling from conscious awareness (vs suppression).  Relieving that people are either all good or all bad at different times due to intolerance of ambiguity. Common in borderline personality disorder.  Replacing an unacceptable wish with a course of action that is similar to the wish but socially acceptable (vs reaction formation).  Alleviating negative feelings via unsolicited generosity, which provides gratification (vs reaction formation).  Intentionally withholding an idea or feeling from conscious awareness (vs repression); temporary.  Aightheartedly expressing uncomfortable feelings

FAS1\_2019\_13-Psych.indd 555 11/7/19 5:28 PM 556 SECTION III

# **PSYCHIATRY** ► PSYCHIATRY—PATHOLOGY

# ▶ PSYCHIATRY—PATHOLOGY

# Infant deprivation effects

Long-term deprivation of affection results in:

- Failure to thrive
- Poor language/socialization skills
- Lack of basic trust
- Reactive attachment disorder (infant withdrawn/unresponsive to comfort)
- Disinhibited social engagement (child indiscriminately attaches to strangers)

Deprivation for > 6 months can lead to irreversible changes.

Severe deprivation can result in infant death.

#### **Child abuse**

	Physical abuse	Sexual abuse	Emotional abuse
SIGNS	Fractures, bruises, or burns. Injuries often in different stages of healing or in patterns resembling possible implements of injury. Includes abusive head trauma (shaken baby syndrome), characterized by subdural hematomas or retinal hemorrhages. Caregivers may delay seeking medical attention for the child or provide explanations inconsistent with the child's developmental stage or pattern of injury.	STIs, UTIs, and genital, anal, or oral trauma. Most often, there are no physical signs; sexual abuse should not be excluded from a differential diagnosis in the absence of physical trauma. Children often exhibit sexual knowledge or behavior incongruent with their age.	Babies or young children may lack a bond with the caregiver but are overly affectionate with less familiar adults.  They may be aggressive toward children and animals or unusually anxious.  Older children are often emotionally labile and prone to angry outbursts. They may distance themselves from caregivers and other children. They can experience vague somatic symptoms for which a medical cause cannot be found.
EPIDEMIOLOGY	40% of deaths related to child abuse or neglect occur in children < 1 year old.	Peak incidence 9–12 years old.	~80% of young adult victims of child emotional abuse meet the criteria for ≥ 1 psychiatric illness by age 21.
Child neglect	Most common form of child mimpaired social/emotional devo	dequate food, shelter, supervision, naltreatment. Signs: poor hygiene, elopment, failure to thrive. hild neglect must be reported to lo	malnutrition, withdrawal,
Vulnerable child syndrome		pecially susceptible to illness or injudicallows a serious illness or life-threedical services.	• •

FAS1\_2019\_13-Psych.indd 556 11/7/19 5:28 PM

# Childhood and early-onset disorders

Attention-deficit hyperactivity disorder	Onset before age 12. ≥ 6 months of limited attention span and/or poor impulse control. Characterized by hyperactivity, impulsivity, and/or inattention in ≥ 2 settings (eg, school, home, places of worship). Normal intelligence, but commonly coexists with difficulties in school. Often persists into adulthood. Commonly coexists with oppositional defiant disorder. Treatment: stimulants (eg, methylphenidate) +/– behavioral therapy; alternatives include atomoxetine, guanfacine, clonidine.
Autism spectrum disorder	Onset in early childhood. Social and communication deficits, repetitive/ritualized behaviors, restricted interests. May be accompanied by intellectual disability and/or above average abilities in specific skills (eg, music). More common in boys. Associated with † head and/or brain size.
Conduct disorder	Repetitive, pervasive behavior violating societal norms or the basic rights of others (eg, aggression toward people and animals, destruction of property, theft). After age 18, often reclassified as antisocial personality disorder. Treatment: psychotherapy (eg, cognitive behavioral therapy [CBT]).
Disruptive mood dysregulation disorder	Onset before age 10. Severe, recurrent temper outbursts out of proportion to situation. Child is constantly angry and irritable between outbursts. Treatment: CBT, stimulants, antipsychotics.
Intellectual disability	Global cognitive deficits (vs specific learning disorder) that affect reasoning, memory, abstract thinking, judgment, language, learning. Adaptive functioning is impaired, leading to major difficulties with education, employment, communication, socialization, independence. Treatment: psychotherapy, occupational therapy, special education.
Oppositional defiant disorder	Enduring pattern of anger and irritability with argumentative, vindictive, and defiant behavior toward authority figures. Treatment: psychotherapy (eg, CBT).
Selective mutism	Onset before age 5. Anxiety disorder lasting ≥ 1 month involving refraining from speech in certain situations despite speaking in other, usually more comfortable situations. Development (eg, speech and language) not typically impaired. Interferes with social, academic, and occupational tasks. Commonly coexists with social anxiety disorder. Treatment: behavioral, family, and play therapy; SSRIs.
Separation anxiety disorder	Overwhelming fear of separation from home or attachment figure lasting ≥ 4 weeks. Can be normal behavior up to age 3–4. May lead to factitious physical complaints to avoid school. Treatment: CBT, play therapy, family therapy.
Specific learning disorder	Onset during school-age years. Inability to acquire or use information from a specific subject (eg, math, reading, writing) near age-expected proficiency for ≥ 6 months despite focused intervention. General functioning and intelligence are normal (vs intellectual disability). Treatment: academic support, counseling, extracurricular activities.
Tourette syndrome	Onset before age 18. Sudden, Sudden, recurrent, nonrhythmic, stereotyped motor and vocal tics that persist for $> 1$ year. Coprolalia (involuntary obscene speech) found in some patients. Associated with OCD and ADHD. Treatment: psychoeducation, behavioral therapy. For intractable and distressing tics, high-potency antipsychotics (eg, haloperidol, fluphenazine), tetrabenazine, $\alpha_2$ -agonists (eg, guanfacine, clonidine), or atypical antipsychotics.
Orientation	Patients' ability to know the date and time, where they are, and who they are (order of loss: time → place → person). Common causes of loss of orientation: alcohol, drugs, fluid/electrolyte imbalance, head trauma, hypoglycemia, infection, nutritional deficiencies, hypoxia.

FAS1\_2019\_13-Psych.indd 557 11/7/19 5:28 PM

### **Amnesias**

Retrograde amnesia	Inability to remember things that occurred before a CNS insult.		
Anterograde amnesia	Inability to remember things that occurred after a CNS insult (\$\dagger\$ acquisition of new memory).		
Korsakoff syndrome	Amnesia (anterograde > retrograde) and disorientation caused by vitamin B <sub>1</sub> deficiency. Associated with disruption and destruction of the limbic system, especially mammillary bodies and anterior thalamus. Seen in alcoholics as a late neuropsychiatric manifestation of Wernicke encephalopathy. Confabulations are characteristic.		
Dissociative disorders			
Depersonalization/ derealization disorder	Persistent feelings of detachment or estrangement from one's own body, thoughts, perceptions, and actions (depersonalization) or one's environment (derealization). Intact reality testing (vs psychosis).		
Dissociative amnesia	Inability to recall important personal information, usually following severe trauma or stress.  May be accompanied by dissociative fugue (abrupt, unexpected travelling away from home).		
Dissociative identity disorder	Formerly called multiple personality disorder. Presence of ≥ 2 distinct identities or personality states. More common in women. Associated with history of sexual abuse, PTSD, depression, substance abuse, borderline personality, somatic symptom disorders.		
Delirium	"Waxing and waning" level of consciousness with acute onset, ↓ attention span, ↓ level of arousal. Characterized by disorganized thinking, hallucinations (often visual), misperceptions (eg, illusions), disturbance in sleep-wake cycle, cognitive dysfunction, agitation. Reversible.  Usually 2° to other identifiable illness (eg, CNS disease, infection, trauma, substance abuse/ withdrawal, metabolic/electrolyte disturbances, hemorrhage, urinary/fecal retention), or medications (eg, anticholinergics), especially in the elderly.  Most common presentation of altered mental status in inpatient setting, especially in the ICU or during prolonged hospital stays. EEG may show diffuse background rhythm slowing.	Delirium = changes in sensorium.  Treatment: identification and management of underlying condition. Orientation protocols (eg, keeping a clock or calendar nearby),  \$\dagger\$ sleep disturbances, and \$\dagger\$ cognitive stimulation to manage symptoms.  Antipsychotics as needed. Avoid unnecessary restraints and drugs that may worsen delirium (eg, anticholinergics, benzodiazepines, opioids).	

FAS1\_2019\_13-Psych.indd 558 11/7/19 5:28 PM

Psychosis	Distorted perception of reality characterized by delusions, hallucinations, and/or disorganized thought/speech. Can occur in patients with medical illness, psychiatric illness, or both.	
Delusions	False, fixed, idiosyncratic beliefs that persist despite evidence to the contrary and are not typical of a patient's culture or religion (eg, a patient who believes that others are reading his thoughts). Types include erotomanic, grandiose, jealous, persecutory, somatic, mixed, and unspecified.	
Disorganized thought	Speech may be incoherent ("word salad"), tangential, or derailed ("loose associations").	
Hallucinations	Perceptions in the absence of external stimuli (eg, seeing a light that is not actually present).  Contrast with misperceptions (eg, illusions) of real external stimuli. Types include:  Auditory—more commonly due to psychiatric illness (eg, schizophrenia) than medical illness.  Visual—more commonly due to medical illness (eg, drug intoxication, delirium) than psychiatric illness.  Tactile—common in alcohol withdrawal and stimulant use (eg, "cocaine crawlies," a type of delusional parasitosis).  Olfactory—often occur as an aura of temporal lobe epilepsy (eg, burning rubber) and in brain tumors.  Gustatory—rare, but seen in epilepsy.  Hypnagogic—occurs while going to sleep. Sometimes seen in narcolepsy.  Hypnopompic—occurs while waking from sleep ("get pomped up in the morning"). Sometimes seen in narcolepsy.	

FAS1\_2019\_13-Psych.indd 559 11/7/19 5:28 PM

# **Schizophrenia**

# spectrum disorders Schizophrenia

Chronic illness causing profound functional impairment. Symptom categories include:

- Positive—hallucinations, delusions, unusual thought processes, disorganized speech, bizarre behavior
- Negative—flat or blunted affect, apathy, anhedonia, alogia, social withdrawal
- Cognitive—reduced ability to understand or make plans, diminished working memory, inattention

Diagnosis requires  $\geq 2$  of the following active symptoms, including  $\geq 1$  from symptoms #1–3:

- 1. Delusions
- 2. Hallucinations, often auditory
- 3. Disorganized speech
- 4. Disorganized or catatonic behavior
- 5. Negative symptoms

Requires ≥ 1 month of active symptoms over the past 6 months; onset  $\geq$  6 months prior to diagnosis.

Associated with altered dopaminergic activity, ↑ serotonergic activity, and ↓ dendritic branching. Ventriculomegaly on brain imaging. Lifetime prevalence—1.5% (males > females). Presents earlier in men (late teens to early 20s) than in women (late 20s to early 30s). † suicide risk.

Heavy cannabis use in adolescence is associated with † incidence and worsened course of psychotic, mood, and anxiety disorders.

Treatment: atypical antipsychotics (eg, risperidone) are first line.

Negative symptoms often persist after treatment, despite resolution of positive symptoms.

Brief psychotic disorder $\ge 1$  positive symptom(s) lasting < 1 month, usually stress-related. Schizophreniform disorder $\ge 2$  symptoms lasting 1–6 months.

### Schizoaffective disorder

Shares symptoms with both schizophrenia and mood disorders (major depressive or bipolar disorder). To differentiate from a mood disorder with psychotic features, patient must have > 2 weeks of psychotic symptoms without a manic or depressive episode.

#### **Delusional disorder**

 $\geq 1$  delusion(s) lasting > 1 month, but without a mood disorder or other psychotic symptoms. Daily functioning, including socialization, may be impacted by the pathological, fixed belief but is otherwise unaffected. Can be shared by individuals in close relationships (folie à deux).

### Schizotypal personality disorder

Cluster A personality disorder that also falls on the schizophrenia spectrum. May include brief psychotic episodes (eg, delusions) that are less frequent and severe than in schizophrenia.

#### **Mood disorder**

Characterized by an abnormal range of moods or internal emotional states and loss of control over them. Severity of moods causes distress and impairment in social and occupational functioning. Includes major depressive, bipolar, dysthymic, and cyclothymic disorders. Episodic superimposed psychotic features (delusions, hallucinations, disorganized speech/behavior) may be present.

#### Manic episode

Distinct period of abnormally and persistently elevated, expansive, or irritable mood and † activity or energy lasting ≥ 1 week. Diagnosis requires hospitalization or marked functional impairment with  $\geq$  3 of the following (manics **DIG FAST**):

- Distractibility
- Impulsivity/Indiscretion—seeks pleasure without regard to consequences (hedonistic)
- Grandiosity—inflated self-esteem
- Flight of ideas—racing thoughts
- † goal-directed Activity/psychomotor **A**gitation
- ↓ need for Sleep
- Talkativeness or pressured speech

FAS1 2019 13-Psych.indd 560 11/7/19 5:28 PM

#### Hypomanic episode

Similar to a manic episode except mood disturbance is not severe enough to cause marked impairment in social and/or occupational functioning or to necessitate hospitalization.

Abnormally ↑ activity or energy usually present. No psychotic features. Lasts ≥ 4 consecutive days.

#### **Bipolar disorder**

**Bipolar I**—≥ 1 manic episode +/– a hypomanic or depressive episode (may be separated by any length of time).

Bipolar II—a hypomanic and a depressive episode (no history of manic episodes).

Patient's mood and functioning usually normalize between episodes. Use of antidepressants can destabilize mood. High suicide risk. Treatment: mood stabilizers (eg, lithium, valproic acid, carbamazepine, lamotrigine), atypical antipsychotics.

**Cyclothymic disorder**—milder form of bipolar disorder fluctuating between mild depressive and hypomanic symptoms. Must last  $\geq 2$  years with symptoms present at least half of the time, with any remission lasting  $\leq 2$  months.

# Major depressive disorder

Recurrent episodes lasting  $\geq 2$  weeks characterized by  $\geq 5$  of 9 diagnostic symptoms (must include depressed mood or anhedonia) (**DIGS SPACE**):

- Depressed mood (or irritability in children)
- ↓ Interest (anhedonia)
- Guilt or feelings of worthlessness
- Sleep disturbances
- Suicidal ideation
- Psychomotor retardation or agitation
- Appetite/weight changes
- Concentration
- ↓ Energy

Screen for previous manic or hypomanic episodes to rule out bipolar disorder.

Treatment: CBT and SSRIs are first line. Also SNRIs, mirtazapine, bupropion, electroconvulsive therapy (ECT).

# MDD with psychotic features

MDD + hallucinations or delusions. Psychotic features are typically mood congruent (eg, depressive themes of inadequacy, guilt, punishment, nihilism, disease, or death) and occur only in the context of major depressive episode (vs schizoaffective disorder). Treatment: antidepressant with atypical antipsychotic, ECT.

# Persistent depressive disorder (dysthymia)

Often milder than MDD;  $\geq 2$  depressive symptoms lasting  $\geq 2$  years ( $\geq 1$  year in children), with any remission lasting  $\leq 2$  months.

# MDD with seasonal pattern

Formerly called seasonal affective disorder. Major depressive episodes occurring only during a particular season (usually winter) in  $\geq 2$  consecutive years and in most years across a lifetime. Atypical symptoms common.

# Depression with atypical features

Characterized by mood reactivity (transient improvement in response to a positive event), hypersomnia, hyperphagia, leaden paralysis (heavy feeling in arms and legs), long-standing interpersonal rejection sensitivity. Most common subtype of depression. Treatment: CBT and SSRIs are first line. MAO inhibitors (MAOIs) are effective but not first line because of their risk profile.

FAS1\_2019\_13-Psych.indd 561 11/7/19 5:28 PM

# 562 SECTION III PSYCHIATRY ► PSYCHIATRY—PATHOLOGY

Peripartum mood disturbances	Onset during or shortly after pregnancy or disorders.	within 4 weeks of delivery. † risk with history of mood
Maternal (postpartum) blues	50–85% incidence rate. Characterized by depressed affect, tearfulness, and fatigue starting 2–3 days after delivery. Usually resolves within 2 weeks. Treatment: supportive. Follow up to assess for possible MDD with peripartum onset.	
MDD with peripartum onset	10–15% incidence rate. Formerly called postpartum depression. Meets MDD criteria with onset no later than 1 year after delivery. Treatment: CBT and SSRIs are first line.	
Postpartum psychosis	0.1–0.2% incidence rate. Characterized by mood-congruent delusions, hallucinations, and thoughts of harming the baby or self. Risk factors include first pregnancy, family history, bipolar disorder, psychotic disorder, recent medication change. Treatment: hospitalization and initiation of atypical antipsychotic; if insufficient, ECT may be used.	
Grief	The five stages of grief per the Kübler-Ross model are denial, anger, bargaining, depression, and acceptance (may occur in any order). Other normal grief symptoms include shock, guilt, sadness, anxiety, yearning, and somatic symptoms that usually occur in waves. Simple hallucinations of the deceased person are common (eg, hearing the deceased speaking). Any thoughts of dying are limited to joining the deceased (vs complicated grief). Duration varies widely; usually resolves within 6–12 months.  Persistent complex bereavement disorder involves obsessive preoccupation with the deceased and causes functional impairment, lasting at least 12 months (6 months in children). Can also meet criteria for major depressive episode.	
Electroconvulsive therapy	Rapid-acting method to treat refractory depression, depression with psychotic symptoms, catatonia, and acute suicidality. Induces tonic-clonic seizure under anesthesia and neuromuscular blockade. Adverse effects include disorientation, headache, partial anterograde/retrograde amnesia usually resolving in 6 months. No absolute contraindications. Safe in pregnant and elderly individuals.	
Risk factors for suicide completion	Sex (male) Age (young adult or elderly) Depression Previous attempt (highest risk factor) Ethanol or drug use Rational thinking loss (psychosis) Sickness (medical illness) Organized plan No spouse or other social support Stated future intent	SAD PERSONS are more likely to complete suicide.  Most common method in US is firearms; access to guns † risk of suicide completion.  Women try more often; men complete more often.  Other risk factors include recent psychiatric hospitalization and family history of completed suicide.
Anxiety disorders	Inappropriate experiences of fear/worry and their physical manifestations incongruent with the magnitude of the stressors. Symptoms are not attributable to another psychiatric disorder, medical condition (eg, hyperthyroidism), or substance abuse. Includes panic disorder, phobias, generalized anxiety disorder, and selective mutism.	

FAS1\_2019\_13-Psych.indd 562 11/7/19 5:28 PM

#### Panic disorder

Recurrent panic attacks involving intense fear and discomfort +/− a known trigger.

Attacks typically peak in 10 minutes with ≥ 4 of the following: palpitations, paresthesias, depersonalization or derealization, abdominal pain, nausea, intense fear of dying, intense fear of losing control, lightheadedness, chest pain, chills, choking, sweating, shaking, shortness of breath. Strong genetic component. † risk of suicide.

Diagnosis requires attack followed by  $\geq 1$  month of  $\geq 1$  of the following:

- Persistent concern of additional attacks
- Worrying about consequences of attack
- Behavioral change related to attacks

Symptoms are systemic manifestations of fear. Treatment: CBT, SSRIs, and venlafaxine are first line. Benzodiazepines occasionally used in acute setting.

#### **Phobias**

Severe, persistent (≥ 6 months) fear or anxiety due to presence or anticipation of a specific object or situation. Person often recognizes fear is excessive. Treatment: CBT with exposure therapy.

**Social anxiety disorder**—exaggerated fear of embarrassment in social situations (eg, public speaking, using public restrooms). Treatment: CBT, SSRIs, venlafaxine. For performance type (eg, anxiety restricted to public speaking), use  $\beta$ -blockers or benzodiazepines as needed.

**Agoraphobia**—irrational fear/anxiety while facing or anticipating ≥ 2 specific situations (eg, open/closed spaces, lines, crowds, public transport). If severe, patients may refuse to leave their homes. Associated with panic disorder. Treatment: CBT, SSRIs.

# Generalized anxiety disorder

Excessive anxiety and worry about different aspects of daily life (eg, work, school, children) for most days of  $\geq 6$  months. Associated with  $\geq 3$  of the following for adults ( $\geq 1$  for kids): restlessness, irritability, sleep disturbance, fatigue, muscle tension, difficulty concentrating. Treatment: CBT, SSRIs, SNRIs are first line. Buspirone, TCAs, benzodiazepines are second line.

# Obsessive-compulsive disorders

Obsessions (recurring intrusive thoughts, feelings, or sensations) that cause severe distress, relieved in part by compulsions (performance of repetitive, often time-consuming actions). Ego-dystonic: behavior inconsistent with one's beliefs and attitudes (vs obsessive-compulsive personality disorder, ego-syntonic). Associated with Tourette syndrome. Treatment: CBT and SSRIs; clomipramine and venlafaxine are second line.

**Body dysmorphic disorder**—preoccupation with minor or imagined defects in appearance. Causes significant emotional distress and repetitive appearance-related behaviors (eg, mirror checking, excessive grooming). Common in eating disorders. Treatment: CBT.

#### **Trichotillomania**



Compulsively pulling out one's hair. Causes significant distress and persists despite attempts to stop. Presents with areas of thinning hair or baldness on any area of the body, most commonly the scalp A. Incidence highest in childhood but spans all ages. Treatment: psychotherapy.

FAS1\_2019\_13-Psych.indd 563 11/7/19 5:28 PM

#### Trauma and stress-related disorders

#### Adjustment disorder

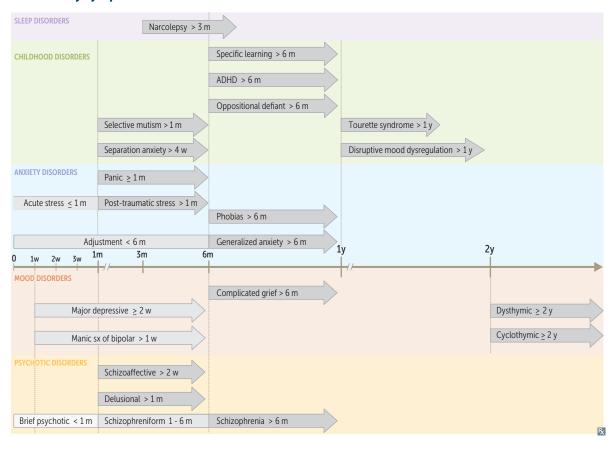
Emotional or behavioral symptoms (eg, anxiety, outbursts) that occur within 3 months of an identifiable psychosocial stressor (eg, divorce, illness) lasting < 6 months once the stressor has ended. If symptoms persist > 6 months after stressor ends, it is GAD. Symptoms do not meet criteria for MDD. Treatment: CBT is first line; antidepressants and anxiolytics may be considered.

# Post-traumatic stress disorder

Experiencing, or discovering that a loved one has experienced, a life-threatening situation (eg, serious injury, rape, witnessing death) → persistent Hyperarousal, Avoidance of associated stimuli, intrusive Re-experiencing of the event (eg, nightmares, flashbacks), changes in cognition or mood (eg, fear, horror, Distress) (having PTSD is HARD). Disturbance lasts > 1 month with significant distress or impaired functioning. Treatment: CBT, SSRIs, and venlafaxine are first line. Prazosin can reduce nightmares.

Acute stress disorder—lasts between 3 days and 1 month. Treatment: CBT; pharmacotherapy is usually not indicated.

#### Diagnostic criteria by symptom duration



FAS1\_2019\_13-Psych.indd 564 11/7/19 5:28 PM

Personality trait	An enduring, repetitive pattern of perceiving, relating to, and thinking about the environment oneself.		
Personality disorder	Inflexible, maladaptive, and rigidly pervasive pattern of behavior causing subjective distress and/or impaired functioning; person is usually not aware of problem (ego-syntonic). Usually presents by early adulthood.  Three clusters: A, B, C; remember as Weird, Wild, and Worried, respectively, based on symptoms.		
Cluster A personality disorders	Odd or eccentric; inability to develop meaningful social relationships. No psychosis; genetic association with schizophrenia.	Cluster A: Accusatory, Aloof, Awkward. "Weird."	
Paranoid	Pervasive distrust (Accusatory), suspiciousness, hypervigilance, and a profoundly cynical view of the world.		
Schizoid	Voluntary social withdrawal (Aloof), limited emotional expression, content with social isolation (vs avoidant).		
Schizotypal	Eccentric appearance, odd beliefs or magical thinking, interpersonal <b>A</b> wkwardness.	Included on the schizophrenia spectrum. Pronounce schizo-type-al: odd-type thoughts.	
Cluster B personality disorders	Dramatic, emotional, or erratic; genetic association with mood disorders and substance abuse.	Cluster B: Bad, Borderline, flamBoyant, must be the Best. "Wild."	
Antisocial	Disregard for the rights of others with lack of remorse. Involves criminality, impulsivity, hostility, and manipulation. Males > females. Must be ≥ 18 years old with evidence of conduct disorder onset before age 15.  Diagnosis is conduct disorder if < 18 years old.	Antisocial = sociopath.  Bad.	
Borderline	Unstable mood and interpersonal relationships, fear of abandonment, impulsivity, selfmutilation, suicidality, sense of emotional emptiness. Females > males. Splitting is a major defense mechanism.	Treatment: dialectical behavior therapy.  Borderline.	
Histrionic	Attention-seeking, dramatic speech and emotional expression, shallow and labile emotions, sexually provocative. May use physical appearance to draw attention.	Flam <mark>B</mark> oyant.	
Narcissistic	Grandiosity, sense of entitlement; lacks empathy and requires excessive admiration; often demands the "best" and reacts to criticism with rage and/or defensiveness. Fragile selfesteem. Often envious of others.	Must be the <b>B</b> est.	

FAS1\_2019\_13-Psych.indd 565 11/7/19 5:28 PM

# 566 SECTION III PSYCHIATRY → PSYCHIATRY—PATHOLOGY

Cluster C personality disorders	Anxious or fearful; genetic association with anxiety disorders.	Cluster C: Cowardly, obsessive-Compulsive, Clingy. "Worried."
Avoidant	Hypersensitive to rejection and criticism, socially inhibited, timid, feelings of inadequacy, desires relationships with others (vs schizoid).	Cowardly.
Obsessive- Compulsive	Preoccupation with order, perfectionism, and control; ego-syntonic: behavior consistent with one's own beliefs and attitudes (vs OCD).	
Dependent	Excessive need for support, low self-confidence. Patients often get stuck in abusive relationships.	Submissive and Clingy.
Malingering	Symptoms are <b>intentional</b> , motivation is <b>intentional</b> . Patient <b>consciously</b> fakes, profoundly exaggerates, or claims to have a disorder in order to attain a specific <b>2°</b> ( <b>external</b> ) <b>gain</b> (eg, avoiding work, obtaining compensation). Poor compliance with treatment or follow-up of diagnostic tests. Complaints cease after gain (vs factitious disorder).	
Factitious disorders	• •	cious. Patient consciously creates physical and/or k role" and to get medical attention and sympathy
Factitious disorder imposed on self	Formerly called Munchausen syndrome. Chronic factitious disorder with predominantly physical signs and symptoms. Characterized by a history of multiple hospital admissions and willingness to undergo invasive procedures. More common in women and healthcare workers.	
Factitious disorder imposed on another	Formerly called Munchausen syndrome by proxy. Illness in a child or elderly patient is caused or fabricated by the caregiver. Motivation is to assume a sick role by proxy. Form of child/elder abuse	
Somatic symptom and related disorders	Symptoms are <b>unconscious</b> , motivation is <b>unconscious</b> . Category of disorders characterized by physical symptoms causing significant distress and impairment. Symptoms not intentionally produced or feigned.	
Somatic symptom disorder	≥ 1 bodily complaints (eg, abdominal pain, fatigue) lasting months to years. Associated with excessive, persistent thoughts and anxiety about symptoms. May co-occur with medical illness. Treatment: regular office visits with the same physician in combination with psychotherapy.	
Conversion disorder	Also called functional neurologic symptom disorder. Loss of sensory or motor function (eg, paralysis, blindness, mutism), often following an acute stressor; patient may be aware of but indifferent toward symptoms ( <i>la belle indifférence</i> ); more common in females, adolescents, and young adults.	
Illness anxiety disorder	Preoccupation with acquiring or having a serious illness, often despite medical evaluation and reassurance; minimal to no somatic symptoms.	

11/7/19 5:28 PM FAS1\_2019\_13-Psych.indd 566

Eating disorders	Most common in young women.
Anorexia nervosa	Intense fear of weight gain, overvaluation of thinness, and body image distortion leading to calorie restriction and severe weight loss resulting in inappropriately low body weight.  Binge-eating/purging type—recurring purging behaviors (eg, laxative or diuretic abuse, self-induced vomiting) or binge eating over the last 3 months.  Restricting type—primary disordered behaviors include dieting, fasting, and/or over-exercising. No recurring purging behaviors or binge eating over the last 3 months.  Refeeding syndrome—often occurs in significantly malnourished patients with sudden ↑ calorie intake → ↑ insulin → ↓ PO₄³-, ↓ K⁺, ↓ Mg²+ → cardiac complications, rhabdomyolysis, seizures.  Treatment: psychotherapy, nutritional rehabilitation, antidepressants (eg, SSRIs).
Bulimia nervosa	Recurring episodes of binge eating with compensatory purging behaviors at least weekly over the last 3 months. BMI often normal or slightly overweight (vs anorexia). Associated with parotid gland hypertrophy (may see † serum amylase), enamel erosion, Mallory-Weiss syndrome, electrolyte disturbances (eg, ↓ K+, ↓ Cl-), metabolic alkalosis, dorsal hand calluses from induced vomiting (Russell sign).  Treatment: psychotherapy, nutritional rehabilitation, antidepressants (eg, SSRIs). Bupropion is contraindicated due to seizure risk.
Binge-eating disorder	Recurring episodes of binge eating without purging behaviors at least weekly over the last 3 months. † diabetes risk. Most common eating disorder in adults.  Treatment: psychotherapy (first line); SSRIs; lisdexamfetamine.
Pica	Recurring episodes of eating non-food substances (eg, dirt, hair, paint chips) over ≥ 1 month that are not culturally or developmentally recognized as normal. May provide temporary emotional relief. Common in children and during pregnancy. Associated with malnutrition, iron deficiency anemia, developmental disabilities, emotional trauma.  Treatment: psychotherapy and nutritional rehabilitation (first line); SSRIs (second line).
Gender dysphoria	Significant incongruence between one's experienced gender and the gender assigned at birth, lasting > 6 months and leading to persistent distress. Individuals may self-identify as another gender, pursue surgery or hormone treatment to rid self of primary/secondary sex characteristics, and/or live as another gender. Gender nonconformity itself is not a mental disorder.
	<b>Transgender</b> —desiring and often making lifestyle changes to live as a different <b>gender</b> . Medical interventions (eg, hormone therapy, sex reassignment surgery) may be utilized during the transition to enable the individual's appearance to match their gender identity.
	<b>Transvestism</b> —deriving pleasure from wearing clothes (eg, a <b>vest</b> ) of the opposite sex (cross-dressing). <b>Transvestic disorder</b> —transvestism that causes significant distress/functional impairment. It is a paraphilia (psychosexual disorder), not part of gender dysphoria.
Sexual dysfunction	Includes sexual desire disorders (hypoactive sexual desire or sexual aversion), sexual arousal disorders (erectile dysfunction), orgasmic disorders (anorgasmia, premature ejaculation), sexual pain disorders (dyspareunia, vaginismus).  Differential diagnosis includes (PENIS):  Psychological (if nighttime erections still occur)  Endocrine (eg, diabetes, low testosterone)  Neurogenic (eg, postoperative, spinal cord injury)  Insufficient blood flow (eg, atherosclerosis)  Substances (eg, antihypertensives, antidepressants, ethanol)

FAS1\_2019\_13-Psych.indd 567 11/7/19 5:28 PM

### **PSYCHIATRY** ▶ PSYCHIATRY—PATHOLOGY

#### Sleep terror disorder

Periods of inconsolable terror with screaming in the middle of the night. Most common in children. Occurs during slow-wave/deep (stage N3) non-REM sleep with no memory of the arousal episode, as opposed to nightmares that occur during **REM** sleep (remembering a scary dream). Triggers include emotional stress, fever, and lack of sleep. Usually self limited.

#### **Enuresis**

Nighttime urinary incontinence ≥ 2 times/week for ≥ 3 months in person > 5 years old. First-line treatment: behavioral modification (eg, scheduled voids, nighttime fluid restriction) and positive reinforcement. For refractory cases: bedwetting alarm, oral desmopressin (ADH analog; preferred over imipramine due to fewer side effects).

#### **Narcolepsy**

Excessive daytime sleepiness (despite awakening well-rested) with recurrent episodes of rapid-onset, overwhelming sleepiness ≥ 3 times/week for the last 3 months. Due to ↓ orexin (hypocretin) production in lateral hypothalamus and dysregulated sleep-wake cycles. Associated with:

- Hypnagogic (just before going to sleep) or hypnopompic (just before awakening; get pomped up in the morning) hallucinations.
- Nocturnal and narcoleptic sleep episodes that start with REM sleep (sleep paralysis).
- Cataplexy (loss of all muscle tone following strong emotional stimulus, such as laughter).

Treatment: good sleep hygiene (scheduled naps, regular sleep schedule), daytime stimulants (eg, amphetamines, modafinil) and/or nighttime sodium oxybate (GHB).

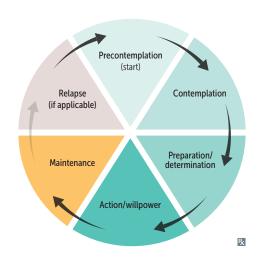
# Substance use disorder

Maladaptive pattern of substance use involving ≥ 2 of the following in the past year:

- Tolerance
- Withdrawal
- Intense, distracting cravings
- Using more, or longer, than intended
- Persistent desire but inability to cut down
- Time-consuming substance acquisition, use, or recovery
- Impaired functioning at work, school, or home
- Social or interpersonal conflicts
- Reduced recreational activities
- > l episode of use involving danger (eg, unsafe sex, driving while impaired)
- Continued use despite awareness of harm

# Stages of change in overcoming addiction

- 1. **Precontemplation**—denying problem
- 2. **Contemplation**—acknowledging problem, but unwilling to change
- Preparation/determination—preparing for behavioral changes
- 4. Action/willpower—changing behaviors
- 5. **Maintenance**—maintaining changes
- 6. **Relapse**—(if applicable) returning to old behaviors and abandoning changes



FAS1\_2019\_13-Psych.indd 568 11/7/19 5:28 PM

## **Psychiatric emergencies**

	CAUSE	MANIFESTATION	TREATMENT
Serotonin syndrome	Any drug that † 5-HT. Psychiatric drugs: MAOIs, SSRIs, SNRIs, TCAs, vilazodone, vortioxetine, buspirone Nonpsychiatric drugs: tramadol, ondansetron, triptans, linezolid, MDMA, dextromethorphan, meperidine, St. John's wort	3 A's: † Activity (neuromuscular; eg, clonus, hyperreflexia, hypertonia, tremor, seizure), Autonomic instability (eg, hyperthermia, diaphoresis, diarrhea), Altered mental status	Cyproheptadine (5-HT <sub>2</sub> receptor antagonist)
Hypertensive crisis	Eating tyramine-rich foods (eg, aged cheeses, cured meats, wine, chocolate) while taking MAOIs	Hypertensive crisis (tyramine displaces other neurotransmitters [eg, NE] in the synaptic cleft  → ↑ sympathetic stimulation)	Phentolamine
Neuroleptic malignant syndrome	Antipsychotics (typical > atypical) + genetic predisposition	Malignant FEVER: Myoglobinuria, Fever, Encephalopathy, Vitals unstable, † Enzymes (eg, CK), muscle Rigidity ("lead pipe")	Dantrolene, dopamine agonist (eg, bromocriptine), discontinue causative agent
Delirium tremens	Alcohol withdrawal; occurs 2–4 days after last drink Classically seen in hospital setting when inpatient cannot drink	Altered mental status, hallucinations, autonomic hyperactivity, anxiety, seizures, tremors, psychomotor agitation, insomnia, nausea	Benzodiazepines (eg, chlordiazepoxide, lorazepam, diazepam)
Acute dystonia	Typical antipsychotics, anticonvulsants (eg, carbamazepine), metoclopramide	Sudden onset of muscle spasms, stiffness, and/or oculogyric crisis occurring hours to days after medication use; can lead to laryngospasm requiring intubation	Benztropine or diphenhydramine
Lithium toxicity	† lithium dosage, ‡ renal elimination (eg, acute kidney injury), medications affecting clearance (eg, ACE inhibitors, thiazide diuretics, NSAIDs). Narrow therapeutic window.	Nausea, vomiting, slurred speech, hyperreflexia, seizures, ataxia, nephrogenic diabetes insipidus	Discontinue lithium, hydrate aggressively with isotonic sodium chloride, consider hemodialysis
Tricyclic antidepressant toxicity	TCA overdose	Respiratory depression, hyperpyrexia, prolonged QT Tri-CyCliC's: Convulsions, Coma, Cardiotoxicity (arrhythmia due to Na+ channel inhibition)	Supportive treatment, monitor ECG, NaHCO <sub>3</sub> (prevents arrhythmia), activated charcoal

FAS1\_2019\_13-Psych.indd 569 11/7/19 5:28 PM

## Psychoactive drug intoxication and withdrawal

DRUG	INTOXICATION	WITHDRAWAL	
Depressants			
	Nonspecific: mood elevation, ↓ anxiety, sedation, behavioral disinhibition, respiratory depression.	Nonspecific: anxiety, tremor, seizures, insomnia.	
Alcohol	Emotional lability, slurred speech, ataxia, coma, blackouts. Serum γ-glutamyltransferase (GGT)—sensitive indicator of alcohol use. <b>AST</b> value is <b>2</b> × <b>AL</b> T value ("To <b>AST 2 AL</b> cohol"). Treatment: benzodiazepines.	Alcoholic hallucinosis (usually visual)  Withdrawal seizures  Tremors, insomnia, diaphoresis, agitation, Gl upset  0 3 6 12 24 36 48 96  Time from last drink (hours)	
Barbiturates	Low safety margin, marked respiratory depression. Treatment: symptom management (eg, assist respiration, † BP).	Delirium, life-threatening cardiovascular collapse.	
Benzodiazepines	Greater safety margin. Ataxia, minor respiratory depression. Treatment: flumazenil (benzodiazepine receptor antagonist, but rarely used as it can precipitate seizures).	Sleep disturbance, depression.	
Opioids	Euphoria, respiratory and CNS depression,  ↓ gag reflex, pupillary constriction (pinpoint pupils), seizures. Most common cause of drug overdose death. Treatment: naloxone.	Sweating, dilated pupils, piloerection ("cold turkey"), rhinorrhea, lacrimation, yawning, nausea, stomach cramps, diarrhea ("flu-like" symptoms). Treatment: symptom management, methadone, buprenorphine.	
Inhalants	Disinhibition, euphoria, slurred speech, disturbed gait, disorientation, drowsiness.	Irritability, dysphoria, sleep disturbance, headache.	
Stimulants			
	Nonspecific: mood elevation, ↓ appetite, psychomotor agitation, insomnia, cardiac arrhythmias, tachycardia, anxiety.	Nonspecific: post-use "crash," including depression, lethargy, † appetite, sleep disturbance, vivid nightmares.	
Amphetamines	Euphoria, grandiosity, pupillary dilation, prolonged wakefulness, hyperalertness, hypertension, paranoia, fever, fractured teeth. Skin excoriations with methamphetamine use. Severe: cardiac arrest, seizures. Treatment: benzodiazepines for agitation and seizures.		
Caffeine	Palpitation, agitation, tremor, insomnia.	Headache, difficulty concentrating, flu-like symptoms.	

FAS1\_2019\_13-Psych.indd 570 11/7/19 5:28 PM

## Psychoactive drug intoxication and withdrawal (continued)

DRUG	INTOXICATION	WITHDRAWAL
Cocaine	Impaired judgment, pupillary dilation, hallucinations (including tactile), paranoia, angina, sudden cardiac death. Chronic use may lead to perforated nasal septum due to vasoconstriction and resulting ischemic necrosis. Treatment: benzodiazepines; consider mixed α-/β-blocker (eg, labetalol) for hypertension and tachycardia. Pure β-blocker usage is controversial as a first-line therapy.	
Nicotine	Restlessness.	Irritability, anxiety, restlessness, ↓ concentration, ↑ appetite/weight. Treatment: nicotine patch, gum, or lozenges; bupropion/varenicline.
Hallucinogens		
Lysergic acid diethylamide	Perceptual distortion (visual, auditory), depersonalization, anxiety, paranoia, psychosis, flashbacks (usually nondisturbing).	
Marijuana (can <mark>nabino</mark> id)	Euphoria, anxiety, paranoid delusions, perception of slowed time, impaired judgment, social withdrawal, † appetite, dry mouth, conjunctival injection, hallucinations. Pharmaceutical form is dronabinol: used as antiemetic (chemotherapy) and appetite stimulant (in AIDS).	Irritability, anxiety, depression, insomnia, restlessness, ↓ appetite.
MDMA (ecstasy)	Hallucinogenic stimulant: euphoria, hallucinations, disinhibition, hyperactivity, † thirst, bruxism, distorted sensory and time perception. Life-threatening effects include hypertension, tachycardia, hyperthermia, hyponatremia, serotonin syndrome.	Depression, fatigue, change in appetite, difficulty concentrating, anxiety.
Phencyclidine	Violence, impulsivity, psychomotor agitation, nystagmus, tachycardia, hypertension, analgesia, psychosis, delirium, seizures.  Trauma is most common complication.	
Alcohol use disorder	Physiologic tolerance and dependence on alcohol interrupted.  Complications: vitamin B <sub>1</sub> (thiamine) deficiency, peripheral neuropathy, testicular atrophy.  Treatment: naltrexone (reduces cravings), acampr abstain from alcohol use). Support groups such a abstinence and supporting patient and family.	alcoholic cirrhosis, hepatitis, pancreatitis,
Wernicke-Korsakoff syndrome	Results from vitamin B <sub>1</sub> deficiency. Symptoms car	oplegia, ataxia (Wernicke encephalopathy). May

FAS1\_2019\_13-Psych.indd 571 11/7/19 5:28 PM

Doughothoromy			
Psychotherapy  Balancia and the arrangements of the second	T 1 1 1 1 1		
Behavioral therapy	Teaches patients how to identify and change maladaptive behaviors or reactions to stimuli. Examples include systematic desensitization for treatment of phobia.		
Cognitive behavioral therapy	Teaches patients to recognize distortions in their thought processes, develop constructive coping skills, and ↓ maladaptive coping behaviors → greater emotional control and tolerance of distress. Examples include recognizing triggers for alcohol consumption.		
Dialectical behavioral therapy	Designed for use in borderline personali as well (eg, depression).	ty disorder, but can be used in other psychiatric conditions	
Interpersonal therapy	Focused on improving interpersonal rela	itionships and communication skills.	
Supportive therapy	Utilizes empathy to help individuals dur	ing a time of hardship to maintain optimism or hope.	
Preferred medications	PSYCHIATRIC CONDITION	PREFERRED DRUGS	
for selected	ADHD	Stimulants (methylphenidate, amphetamines)	
psychiatric conditions	Alcohol withdrawal	Benzodiazepines (eg, chlordiazepoxide, lorazepam, diazepam)	
	Bipolar disorder	Lithium, valproic acid, carbamazepine, lamotrigine, atypical antipsychotics	
	Bulimia nervosa	SSRIs	
	Depression	SSRIs	
	Generalized anxiety disorder	SSRIs, SNRIs	
	Obsessive-compulsive disorder	SSRIs, venlafaxine, clomipramine	
	Panic disorder	SSRIs, venlafaxine, benzodiazepines	
	PTSD	SSRIs, venlafaxine	
	Schizophrenia	Atypical antipsychotics	
	Social anxiety disorder	SSRIs, venlafaxine Performance only: β-blockers, benzodiazepines	
	Tourette syndrome	Antipsychotics (eg, fluphenazine, risperidone), tetrabenazine	
Central nervous system stimulants	Methylphenidate, dextroamphetamine,	methamphetamine, lisdexamfetamine.	
MECHANISM	† catecholamines in the synaptic cleft, e	specially norepinephrine and dopamine.	
CLINICAL USE	ADHD, narcolepsy, binge-eating disorde		
ADVERSE EFFECTS	Nervousness, agitation, anxiety, insomnia, anorexia, tachycardia, hypertension, weight loss, tics, bruxism.		

FAS1\_2019\_13-Psych.indd 572 11/7/19 5:28 PM

<b>Typical antipsychotics</b>	Haloperidol, pimozide, trifluoperazine, fluphenazine, thioridazine, chlorpromazine.		
MECHANISM	Block dopamine D <sub>2</sub> receptor († cAMP).		
CLINICAL USE	Schizophrenia (1° positive symptoms), psychosis, bipolar disorder, delirium, Tourette syndrome, Huntington disease, OCD. Use with caution in dementia.		
POTENCY	<ul> <li>High potency: Haloperidol, Trifluoperazine, Fluphenazine (Hal Tries to Fly High)—more neurologic side effects (eg, extrapyramidal symptoms [EPS]).</li> <li>Low potency: Chlorpromazine, Thioridazine (Cheating Thieves are low)—more anticholinergic, antihistamine, α₁-blockade effects.</li> </ul>		
ADVERSE EFFECTS	Lipid soluble → stored in body fat → slow to be removed from body.  Endocrine: dopamine receptor antagonism → hyperprolactinemia → galactorrhea, oligomenorrhea, gynecomastia.  Metabolic: dyslipidemia, weight gain, hyperglycemia.  Antimuscarinic: dry mouth, constipation.  Antihistamine: sedation.  α₁-blockade: orthostatic hypotension.  Cardiac: QT prolongation.  Ophthalmologic: Chlorpromazine—Corneal deposits; Thioridazine—reTinal deposits.  Neuroleptic malignant syndrome.  Extrapyramidal symptoms— ADAPT:  Hours to days: Acute Dystonia (muscle spasm, stiffness, oculogyric crisis). Treatment: benztropine, diphenhydramine.  Days to months:  Akathisia (restlessness). Treatment: β-blockers, benztropine, benzodiazepines.  Parkinsonism (bradykinesia). Treatment: benztropine, amantadine.  Months to years: Tardive dyskinesia (chorea, especially orofacial). Treatment: atypical antipsychotics (eg, clozapine), valbenazine, deutetrabenazine.		
Atypical antipsychotics	Aripiprazole, asenapine, clozapine, olanzapine, quetiapine, iloperidone, paliperidone, risperidone, lurasidone, ziprasidone.		
MECHANISM	Not completely understood. Most are 5-HT <sub>2</sub> and D <sub>2</sub> antagonists; aripiprazole is a D <sub>2</sub> partial agonist. Varied effects on $\alpha$ and H <sub>1</sub> receptors.		
CLINICAL USE	Schizophrenia—both positive and negative symptoms. Also used for bipolar disorder, OCD, anxiety disorders, depression, mania, Tourette syndrome.	Use clozapine for treatment-resistant schizophrenia or schizoaffective disorder and for suicidality in schizophrenia.	
ADVERSE EFFECTS	All—prolonged QT, fewer EPS and anticholinergic side effects than typical antipsychotics.  "-apines"—metabolic syndrome (weight gain, diabetes, dyslipidemia).  Clozapine—agranulocytosis (monitor WBCs frequently) and seizures (dose related).  Risperidone—hyperprolactinemia (amenorrhea, galactorrhea, gynecomastia).	Olanzapine, clOzapine → Obesity  Must watch bone marrow clozely with clozapine.	

FAS1\_2019\_13-Psych.indd 573 11/7/19 5:28 PM

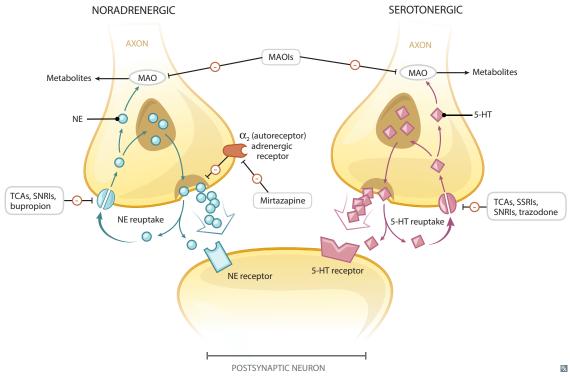
### Lithium

MECHANISM	Not established; possibly related to inhibition of phosphoinositol cascade.	LiTHIUM: Low Thyroid (hypothyroidism)
CLINICAL USE	Mood stabilizer for bipolar disorder; treats acute manic episodes and prevents relapse.	Heart (Ebstein anomaly) Insipidus (nephrogenic diabetes insipidus)
ADVERSE EFFECTS	Tremor, thyroid abnormalities (eg, hypothyroidism), polyuria (causes nephrogenic diabetes insipidus), teratogenesis. Causes Ebstein anomaly in newborn if taken by pregnant mother. Narrow therapeutic window requires close monitoring of serum levels. Almost exclusively excreted by kidneys; most is reabsorbed at PCT via Na <sup>+</sup> channels. Thiazides, NSAIDs, and other drugs affecting clearance are implicated in lithium toxicity.	Unwanted Movements (tremor)

### **Buspirone**

MECHANISM	Stimulates 5-H $T_{1A}$ receptors.	I get anxious if the bus doesn't arrive at one, so
CLINICAL USE	Generalized anxiety disorder. Does not cause sedation, addiction, or tolerance. Begins to take effect after 1–2 weeks. Does not interact with alcohol (vs barbiturates, benzodiazepines).	I take <mark>bus</mark> pirone.

### **Antidepressants**



FAS1\_2019\_13-Psych.indd 574 11/7/19 5:28 PM

Selective serotonin reuptake inhibitors	Fluoxetine, fluvoxamine, paroxetine, sertraline, escitalopram, citalopram.			
MECHANISM	Inhibit 5-HT reuptake.	It normally takes 4–8 weeks for antidepressants		
CLINICAL USE	Depression, generalized anxiety disorder, panic disorder, OCD, bulimia, binge-eating disorder, social anxiety disorder, PTSD, premature ejaculation, premenstrual dysphoric disorder.	to show appreciable effect.		
ADVERSE EFFECTS	Fewer than TCAs. Serotonin syndrome, GI distress, SIADH, sexual dysfunction (anorgasmia, ↓ libido).			
Serotonin- norepinephrine				
reuptake inhibitors	Venlafaxine, desvenlafaxine, duloxetine, levomiln	nacipran, milnacipran.		
MECHANISM	Inhibit 5-HT and NE reuptake.	· ·		
CLINICAL USE	Depression, generalized anxiety disorder, diabetic neuropathy. Venlafaxine is also indicated for social anxiety disorder, panic disorder, PTSD, OCD. Duloxetine and milnacipran are also indicated for fibromyalgia.			
ADVERSE EFFECTS	† BP, stimulant effects, sedation, nausea.			
Tricyclic antidepressants	Amitriptyline, nortriptyline, imipramine, desiprar	nine, clomipramine, doxepin, amoxapine.		
MECHANISM	TCAs inhibit 5-HT and NE reuptake.			
CLINICAL USE	MDD, peripheral neuropathy, chronic neuropathic pain, migraine prophylaxis, OCD (clomipramine), nocturnal enuresis (imipramine, although adverse effects may limit use).			
ADVERSE EFFECTS	Sedation, α <sub>1</sub> -blocking effects including postural hypotension, and atropine-like (anticholinergic) side effects (tachycardia, urinary retention, dry mouth). 3° TCAs (amitriptyline) have more anticholinergic effects than 2° TCAs (nortriptyline). Can prolong QT interval.  Tri-CyCliC's: Convulsions, Coma, Cardiotoxicity (arrhythmia due to Na <sup>+</sup> channel inhibition); also respiratory depression, hyperpyrexia. Confusion and hallucinations are more common in the elderly due to anticholinergic side effects (2° amines [eg, nortriptyline] better tolerated). Treatment: NaHCO <sub>3</sub> to prevent arrhythmia.			
Monoamine oxidase inhibitors	Tranylcypromine, Phenelzine, Isocarboxazid, Selegiline (selective MAO-B inhibitor). (MAO Takes Pride In Shanghai).			
MECHANISM	Nonselective MAO inhibition → ↑ levels of amine neurotransmitters (norepinephrine, 5-HT, dopamine).			
CLINICAL USE	Atypical depression, anxiety. Parkinson disease (se	elegiline).		
ADVERSE EFFECTS	CNS stimulation; hypertensive crisis, most notably SSRIs, TCAs, St. John's wort, meperidine, dextro serotonin syndrome).  Wait 2 weeks after stopping MAOIs before starting restrictions.	methorphan, linezolid (to avoid precipitating		

FAS1\_2019\_13-Psych.indd 575 11/7/19 5:28 PM

## **Atypical antidepressants**

Bupropion	Inhibits NE and DA reuptake. Also used for smoking cessation. Toxicity: stimulant effects (tachycardia, insomnia), headache, seizures in patients with bulimia and anorexia nervosa. Favorable sexual side effect profile.		
Mirtazapine	<ul> <li>α<sub>2</sub>-antagonist († release of NE and 5-HT), potent 5-HT<sub>2</sub> and 5-HT<sub>3</sub> receptor antagonist, and H<sub>1</sub> antagonist. Toxicity: sedation (which may be desirable in depressed patients with insomnia),</li> <li>† appetite, weight gain (which may be desirable in underweight patients), dry mouth.</li> </ul>		
Trazodone	Primarily blocks 5-HT <sub>2</sub> , $\alpha_1$ -adrenergic, and H <sub>1</sub> receptors; also weakly inhibits 5-HT reuptake. Used primarily for insomnia, as high doses are needed for antidepressant effects. Toxicity: sedation, nausea, priapism, postural hypotension. Think tra <b>ZZZobone</b> due to sedative and male-specific side effects.		
Varenicline	Nicotinic ACh receptor partial agonist. Used for smoking cessation. Toxicity: sleep disturbance, depressed mood, suicidal ideation. Varenicline helps nicotine cravings decline.		
Vilazodone	Inhibits 5-HT reuptake; 5-HT <sub>IA</sub> receptor partial agonist. Used for MDD. Toxicity: headache, diarrhea, nausea, anticholinergic effects. May cause serotonin syndrome if taken with other serotonergic agents.		
Vortioxetine	Inhibits 5-HT reuptake; 5-HT <sub>IA</sub> receptor agonist and 5-HT <sub>3</sub> receptor antagonist. Used for MDD. Toxicity: nausea, sexual dysfunction, sleep disturbances, anticholinergic effects. May cause serotonin syndrome if taken with other serotonergic agents.		
Opioid detoxification and relapse prevention	Intravenous drug users at † risk for hepatitis, HIV, abscesses, bacteremia, right-heart endocarditis.		
Methadone	Long-acting oral opiate used for heroin detoxification or long-term maintenance therapy.		
Buprenorphine	Sublingual form (partial agonist) used to prevent relapse.		
Naloxone	Short-acting opioid antagonist given IM, IV, or as a nasal spray to treat acute opioid overdose, particularly to reverse respiratory and CNS depression.		
Naltrexone	Long-acting oral opioid antagonist used after detoxification to prevent relapse. Use naltrexone for the long trex back to sobriety.		

FAS1\_2019\_13-Psych.indd 576 11/7/19 5:28 PM

# HIGH-YIELD SYSTEMS

# Renal

"But I know all about love already. I know precious little still about kidneys."

—Aldous Huxley, Antic Hay

"This too shall pass. Just like a kidney stone."

-Hunter Madsen

"I drink too much. The last time I gave a urine sample it had an olive in it."

—Rodney Dangerfield

Being able to understand and apply renal physiology will be critical for the exam. Important topics include electrolyte disorders, acid-base derangements, glomerular disorders (including histopathology), acute and chronic kidney disease, urine casts, diuretics, ACE inhibitors, and AT-II receptor blockers. Renal anomalies associated with various congenital defects are also high-yield associations to think about when evaluating pediatric vignettes.

▶Embryology	578
▶ Anatomy	580
▶ Physiology	581
▶ Pathology	594
▶ Pharmacology	607

FAS1\_2019\_14-Renal.indd 577 11/7/19 5:42 PM

### ▶ RENAL—EMBRYOLOGY

#### **Kidney embryology**

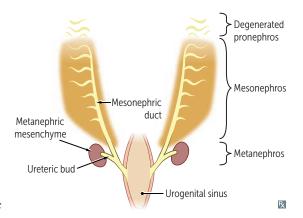
Pronephros—week 4; then degenerates. Mesonephros—functions as interim kidney for 1st trimester; later contributes to male genital system.

Metanephros—permanent; first appears in 5th week of gestation; nephrogenesis continues through weeks 32–36 of gestation.

- Ureteric bud (metanephric diverticulum) derived from caudal end of mesonephric duct; gives rise to ureter, pelvises, calyces, collecting ducts; fully canalized by 10th week
- Metanephric mesenchyme (ie, metanephric blastema)—ureteric bud interacts with this tissue; interaction induces differentiation and formation of glomerulus through to distal convoluted tubule (DCT)
- Aberrant interaction between these 2 tissues may result in several congenital malformations of the kidney (eg, renal agenesis, multicystic dysplastic kidney)

Ureteropelvic junction—last to canalize

→ congenital obstruction. Most common
cause of prenatal hydronephrosis. Detected by
prenatal ultrasound.



# Potter sequence (syndrome)



Oligohydramnios → compression of developing fetus → limb deformities, facial anomalies (eg, low-set ears and retrognathia A, flattened nose), compression of chest and lack of amniotic fluid aspiration into fetal lungs → pulmonary hypoplasia (cause of death).

Causes include ARPKD, obstructive uropathy (eg, posterior urethral valves), bilateral renal agenesis, chronic placental insufficiency.

Babies who can't "Pee" in utero develop Potter sequence.

**POTTER** sequence associated with:

Pulmonary hypoplasia

Oligohydramnios (trigger)

Twisted face

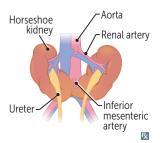
Twisted skin

Extremity defects

Renal failure (in utero)

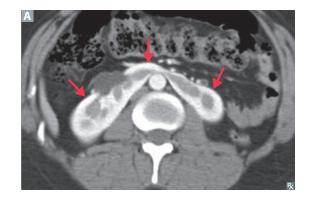
FAS1\_2019\_14-Renal.indd 578 11/7/19 5:42 PM

#### Horseshoe kidney



Inferior poles of both kidneys fuse abnormally A. As they ascend from pelvis during fetal development, horseshoe kidneys get trapped under inferior mesenteric artery and remain low in the abdomen. Kidneys function normally. Associated with hydronephrosis (eg, ureteropelvic junction obstruction), renal stones, infection, † risk of renal cancer.

Higher incidence in chromosomal aneuploidy (eg, Turner syndrome, trisomies 13, 18, 21).



# Congenital solitary functioning kidney

Condition of being born with only one functioning kidney. Majority asymptomatic with compensatory hypertrophy of contralateral kidney, but anomalies in contralateral kidney are common. Often diagnosed prenatally via ultrasound.

# Unilateral renal agenesis

Ureteric bud fails to develop and induce differentiation of metanephric mesenchyme → complete absence of kidney and ureter.

# Multicystic dysplastic kidney

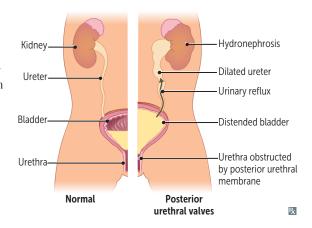
Ureteric bud fails to induce differentiation of metanephric mesenchyme → nonfunctional kidney consisting of cysts and connective tissue. Predominantly nonhereditary and usually unilateral; bilateral leads to Potter sequence.

# **Duplex collecting** system

Bifurcation of ureteric bud before it enters the metanephric blastema creates a Y-shaped bifid ureter. Duplex collecting system can alternatively occur through two ureteric buds reaching and interacting with metanephric blastema. Strongly associated with vesicoureteral reflux and/or ureteral obstruction, † risk for UTIs.

# Posterior urethral valves

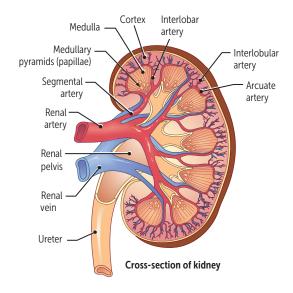
Membrane remnant in the posterior urethra in males; its persistence can lead to urethral obstruction. Can be diagnosed prenatally by bilateral hydronephrosis and dilated or thickwalled bladder on ultrasound. Most common cause of bladder outlet obstruction in male infants. Associated with oligohydramnios in cases of severe obstruction.

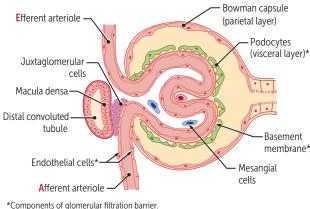


FAS1\_2019\_14-Renal.indd 579 11/7/19 5:42 PM

### ▶ RENAL—ANATOMY

#### Kidney anatomy and glomerular structure





\*Components of glomerular filtration barrier

Cross-section of glomerulus

Left kidney is taken during living donor transplantation because it has a longer renal vein.

Afferent = Arriving.

 $\mathbf{E}$ fferent =  $\mathbf{E}$ xiting.

Renal blood flow: renal artery → segmental artery → interlobar artery → arcuate artery

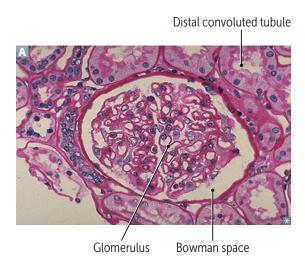
→ interlobular artery → afferent arteriole

→ glomerulus A → efferent arteriole → vasa recta/peritubular capillaries → venous outflow.

Left renal vein receives two additional veins: left suprarenal and left gonadal veins.

Despite high overall renal blood flow, renal medulla receives significantly less blood flow than renal cortex → very sensitive to hypoxia

→ vulnerable to ischemic damage.



FAS1\_2019\_14-Renal.indd 580 11/7/19 5:42 PM

Ŗ

#### **Course of ureters**



Course of ureter A: arises from renal pelvis, travels under gonadal arteries → over common iliac artery → under uterine artery/vas deferens (retroperitoneal).

Gynecologic procedures (eg, ligation of uterine or ovarian vessels) may damage ureter → ureteral obstruction or leak.

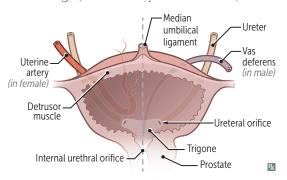
Bladder contraction compresses the intravesical ureter, preventing urine reflux.

Blood supply to ureter:

- Proximal—renal arteries
- Middle—gonadal artery, aorta, common and internal iliac arteries
- Distal—internal iliac and superior vesical arteries

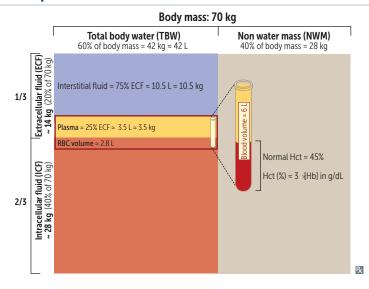
3 common points of ureteral obstruction: ureteropelvic junction, pelvic inlet, ureterovesical junction.

Water (ureters) flows **over** the iliacs and **under** the bridge (uterine artery or vas deferens).



### ▶ RENAL—PHYSIOLOGY

#### Fluid compartments



#### HIKIN': HIgh K+ INtracellularly.

60–40–20 rule (% of body weight for average person):

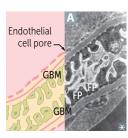
- 60% total body water
- 40% ICF, mainly composed of K<sup>+</sup>, Mg<sup>2+</sup>, organic phosphates (eg, ATP)
- 20% ECF, mainly composed of Na<sup>+</sup>, Cl<sup>-</sup>, HCO<sub>3</sub><sup>-</sup>, albumin

Plasma volume can be measured by radiolabeling albumin.

Extracellular volume can be measured by inulin or mannitol.

Serum osmolality = 285-295 mOsm/kg H<sub>2</sub>O. Plasma volume = TBV × (1 – Hct).

# Glomerular filtration barrier



Responsible for filtration of plasma according to size and charge selectivity.

Composed of:

- Fenestrated capillary endothelium
- Basement membrane with type IV collagen chains and heparan sulfate
- Visceral epithelial layer consisting of podocyte foot processes (FPs)

Charge barrier—all 3 layers contain ⊖ charged glycoproteins that prevent entry of ⊖ charged molecules (eg, albumin).

Size barrier—fenestrated capillary endothelium (prevents entry of > 100 nm molecules/blood cells); podocyte foot processes interpose with glomerular basement membrane (GBM); slit diaphragm (prevents entry of molecules > 50–60 nm).

FAS1\_2019\_14-Renal.indd 581 11/7/19 5:42 PM

#### **Renal clearance**

 $C_x = (U_x V)/P_x = \text{volume of plasma from which}$  the substance is completely cleared in the urine per unit time.

If C<sub>x</sub> < GFR: net tubular reabsorption and/or not freely filtered.

If  $C_x > GFR$ : net tubular secretion of X.

If  $C_x = GFR$ : no net secretion or reabsorption.

 $C_{y}$  = clearance of X (mL/min).

 $U_x$  = urine concentration of X (eg, mg/mL).

P = plasma concentration of X (eg, mg/mL).

 $\hat{V}$  = urine flow rate (mL/min).

# Glomerular filtration rate

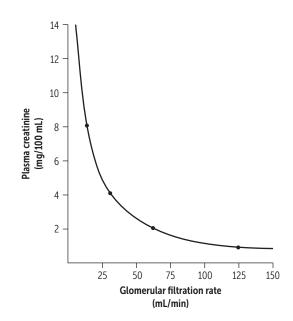
Inulin clearance can be used to calculate GFR because it is freely filtered and is neither reabsorbed nor secreted.

$$\begin{split} \boldsymbol{C}_{\mathrm{inulin}} &= \boldsymbol{GFR} = \boldsymbol{U}_{\mathrm{inulin}} \times \boldsymbol{V/P}_{\mathrm{inulin}} \\ &= \boldsymbol{K}_{f} \left[ (\boldsymbol{P}_{\mathrm{GC}} - \boldsymbol{P}_{\mathrm{BS}}) - (\boldsymbol{\pi}_{\mathrm{GC}} - \boldsymbol{\pi}_{\mathrm{BS}}) \right] \end{split}$$

(GC = glomerular capillary; BS = Bowman space;  $\pi_{\rm BS}$  normally equals zero;  $K_{\rm f}$  = filtration coefficient).

Normal GFR ≈ 100 mL/min.

Creatinine clearance is an approximate measure of GFR. Slightly overestimates GFR because creatinine is moderately secreted by renal tubules.



# **Effective renal plasma** flow

Effective renal plasma flow (eRPF) can be estimated using *para*-aminohippuric acid (PAH) clearance. Between filtration and secretion, there is nearly 100% excretion of all PAH that enters the kidney.

$$eRPF = U_{PAH} \times V/P_{PAH} = C_{PAH}.$$

Renal blood flow (RBF) = RPF/(1 - Hct). Usually 20–25% of cardiac output.

eRPF underestimates true renal plasma flow (RPF) slightly.

FAS1\_2019\_14-Renal.indd 582 11/7/19 5:42 PM

#### **Filtration**

Filtration fraction (FF) = GFR/RPF. Normal FF = 20%.

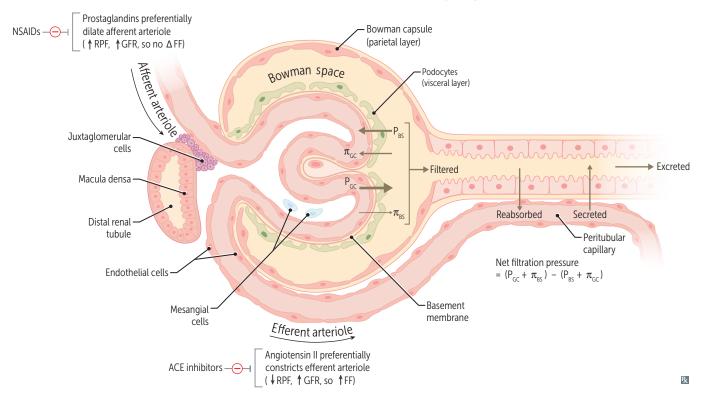
Filtered load (mg/min) = GFR (mL/min) × plasma concentration (mg/mL).

GFR can be estimated with creatinine clearance.

RPF is best estimated with PAH clearance.

Prostaglandins Dilate Afferent arteriole (PDA).

Angiotensin II Constricts Efferent arteriole (ACE).



#### **Changes in glomerular dynamics**

	GFR	RPF	FF (GFR/RPF)
Afferent arteriole constriction	<b>1</b>	<b>↓</b>	_
Efferent arteriole constriction	<b>†</b>	<b>↓</b>	<b>†</b>
† plasma protein concentration	<b>↓</b>	_	<b>↓</b>
↓ plasma protein concentration	<b>†</b>	_	<b>†</b>
Constriction of ureter	<b>↓</b>	_	<b>†</b>
Dehydration	<b>↓</b>	↓↓	<b>†</b>

FAS1\_2019\_14-Renal.indd 583 11/7/19 5:42 PM

# Calculation of reabsorption and secretion rate

Filtered load =  $GFR \times P_x$ . Excretion rate =  $V \times U_y$ .

Reabsorption rate = filtered - excreted. Secretion rate = excreted - filtered.  $Fe_{Na}$  = fractional excretion of sodium.

$$Fe_{Na} = \frac{Na^+ \ excreted}{Na^+ \ filtered} = \frac{V \times U_{Na}}{GFR \times P_{Na}} = \frac{P_{Cr} \times U_{Na}}{U_{Cr} \times P_{Na}} \ \ where \ GFR = \frac{U_{Cr} \times V}{P_{Cr}}$$

#### **Glucose clearance**

Glucose at a normal plasma level (range 60–120 mg/dL) is completely reabsorbed in proximal convoluted tubule (PCT) by Na+/glucose cotransport.

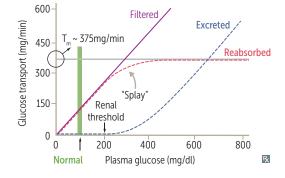
In adults, at plasma glucose of  $\sim 200$  mg/dL, glucosuria begins (threshold). At rate of  $\sim 375$  mg/min, all transporters are fully saturated ( $T_{\rm m}$ ).

Normal pregnancy is associated with ↑ GFR. With ↑ filtration of all substances, including glucose, the glucose threshold occurs at lower plasma glucose concentrations → glucosuria at normal plasma glucose levels.

Sodium-glucose cotransporter 2 (SGLT2) inhibitors (eg, -flozin drugs) result in glucosuria at plasma concentrations < 200 mg/dL.

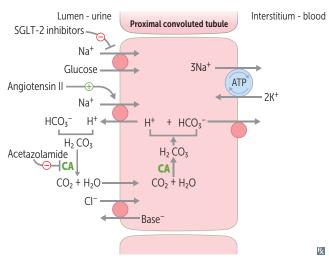
Glucosuria is an important clinical clue to diabetes mellitus.

Splay phenomenon— $T_m$  for glucose is reached gradually rather than sharply due to the heterogeneity of nephrons (ie, different  $T_m$  points); represented by the portion of the titration curve between threshold and  $T_m$ .



FAS1\_2019\_14-Renal.indd 584 11/7/19 5:42 PM

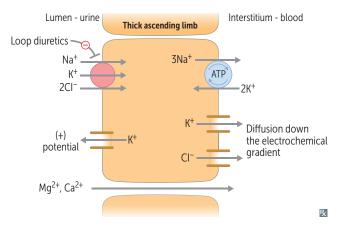
#### **Nephron transport physiology**



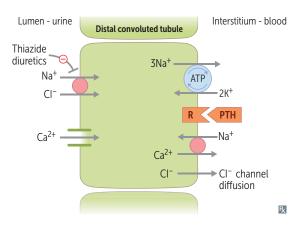
Early PCT—contains brush border. Reabsorbs all glucose and amino acids and most HCO<sub>3</sub><sup>-</sup>, Na<sup>+</sup>, Cl<sup>-</sup>, PO<sub>4</sub><sup>3-</sup>, K<sup>+</sup>, H<sub>2</sub>O, and uric acid. Isotonic absorption. Generates and secretes NH<sub>3</sub>, which enables the kidney to secrete more H<sup>+</sup>.

PTH—inhibits Na+/PO<sub>4</sub><sup>3-</sup> cotransport  $\rightarrow$  † PO<sub>4</sub><sup>3-</sup> excretion. AT II—stimulates Na+/H+ exchange  $\rightarrow$  † Na+, H<sub>2</sub>O, and HCO<sub>3</sub><sup>-</sup> reabsorption (permitting contraction alkalosis). 65–80% Na+ and H<sub>2</sub>O reabsorbed.

Thin descending loop of Henle—passively reabsorbs H<sub>2</sub>O via medullary hypertonicity (impermeable to Na<sup>+</sup>). Concentrating segment. Makes urine hypertonic.

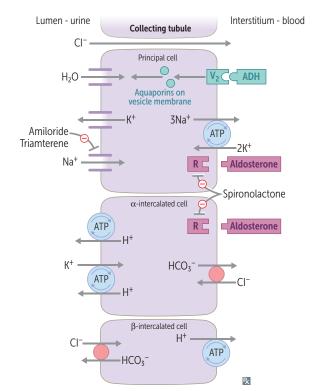


Thick ascending loop of Henle—reabsorbs Na<sup>+</sup>, K<sup>+</sup>, and Cl<sup>−</sup>. Indirectly induces paracellular reabsorption of Mg<sup>2+</sup> and Ca<sup>2+</sup> through ⊕ lumen potential generated by K<sup>+</sup> backleak. Impermeable to H<sub>2</sub>O. Makes urine less concentrated as it ascends. 10–20% Na<sup>+</sup> reabsorbed.



Early DCT—reabsorbs Na<sup>+</sup>, Cl<sup>-</sup>. Impermeable to H<sub>2</sub>O. Makes urine fully dilute (hypotonic).

PTH—† Ca<sup>2+</sup>/Na<sup>+</sup> exchange → † Ca<sup>2+</sup> reabsorption.
5–10% Na<sup>+</sup> reabsorbed.



Collecting tubule—reabsorbs Na<sup>+</sup> in exchange for secreting K<sup>+</sup> and H<sup>+</sup> (regulated by aldosterone).

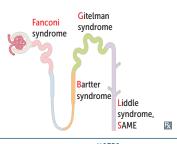
Aldosterone—acts on mineralocorticoid receptor → mRNA → protein synthesis. In principal cells: ↑ apical K<sup>+</sup> conductance, ↑ Na<sup>+</sup>/K<sup>+</sup> pump, ↑ epithelial Na<sup>+</sup> channel (ENaC) activity → lumen negativity → K<sup>+</sup> secretion. In

(ENaC) activity → lumen negativity → K<sup>+</sup> secretion. In α-intercalated cells: lumen negativity → ↑ H<sup>+</sup> ATPase activity → ↑ H<sup>+</sup> secretion → ↑ HCO<sub>3</sub><sup>-</sup>/Cl<sup>-</sup> exchanger activity.

ADH—acts at V<sub>2</sub> receptor → insertion of aquaporin H<sub>2</sub>O channels on apical side. 3–5% Na<sup>+</sup> reabsorbed.

FAS1\_2019\_14-Renal.indd 585 11/7/19 5:42 PM

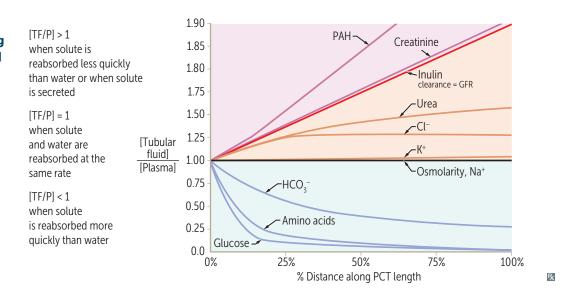
Renal tubular defects Order: Fanconi's BaGeLS



				SAME
	DEFECTS	EFFECTS	CAUSES	NOTES
Fanconi syndrome	Generalized reabsorption defect in PCT → † excretion of amino acids, glucose, HCO <sub>3</sub> -, and PO <sub>4</sub> <sup>3-</sup> , and all substances reabsorbed by the PCT	May lead to metabolic acidosis (proximal RTA), hypophosphatemia, osteopenia	Hereditary defects (eg, Wilson disease, tyrosinemia, glycogen storage disease), ischemia, multiple myeloma, nephrotoxins/drugs (eg, ifosfamide, cisplatin), lead poisoning	
Bartter syndrome	Reabsorption defect in thick ascending loop of Henle (affects Na+/K+/2Cl- cotransporter)	Metabolic alkalosis, hypokalemia, hypercalciuria	Autosomal recessive	Presents similarly to chronic loop diuretic use
Gitelman syndrome	Reabsorption defect of NaCl in DCT	Metabolic alkalosis, hypomagnesemia, hypokalemia, hypocalciuria	Autosomal recessive	Presents similarly to lifelong thiazide diuretic use Less severe than Bartter syndrome
Liddle syndrome	Gain of function mutation → ↓ Na <sup>+</sup> channel degradation → ↑ Na <sup>+</sup> reabsorption in collecting tubules	Metabolic alkalosis, hypokalemia, hypertension, ↓ aldosterone	Autosomal dominant	Presents similarly to hyperaldosteronism, but aldosterone is nearly undetectable Treatment: amiloride
Syndrome of Apparent Mineralocorticoid Excess	Cortisol activates mineralocorticoid receptors. 11β-HSD converts cortisol to cortisone (inactive on these receptors) Hereditary 11β-HSD deficiency → ↑ cortisol → ↑ mineralocorticoid receptor activity	Metabolic alkalosis, hypokalemia, hypertension ↓ serum aldosterone level; cortisol tries to be the SAME as aldosterone	Autosomal recessive Can acquire disorder from glycyrrhetinic acid (present in licorice), which blocks activity of 11β-hydroxysteroid dehydrogenase	Treatment: K+-sparing diuretics (↓ mineralocorticoid effects) or corticosteroids (exogenous corticosteroid ↓ endogenous cortisol production → ↓ mineralocorticoid receptor activation)

FAS1\_2019\_14-Renal.indd 586 11/7/19 5:42 PM

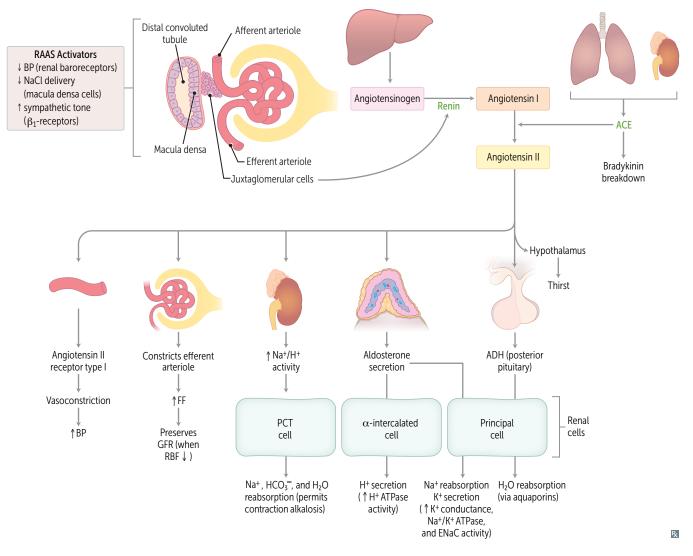
### Relative concentrations along proximal convoluted tubules



Tubular inulin † in concentration (but not amount) along the PCT as a result of water reabsorption. Cl<sup>-</sup> reabsorption occurs at a slower rate than Na<sup>+</sup> in early PCT and then matches the rate of Na<sup>+</sup> reabsorption more distally. Thus, its relative concentration † before it plateaus.

FAS1\_2019\_14-Renal.indd 587 11/7/19 5:42 PM

### Renin-angiotensin-aldosterone system



Renin	Secreted by JG cells in response to $\downarrow$ renal perfusion pressure (detected by renal baroreceptors in afferent arteriole), $\uparrow$ renal sympathetic discharge ( $\beta_1$ effect), and $\downarrow$ NaCl delivery to macula densa cells.
AT II	Helps maintain blood volume and blood pressure. Affects baroreceptor function; limits reflex bradycardia, which would normally accompany its pressor effects.
ANP, BNP	Released from atria (ANP) and ventricles (BNP) in response to $\uparrow$ volume; inhibits renin-angiotensin-aldosterone system; relaxes vascular smooth muscle via cGMP $\rightarrow \uparrow$ GFR, $\downarrow$ renin. Dilates afferent arteriole, promotes natriuresis.
ADH	Primarily regulates serum osmolality; also responds to low blood volume states. Stimulates reabsorption of water in collecting ducts. Also stimulates reabsorption of urea in collecting ducts to maximizes corticopapillary osmotic gradient.
Aldosterone	Primarily regulates ECF volume and Na <sup>+</sup> content; ↑ release in ↓ blood volume states. Responds to hyperkalemia by ↑ K <sup>+</sup> excretion.

FAS1\_2019\_14-Renal.indd 588 11/7/19 5:42 PM

### Juxtaglomerular apparatus

Consists of mesangial cells, JG cells (modified smooth muscle of afferent arteriole), and the macula densa (NaCl sensor, located at distal end of loop of Henle). JG cells secrete renin in response to ↓ renal blood pressure and † sympathetic tone ( $\beta_1$ ). Macula densa cells sense ↓ NaCl delivery to DCT → ↑ renin release → efferent arteriole vasoconstriction → † GFR.

JGA maintains GFR via renin-angiotensinaldosterone system.

In addition to vasodilatory properties,  $\beta$ -blockers can decrease BP by inhibiting  $\beta_1$ -receptors of the JGA  $\rightarrow$   $\downarrow$  renin release.

SECTION III

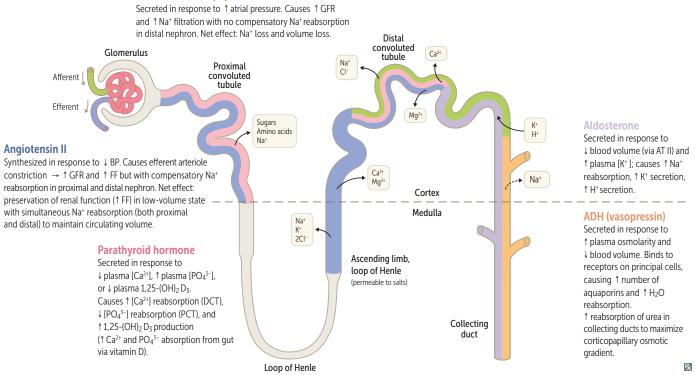
### **Kidney endocrine functions**

Erythropoietin	Released by interstitial cells in peritubular capillary bed in response to hypoxia.	Stimulates RBC proliferation in bone marrow Administered for anemia secondary to chroni kidney disease. † risk of HTN.		
Calciferol (vitamin D)	PCT cells convert 25-OH vitamin $D_3$ to 1,25- $(OH)_2$ vitamin $D_3$ (calcitriol, active form).	25-OH D <sub>3</sub> $\longrightarrow$ 1,25-(OH) <sub>2</sub> D <sub>3</sub> (calcidiol) $1\alpha$ -hydroxylase (calcitriol)		
Prostaglandins  Paracrine secretion vasodilates the afferent arterioles to † RBF.		NSAIDs block renal-protective prostaglandin synthesis → constriction of afferent arteriole and ↓ GFR; this may result in acute kidney injury in low renal blood flow states.		
Dopamine	Secreted by PCT cells, promotes natriuresis. At low doses; dilates interlobular arteries, afferent arterioles, efferent arterioles → ↑ RBF, little or no change in GFR. At higher doses; acts as vasoconstrictor.			

FAS1\_2019\_14-Renal.indd 589 11/7/19 5:42 PM

### Hormones acting on kidney

### Atrial natriuretic peptide



#### **Potassium shifts**

SHIFTS K+ INTO CELL (CAUSING HYPOKALEMIA)	SHIFTS K+ OUT OF CELL (CAUSING HYPERKALEMIA)		
	Digitalis (blocks Na+/K+ ATPase)		
Hypo-osmolarity	HyperOsmolarity		
	<b>L</b> ysis of cells (eg, crush injury, rhabdomyolysis, tumor lysis syndrome)		
Alkalosis	<b>A</b> cidosis		
β-adrenergic agonist († Na+/K+ ATPase)	β-blocker		
Insulin († Na+/K+ ATPase)	High blood <mark>S</mark> ugar (insulin deficiency)		
Insulin shifts K <sup>+</sup> into cells	Succinylcholine († risk in burns/muscle trauma)		
	Hyperkalemia? DO LAβSS		

FAS1\_2019\_14-Renal.indd 590 11/7/19 5:42 PM

### **Electrolyte disturbances**

ELECTROLYTE	LOW SERUM CONCENTRATION	HIGH SERUM CONCENTRATION	
Sodium	Nausea, malaise, stupor, coma, seizures	Irritability, stupor, coma	
Potassium	U waves and flattened T waves on ECG, arrhythmias, muscle cramps, spasm, weakness	Wide QRS and peaked T waves on ECG, arrhythmias, muscle weakness  Stones (renal), bones (pain), groans (abdominal pain), thrones († urinary frequency), psychiatric overtones (anxiety, altered mental status)	
Calcium	Tetany, seizures, QT prolongation, twitching (eg, Chvostek sign), spasm (eg, Trousseau sign)		
Magnesium	Tetany, torsades de pointes, hypokalemia, hypocalcemia (when $[Mg^{2+}] < 1.0 \text{ mEq/L}$ )	↓ DTRs, lethargy, bradycardia, hypotension, cardiac arrest, hypocalcemia	
Phosphate	Bone loss, osteomalacia (adults), rickets (children)	Renal stones, metastatic calcifications, hypocalcemia	

### **Features of renal disorders**

CONDITION	BLOOD PRESSURE	PLASMA RENIN	ALDOSTERONE	SERUM Mg <sup>2+</sup>	URINE Ca <sup>2+</sup>
SIADH	—/ <b>†</b>	<b>+</b>	<b>↓</b>		
Primary hyperaldosteronism	1	1	t		
Renin-secreting tumor	<b>†</b>	†	†		
Bartter syndrome		†	<b>†</b>		†
Gitelman syndrome		†	<b>†</b>	Ţ	ţ
Liddle syndrome, syndrome of apparent mineralocorticoid excess	1	<b>↓</b>	<b>↓</b>		

 $<sup>\</sup>uparrow \downarrow$  = important differentiating feature.

FAS1\_2019\_14-Renal.indd 591 11/7/19 5:42 PM

#### **Acid-base physiology**

	рН	Pco <sub>2</sub>	[HCO <sub>3</sub> <sup>-</sup> ]	COMPENSATORY RESPONSE
Metabolic acidosis	1	<b>↓</b>	<b>↓</b>	Hyperventilation (immediate)
Metabolic alkalosis	†	†	†	Hypoventilation (immediate)
Respiratory acidosis	1	<b>†</b>	†	↑ renal [HCO <sub>3</sub> -] reabsorption (delayed)
Respiratory alkalosis	<b>†</b>	<b>↓</b>	<b>†</b>	↓ renal [HCO₃⁻] reabsorption (delayed)

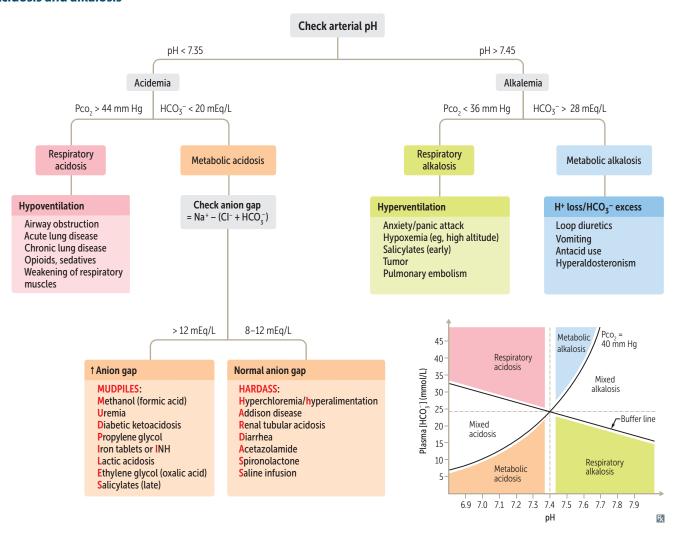
Key:  $\downarrow \uparrow$  = compensatory response.

Henderson-Hasselbalch equation: pH = 6.1 + 
$$\log \frac{[HCO_3^-]}{0.03 \text{ Pco}_2}$$

Predicted respiratory compensation for a simple metabolic acidosis can be calculated using the Winters formula. If measured Pco₂ > predicted Pco₂ → concomitant respiratory acidosis; if measured Pco₂ < predicted Pco₂ → concomitant respiratory alkalosis:

$$Pco_{2} = 1.5 [HCO_{3}^{-}] + 8 \pm 2$$

#### **Acidosis and alkalosis**



FAS1\_2019\_14-Renal.indd 592 11/7/19 5:42 PM

## **Renal tubular** acidosis

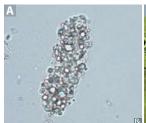
Disorder of the renal tubules that causes normal anion gap (hyperchloremic) metabolic acidosis.

RTA TYPE	DEFECT	URINE PH	SERUM K <sup>+</sup>	M K <sup>+</sup> Causes Associations	
Distal renal tubular acidosis (type 1)	Inability of α-intercalated cells to secrete H <sup>+</sup> → no new HCO <sub>3</sub> <sup>-</sup> is generated → metabolic acidosis	> 5.5	ţ	Amphotericin B toxicity, analgesic nephropathy, congenital anomalies (obstruction) of urinary tract, autoimmune diseases (eg, SLE)	† risk for calcium phosphate kidney stones (due to † urine pH and † bone turnover related to buffering)
Proximal renal tubular acidosis (type 2)	Defect in PCT  HCO <sub>3</sub> <sup>-</sup> reabsorption  → ↑ excretion of  HCO <sub>3</sub> <sup>-</sup> in urine  → metabolic acidosis  Urine can be acidified by  α-intercalated cells in  collecting duct, but not enough to overcome  ↑ HCO <sub>3</sub> <sup>-</sup> excretion	> 5.5 when resorptive threshold for serum HCO <sub>3</sub> <sup>-</sup> exceeded; < 5.5 when HCO <sub>3</sub> <sup>-</sup> depleted below resorptive threshold	1	Fanconi syndrome, multiple myeloma, carbonic anhydrase inhibitors	† risk for hypophosphatemic rickets (in Fanconi syndrome)
Hyperkalemic tubular acidosis (type 4)	Hypoaldosteronism or aldosterone resistance; hyperkalemia → ↓ NH <sub>3</sub> synthesis in PCT → ↓ NH <sub>4</sub> <sup>+</sup> excretion	< 5.5 (or variable)	†	↓ aldosterone production (eg, diabetic hyporeninism, ACE inhibitors, ARBs, NSAIDs, heparin, cyclosporine, adrenal insufficiency) or aldosterone resistance (eg, K⁺-sparing diuretics, nephropathy due to obstruction, TMP-SMX)	

11/7/19 5:42 PM FAS1\_2019\_14-Renal.indd 593

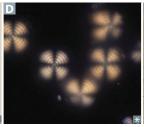
# ▶ RENAL—PATHOLOGY

Casts in urine	Presence of casts indicates that hematuria/pyuria is of glomerular or renal tubular origin.  Bladder cancer, kidney stones → hematuria, no casts.  Acute cystitis → pyuria, no casts.
RBC casts A	Glomerulonephritis, hypertensive emergency.
WBC casts B	Tubulointerstitial inflammation, acute pyelonephritis, transplant rejection.
Granular casts C	Acute tubular necrosis (ATN). Can be "muddy brown" in appearance.
Fatty casts ("oval fat bodies")	Nephrotic syndrome. Associated with "Maltese cross" sign <b>□</b> .
Waxy casts	End-stage renal disease/chronic kidney disease.
Hyaline casts <b>E</b>	Nonspecific, can be a normal finding. Form via solidification of Tamm–Horsfall mucoprotein (secreted by renal tubular cells).









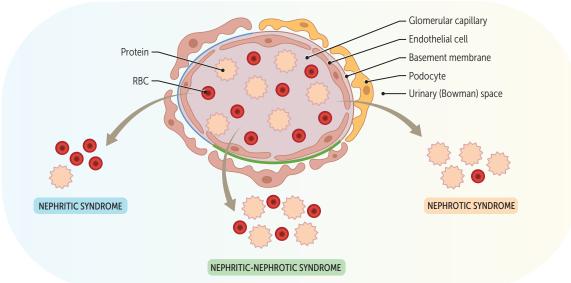


## Nomenclature of glomerular disorders

ТҮРЕ	CHARACTERISTICS	EXAMPLE
Focal	< 50% of glomeruli are involved	Focal segmental glomerulosclerosis
Diffuse	> 50% of glomeruli are involved	Diffuse proliferative glomerulonephritis
Proliferative	Hypercellular glomeruli	Membranoproliferative glomerulonephritis
Membranous	Thickening of glomerular basement membrane (GBM)	Membranous nephropathy
Primary glomerular disease	l° disease of the kidney specifically impacting the glomeruli	Minimal change disease
Secondary glomerular disease	Systemic disease or disease of another organ system that also impacts the glomeruli	SLE, diabetic nephropathy

FAS1\_2019\_14-Renal.indd 594 11/7/19 5:42 PM

### **Glomerular diseases**



			R
TYPE	ETIOLOGY	CLINICAL PRESENTATION	EXAMPLES
Nephritic syndrome	Glomerular inflammation  → GBM damage → loss of RBCs into urine → hematuria	Hematuria, RBC casts in urine  ↓ GFR → oliguria, azotemia,  † renin release, HTN  Proteinuria often in the subnephrotic range (< 3.5 g/ day) but in severe cases may be in nephrotic range	<ul> <li>Acute poststreptococcal glomerulonephritis</li> <li>Rapidly progressive glomerulonephritis</li> <li>IgA nephropathy (Berger disease)</li> <li>Alport syndrome</li> <li>Membranoproliferative glomerulonephritis</li> </ul>
Nephrotic syndrome	Podocyte damage → impaired charge barrier → proteinuria	Massive proteinuria (> 3.5 g/ day) with hypoalbuminemia, edema Frothy urine with fatty casts Associated with hypercoagulable state due to antithrombin III loss in urine and † risk of infection (loss of IgGs in urine and soft tissue compromise by edema)	May be 1° (eg, direct podocyte damage) or 2° (podocyte damage from systemic process):  • Focal segmental glomerulosclerosis (1° or 2°)  • Minimal change disease (1° or 2°)  • Membranous nephropathy (1° or 2°)  • Amyloidosis (2°)  • Diabetic glomerulonephropathy (2°)
Nephritic-nephrotic syndrome	Severe GBM damage → loss of RBCs into urine + impaired charge barrier → hematuria + proteinuria	Nephrotic-range proteinuria (> 3.5 g/day) and concomitant features of nephrotic syndrome	Can occur with any form of nephritic syndrome, but is most common with:  Diffuse proliferative glomerulonephritis  Membranoproliferative glomerulonephritis

FAS1\_2019\_14-Renal.indd 595 11/7/19 5:42 PM

#### **Nephritic syndrome** NephrItic syndrome = Inflammatory process. Most frequently seen in children. ~ 2–4 weeks after group A streptococcal infection of pharynx or **Acute** poststreptococcal skin. Resolves spontaneously in most children; may progress to renal insufficiency in adults. Type glomerulonephritis III hypersensitivity reaction. Presents with peripheral and periorbital edema, tea or cola-colored urine, HTN. ⊕ strep titers/serologies, ↓ complement levels (C3) due to consumption. LM—glomeruli enlarged and hypercellular A • IF—("starry sky") granular appearance ("lumpy-bumpy") B due to IgG, IgM, and C3 deposition along GBM and mesangium EM—subepithelial IC humps Poor prognosis, rapidly deteriorating renal function (days to weeks). Rapidly progressive (crescentic) LM—crescent moon shape C. Crescents consist of fibrin and plasma proteins (eg, C3b) with glomerulonephritis glomerular parietal cells, monocytes, macrophages Several disease processes may result in this pattern which may be delineated via IF pattern. Linear IF due to antibodies to GBM and alveolar basement membrane: Goodpasture syndrome—hematuria/hemoptysis; type II hypersensitivity reaction. Treatment: plasmapheresis Negative IF/Pauci-immune (no Ig/C3 deposition): granulomatosis with polyangiitis (Wegener)—PR3-ANCA/c-ANCA, eosinophilic granulomatosis with polyangiitis (Churg-Strauss) or Microscopic polyangiitis—MPO-ANCA/p-ANCA Granular IF—PSGN or DPGN Diffuse proliferative Often due to SLE (think "wire lupus"). DPGN and MPGN often present as nephrotic syndrome glomerulonephritis and nephritic syndrome concurrently. ■ LM—"wire looping" of capillaries **D** IF—granular; EM—subendothelial, sometimes subepithelial or intramembranous IgG-based ICs often with C3 deposition IgA nephropathy Episodic hematuria that usually occurs concurrently with respiratory or GI tract infections (IgA is (Berger disease) secreted by mucosal linings). Renal pathology of IgA vasculitis (HSP). LM—mesangial proliferation IF—IgA-based IC deposits in mesangium; EM—mesangial IC deposition Alport syndrome Mutation in type IV collagen → thinning and splitting of glomerular basement membrane. Most commonly X-linked dominant. Eye problems (eg, retinopathy, anterior lenticonus), glomerulonephritis, sensorineural deafness; "can't see, can't pee, can't hear a bee." EM—"basket-weave" appearance due to irregular thickening of GBM Membrano-MPGN is a nephritic syndrome that often co-presents with nephrotic syndrome. proliferative Type I may be 2° to hepatitis B or C infection. May also be idiopathic. Subendothelial IC deposits with granular IF glomerulonephritis Type II is associated with C3 nephritic factor (IgG autoantibody that stabilizes C3 convertase → persistent complement activation → ↓ C3 levels).

Intramembranous deposits, also called dense deposit disease

Both types: mesangial ingrowth → GBM splitting → "tram-track" on H&E and PAS **E** stains.

FAS1 2019 14-Renal.indd 596 11/7/19 5:42 PM

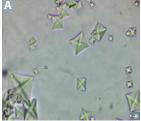
Nephrotic syndrome	NephrOtic syndrome—massive prOteinuria (> 3.5 g/day)			
Minimal change disease	Also known as lipoid nephrosis. Most common cause of nephrotic syndrome in children.  Often 1° (Idiopathic) and may be triggered by recent Infection, Immunization, Immune stimulus (4 I's of MCD). Rarely, may be 2° to lymphoma (eg, cytokine-mediated damage).  1° disease has excellent response to corticosteroids.  ■ LM—Normal glomeruli (lipid may be seen in PCT cells)  ■ IF—⊝  ■ EM—effacement of podocyte foot processes ■			
Focal segmental glomerulosclerosis	Most common cause of nephrotic syndrome in African-Americans and Hispanics.  Can be 1° (idiopathic) or 2° to other conditions (eg, HIV infection, sickle cell disease, heroin abuse, massive obesity, interferon treatment, or congenital malformations).  1° disease has inconsistent response to steroids. May progress to CKD.  ■ LM—segmental sclerosis and hyalinosis ■  ■ IF—often ⊖ but may be ⊕ for nonspecific focal deposits of IgM, C3, C1  ■ EM—effacement of foot processes similar to minimal change disease			
Membranous nephropathy	Also known as membranous glomerulonephritis.  Can be 1° (eg, antibodies to phospholipase A <sub>2</sub> receptor) or 2° to drugs (eg, NSAIDs, penicillamine, gold), infections (eg, HBV, HCV, syphilis), SLE, or solid tumors.  1° disease has poor response to steroids. May progress to CKD.  • LM—diffuse capillary and GBM thickening  • IF—granular due to immune complex (IC) deposition  • EM—"Spike and dome" appearance of subepithelial deposits			
Amyloidosis	Kidney is the most commonly involved organ (systemic amyloidosis). Associated with chronic conditions that predispose to amyloid deposition (eg, AL amyloid, AA amyloid).  • LM—Congo red stain shows apple-green birefringence under polarized light due to amyloid deposition in the mesangium			
Diabetic glomerulo- nephropathy	Most common cause of ESRD in the United States.  Hyperglycemia → nonenzymatic glycation of tissue proteins → mesangial expansion; GBM thickening and ↑ permeability. Hyperfiltration (glomerular HTN and ↑ GFR) → glomerular hypertrophy and glomerular scarring (glomerulosclerosis) → further progression of nephropathy.  ■ LM—Mesangial expansion, GBM thickening, eosinophilic nodular glomerulosclerosis (Kimmelstiel-Wilson lesions □)			
	A D D			

FAS1\_2019\_14-Renal.indd 597 11/7/19 5:42 PM

# Kidney stones

Can lead to severe complications such as hydronephrosis, pyelonephritis, and acute kidney injury. Obstructed stone presents with unilateral flank tenderness, colicky pain radiating to groin, hematuria. Treat and prevent by encouraging fluid intake.

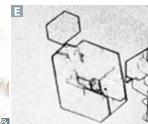
CONTENT	PRECIPITATES WITH	X-RAY FINDINGS	CT FINDINGS	URINE CRYSTAL	NOTES
Calcium	Calcium oxalate: hypocitraturia	Radiopaque	Radiopaque	Shaped like envelope A or dumbbell	Calcium stones most common (80%); calcium oxalate more common than calcium phosphate stones.  Can result from ethylene glycol (antifreeze) ingestion, vitamin C abuse, hypocitraturia (associated with ↓ urine pH), malabsorption (eg, Crohn disease).  Treatment: thiazides, citrate, low-sodium diet.
	Calcium phosphate: † pH	Radiopaque	Radiopaque	Wedge- shaped prism	Treatment: low-sodium diet, thiazides.
Ammonium magnesium phosphate (struvite)	↑ pH	Radiopaque	Radiopaque	Coffin lid <b>B</b>	Account for 15% of stones. Caused by infection with urease ⊕ bugs (eg, Proteus mirabilis, Staphylococcus saprophyticus, Klebsiella) that hydrolyze urea to ammonia → urine alkalinization. Commonly form staghorn calculi .  Treatment: eradication of underlying infection, surgical removal of stone.
Uric acid	↓ pH	Radiol <b>U</b> cent	Minimally visible	Rhomboid or rosettes	About 5% of all stones. Risk factors: \(\psi\) urine volume, arid climates, acidic pH.  Strong association with hyperuricemia (eg, gout). Often seen in diseases with \(\dagger\) cell turnover (eg, leukemia).  Treatment: alkalinization of urine, allopurinol.
Cystine	↓ pH	Faintly radiopaque	Moderately radiopaque	Hexagonal <b>E</b>	Hereditary (autosomal recessive) condition in which Cystine-reabsorbing PCT transporter loses function, causing cystinuria. Transporter defect also results in poor reabsorption of Ornithine, Lysine, Arginine (COLA). Cystine is poorly soluble, thus stones form in urine. Usually begins in childhood. Can form staghorn calculi. Sodium cyanide nitroprusside test ⊕.  "SIXtine" stones have SIX sides.  Treatment: low sodium diet, alkalinization of urine, chelating agents (eg, penicillamine) if refractory.











FAS1\_2019\_14-Renal.indd 598 11/7/19 5:42 PM

### **Hydronephrosis**



Distention/dilation of renal pelvis and calyces A. Usually caused by urinary tract obstruction (eg, renal stones, severe BPH, congenital obstructions, cervical cancer, injury to ureter); other causes include retroperitoneal fibrosis, vesicoureteral reflux. Dilation occurs proximal to site of pathology. Serum creatinine becomes elevated if obstruction is bilateral or if patient has an obstructed solitary kidney. Leads to compression and possible atrophy of renal cortex and medulla.

	Stress incontinence	Urgency incontinence	Overflow incontinence
MECHANISM	Outlet incompetence (urethral hypermobility or intrinsic sphincter deficiency) → leak with ↑ intra-abdominal pressure (eg, sneezing, lifting) ⊕ bladder stress test (directly observed leakage from urethra upon coughing or Valsalva maneuver)	Detrusor overactivity → leak with urge to void immediately	Incomplete emptying (detrusor underactivity or outlet obstruction) → leak with overfilling, ↑ postvoid residual on catheterization or ultrasound
ASSOCIATIONS	Obesity, vaginal delivery, prostate surgery	UTI	Polyuria (eg, diabetes), bladder outlet obstruction (eg, BPH), neurogenic bladder (eg, MS)
TREATMENT	Pelvic floor muscle strengthening (Kegel) exercises, weight loss, pessaries	Kegel exercises, bladder training (timed voiding, distraction or relaxation techniques), antimuscarinics (eg, oxybutynin for overactive bladder), mirabegron	Catheterization, relieve obstruction (eg, $\alpha$ -blockers for BPH)

FAS1\_2019\_14-Renal.indd 599 11/7/19 5:42 PM 600 SECTION III

### **RENAL** ▶ RENAL—PATHOLOGY

#### **Acute cystitis**

Inflammation of urinary bladder. Presents as suprapubic pain, dysuria, urinary frequency, urgency. Systemic signs (eg, high fever, chills) are usually absent.

Risk factors include female sex (short urethra), sexual intercourse, indwelling catheter, diabetes mellitus, impaired bladder emptying.

#### Causes:

- *E coli* (most common)
- Staphylococcus saprophyticus—seen in sexually active young women (E coli is still more common in this group)
- Klebsiella
- Proteus mirabilis—urine has ammonia scent

Labs: ⊕ leukocyte esterase. ⊕ nitrites (indicate gram ⊖ organisms). Sterile pyuria (pyuria with ⊖ urine cultures) could suggest urethritis by *Neisseria gonorrhoeae* or *Chlamydia trachomatis*. Treatment: antibiotics (eg, TMP-SMX, nitrofurantoin).

### **Pyelonephritis**

#### **Acute pyelonephritis**

Neutrophils infiltrate renal interstitium A. Affects cortex with relative sparing of glomeruli/vessels. Presents with fevers, flank pain (costovertebral angle tenderness), nausea/vomiting, chills. Causes include ascending UTI (*E coli* is most common), hematogenous spread to kidney. Presents with WBCs in urine +/– WBC casts. CT would show striated parenchymal enhancement B. Risk factors include indwelling urinary catheter, urinary tract obstruction, vesicoureteral reflux, diabetes mellitus, pregnancy.

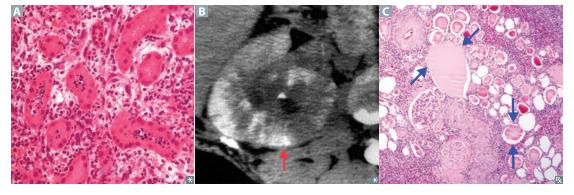
Complications include chronic pyelonephritis, renal papillary necrosis, perinephric abscess, urosepsis.

Treatment: antibiotics.

# Chronic pyelonephritis

The result of recurrent or inadequately treated episodes of acute pyelonephritis. Typically requires predisposition to infection such as vesicoureteral reflux or chronically obstructing kidney stones. Coarse, asymmetric corticomedullary scarring, blunted calyx. Tubules can contain eosinophilic casts resembling thyroid tissue (thyroidization of kidney).

**Xanthogranulomatous pyelonephritis**—rare; grossly orange nodules that can mimic tumor nodules; characterized by widespread kidney damage due to granulomatous tissue containing foamy macrophages. Associated with *Proteus* infection.



FAS1\_2019\_14-Renal.indd 600 11/7/19 5:42 PM

### **Acute kidney injury**

	Prerenal azotemia	Intrinsic renal failure	Postrenal azotemia
ETIOLOGY	Hypovolemia  ↓ cardiac output  ↓ effective circulating volume (eg, HF, liver failure)	Tubules and interstitium:  Acute tubular necrosis (ischemia, sepsis, infection, nephrotoxins)  Acute interstitial nephritis Glomerulus:  Acute glomerulonephritis Vascular:  Vasculitis  Malignant hypertension  TTP-HUS	Stones BPH Neoplasm Congenital anomalies
PATHOPHYSIOLOGY	↓ RBF → ↓ GFR → ↑ reabsorption of Na <sup>+</sup> /H <sub>2</sub> O and urea	In ATN, patchy necrosis  → debris obstructing tubules and fluid backflow → ↓ GFR In ATN, epithelial/granular casts	Outflow obstruction (bilateral)
URINE OSMOLALITY (mOsm/kg)	>500	<350	<350
URINE Na+ (mEq/L)	<20	>40	Varies
FE <sub>Na</sub>	<1%	>2%	Varies
SERUM BUN/Cr	>20	<15	Varies

# Acute interstitial nephritis

Also called tubulointerstitial nephritis. Acute interstitial renal inflammation. Pyuria (classically eosinophils) and azotemia occurring after administration of drugs that act as haptens, inducing hypersensitivity (eg, diuretics, NSAIDs, penicillin derivatives, proton pump inhibitors, rifampin, quinolones, sulfonamides). Less commonly may be 2° to other processes such as systemic infections (eg, *Mycoplasma*) or autoimmune diseases (eg, Sjögren syndrome, SLE, sarcoidosis).

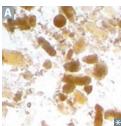
Associated with fever, rash, hematuria, pyuria, and costovertebral angle tenderness, but can be asymptomatic.

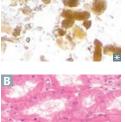
Remember these **5 P'S**:

- Pee (diuretics)
- Pain-free (NSAIDs)
- Penicillins and cephalosporins
- Proton pump inhibitors
- RifamPin
- Sulfa drugs

FAS1\_2019\_14-Renal.indd 601 11/7/19 5:42 PM

#### **Acute tubular necrosis**





Most common cause of acute kidney injury in hospitalized patients. Spontaneously resolves in many cases. Can be fatal, especially during initial oliguric phase. †  ${\rm FE_{Na}}$ .

Key finding: granular casts (often muddy brown in appearance) A.

3 stages:

- 1. Inciting event
- 2. Maintenance phase—oliguric; lasts 1–3 weeks; risk of hyperkalemia, metabolic acidosis, uremia
- 3. Recovery phase—polyuric; BUN and serum creatinine fall; risk of hypokalemia and renal wasting of other electrolytes and minerals

Can be caused by ischemic or nephrotoxic injury:

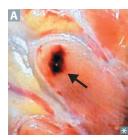
- Nephrotoxic—2° to injury resulting from toxic substances (eg, aminoglycosides, radiocontrast agents, lead, cisplatin, ethylene glycol), crush injury (myoglobinuria), hemoglobinuria. Proximal tubules are particularly susceptible to injury.

# Diffuse cortical necrosis

Acute generalized cortical infarction of both kidneys. Likely due to a combination of vasospasm and DIC.

Associated with obstetric catastrophes (eg, abruptio placentae), septic shock.

# Renal papillary necrosis



Sloughing of necrotic renal papillae A → gross hematuria and proteinuria. May be triggered by recent infection or immune stimulus.

Associated with: Sickle cell disease or trait,
Acute pyelonephritis, Analgesics (NSAIDs),
Diabetes mellitus (SAAD papa with
papillary necrosis).

FAS1\_2019\_14-Renal.indd 602 11/7/19 5:42 PM

### **Consequences of renal** failure

Decline in renal filtration can lead to excess retained nitrogenous waste products and electrolyte disturbances.

Consequences (MAD HUNGER):

- Metabolic Acidosis
- Dyslipidemia (especially † triglycerides)
- High potassium
- Uremia—clinical syndrome marked by:
  - Nausea and anorexia
  - Pericarditis
  - Asterixis
  - Encephalopathy
  - Platelet dysfunction
- Na+/H<sub>2</sub>O retention (HF, pulmonary edema, hypertension)
- Growth retardation and developmental delay
- Erythropoietin deficiency (anemia)
- Renal osteodystrophy

2 forms of renal failure: acute (eg, ATN) and chronic (eg, hypertension, diabetes mellitus, congenital anomalies).

Incremental reductions in GFR define the stages of chronic kidney disease.

### **Renal osteodystrophy**

Hypocalcemia, hyperphosphatemia, and failure of vitamin D hydroxylation associated with chronic kidney disease → 2° hyperparathyroidism → 3° hyperparathyroidism (if 2° poorly managed). High serum phosphate can bind with  $Ca^{2+} \rightarrow t$  issue deposits  $\rightarrow \downarrow$  serum  $Ca^{2+}$ .  $\downarrow 1,25$ -(OH),  $D_2$ → ↓ intestinal Ca<sup>2+</sup> absorption. Causes subperiosteal thinning of bones.

FAS1\_2019\_14-Renal.indd 603 11/7/19 5:42 PM 604

**SECTION III** 

#### **RENAL** ▶ RENAL—PATHOLOGY

#### **Renal cyst disorders**

# Autosomal dominant polycystic kidney disease

Numerous cysts in cortex and medulla  $\blacksquare$  causing bilateral enlarged kidneys ultimately destroy kidney parenchyma. Presents with flank pain, hematuria, hypertension, urinary infection, progressive renal failure in  $\sim 50\%$  of individuals.

Mutation in *PKD1* (85% of cases, chromosome 16) or *PKD2* (15% of cases, chromosome 4). Complications include chronic kidney disease and hypertension (caused by † renin production). Associated with berry aneurysms, mitral valve prolapse, benign hepatic cysts, diverticulosis. Treatment: If hypertension or proteinuria develops, treat with ACE inhibitors or ARBs.

# Autosomal recessive polycystic kidney disease

Cystic dilation of collecting ducts **B**. Often presents in infancy. Associated with congenital hepatic fibrosis. Significant oliguric renal failure in utero can lead to Potter sequence. Concerns beyond neonatal period include systemic hypertension, progressive renal insufficiency, and portal hypertension from congenital hepatic fibrosis.

# Autosomal dominant tubulointerstitial kidney disease

Also called medullary cystic kidney disease. Causes tubulointerstitial fibrosis and progressive renal insufficiency with inability to concentrate urine. Medullary cysts usually not visualized; smaller kidneys on ultrasound. Poor prognosis.

# Simple vs complex renal cysts

Simple cysts are filled with ultrafiltrate (anechoic on ultrasound **(**). Very common and account for majority of all renal masses. Found incidentally and typically asymptomatic.

Complex cysts, including those that are septated, enhanced, or have solid components on imaging require follow-up or removal due to risk of renal cell carcinoma.







#### Renovascular disease

Renal impairment due to ischemia from renal artery stenosis or microvascular disease.

↓ renal perfusion (one or both kidneys)

 $\rightarrow$  † renin  $\rightarrow$  † angiotensin  $\rightarrow$  HTN.

Main causes of renal artery stenosis:

- Atherosclerotic plaques—proximal 1/3 of renal artery, usually in older males, smokers.
- Fibromuscular dysplasia—distal 2/3 of renal artery or segmental branches, usually young or middle-aged females.

Clinically, patients can have refractory HTN with negative family history of HTN, asymmetric renal size, epigastric/flank bruits. Most common cause of 2° HTN in adults. Other large vessels are often involved.

FAS1\_2019\_14-Renal.indd 604 11/7/19 5:42 PM

#### Renal cell carcinoma

Polygonal clear cells A filled with accumulated lipids and carbohydrate. Often golden-yellow B due to † lipid content.

Originates from PCT → invades renal vein (may develop varicocele if left sided) → IVC → hematogenous spread → metastasis to lung and bone.

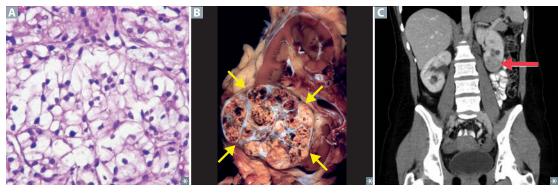
Manifests with hematuria, palpable masses, 2° polycythemia, flank pain, fever, weight loss. Treatment: surgery/ablation for localized disease. Immunotherapy (eg, aldesleukin) or targeted

therapy for metastatic disease, rarely curative. Resistant to chemotherapy and radiation therapy.

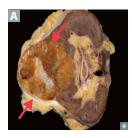
Most common 1° renal malignancy C. Most common in men 50-70 years old, † incidence with smoking and obesity. Associated with paraneoplastic syndromes, eg, PTHrP, Ectopic EPO, ACTH, Renin ("PEAR"-aneoplastic).

Clear cell (most common subtype) associated with gene deletion on chromosome 3 (sporadic, or inherited as von Hippel-Lindau syndrome).

RCC = 3 letters = chromosome 3.

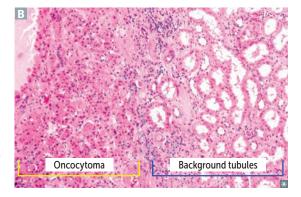


#### **Renal oncocytoma**



Benign epithelial cell tumor arising from collecting ducts (arrows in A point to wellcircumscribed mass with central scar). Large eosinophilic cells with abundant mitochondria without perinuclear clearing **B** (vs chromophobe renal cell carcinoma). Presents with painless hematuria, flank pain, abdominal mass.

Often resected to exclude malignancy (eg, renal cell carcinoma).



FAS1\_2019\_14-Renal.indd 605 11/7/19 5:42 PM

#### **RENAL** ▶ RENAL—PATHOLOGY

#### Nephroblastoma



Also called Wilms tumor. Most common renal malignancy of early childhood (ages 2–4). Contains embryonic glomerular structures. Presents with large, palpable, unilateral flank mass A and/or hematuria and possible HTN.

"Loss of function" mutations of tumor suppressor genes WT1 or WT2 on chromosome 11. May be a part of several syndromes:

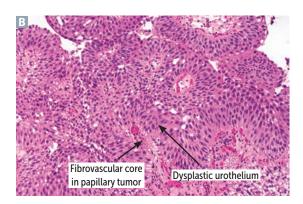
- WAGR complex—Wilms tumor, Aniridia (absence of iris), Genitourinary malformations, mental Retardation/intellectual disability (WT1 deletion)
- Denys-Drash syndrome—Wilms tumor, Diffuse mesangial sclerosis (early-onset nephrotic syndrome), Dysgenesis of gonads (male pseudohermaphroditism), WT1 mutation
- Beckwith-Wiedemann syndrome—Wilms tumor, macroglossia, organomegaly, hemihyperplasia (WT2 mutation), omphalocele

### Urothelial carcinoma of the bladder



Also called transitional cell carcinoma. Most common tumor of urinary tract system (can occur in renal calyces, renal pelvis, ureters, and bladder) A B. Can be suggested by painless hematuria (no casts).

Associated with problems in your Pee SAC:
Phenacetin, Smoking, Aniline dyes, and
Cyclophosphamide.



# Squamous cell carcinoma of the bladder

Chronic irritation of urinary bladder → squamous metaplasia → dysplasia and squamous cell carcinoma.

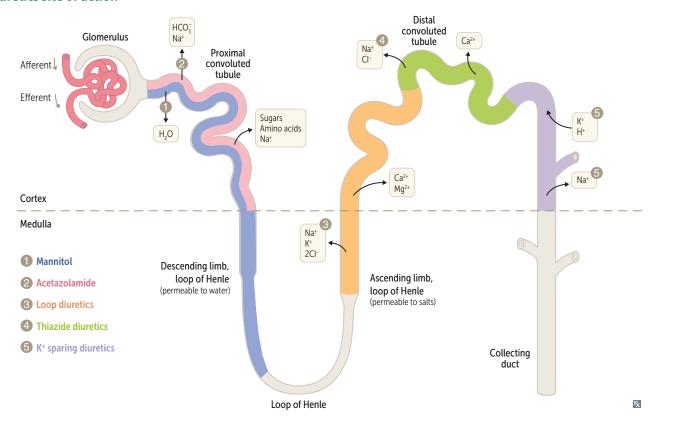
Risk factors include *Schistosoma haematobium* infection (Middle East), chronic cystitis, smoking, chronic nephrolithiasis. Presents with painless hematuria (no casts).

FAS1\_2019\_14-Renal.indd 606 11/7/19 5:42 PM

**SECTION III** 

#### ► RENAL—PHARMACOLOGY

#### **Diuretics site of action**



#### **Mannitol**

MECHANISM	Osmotic diuretic. ↑ tubular fluid osmolarity → ↑ urine flow, ↓ intracranial/intraocular pressure.
CLINICAL USE	Drug overdose, elevated intracranial/intraocular pressure.
ADVERSE EFFECTS	Pulmonary edema, dehydration, hypo- or hypernatremia. Contraindicated in anuria, HF.

FAS1\_2019\_14-Renal.indd 607 11/7/19 5:42 PM

#### Acetazolamide

MECHANISM	Carbonic anhydrase inhibitor. Causes self- limited NaHCO₃ diuresis and ↓ total body HCO₃⁻ stores. Alkalinizes urine.	
CLINICAL USE	Glaucoma, metabolic alkalosis, altitude sickness, idiopathic intracranial hypertension.	
ADVERSE EFFECTS	Proximal renal tubular acidosis, paresthesias, NH, toxicity, sulfa allergy, hypokalemia. Promotes calcium phosphate stone formation (insoluble at high pH).	"Acid" azolamide causes Acidosis.

#### **Loop diuretics**

Furosemide, bum	etanide, torsemide	
MECHANISM	Sulfonamide loop diuretics. Inhibit cotransport system (Na+/K+/2Cl-) of thick ascending limb of loop of Henle. Abolish hypertonicity of medulla, preventing concentration of urine. Associated with † PGE (vasodilatory effect on afferent arteriole); inhibited by NSAIDs. † Ca <sup>2+</sup> excretion. Loops Lose Ca <sup>2+</sup> .	
CLINICAL USE	Edematous states (HF, cirrhosis, nephrotic syndrome, pulmonary edema), hypertension, hypercalcemia.	
ADVERSE EFFECTS	Ototoxicity, Hypokalemia, Hypomagnesemia, Dehydration, Allergy (sulfa), metabolic Alkalosis, Nephritis (interstitial), Gout.	OHH DAANG!
Ethacrynic acid		
MECHANISM	Nonsulfonamide inhibitor of cotransport system (Na+/K+/2Cl-) of thick ascending limb of loop of Henle.	
CLINICAL USE	Diuresis in patients allergic to sulfa drugs.	
ADVERSE EFFECTS	Similar to furosemide, but more ototoxic.	Loop earrings hurt your ears.

FAS1\_2019\_14-Renal.indd 608 11/7/19 5:42 PM

Urine Ca<sup>2+</sup>

Thiazide diuretics	Hydrochlorothiazide, chlorthalidone, metolazone.	
MECHANISM	Inhibit NaCl reabsorption in early DCT  → ↓ diluting capacity of nephron. ↓ Ca <sup>2+</sup> excretion.	
CLINICAL USE	Hypertension, HF, idiopathic hypercalciuria, nephrogenic diabetes insipidus, osteoporosis.	
ADVERSE EFFECTS	Hypokalemic metabolic alkalosis, hyponatremia, hyperGlycemia, hyperLipidemia, hyperUricemia, hyperCalcemia. Sulfa allergy.	HyperGLUC.
Potassium-sparing diuretics	Spironolactone, Eplerenone, Amiloride, Triamterene.	Keep your SEAT
MECHANISM	Spironolactone and eplerenone are competitive aldosterone receptor antagonists in cortical collecting tubule. Triamterene and amiloride block Na <sup>+</sup> channels at the same part of the tubule.	
CLINICAL USE	Hyperaldosteronism, K <sup>+</sup> depletion, HF, hepatic ascites (spironolactone), nephrogenic DI (amiloride), antiandrogen.	
ADVERSE EFFECTS	Hyperkalemia (can lead to arrhythmias), endocrine effects with spironolactone (eg, gynecomastia, antiandrogen effects).	
Diuretics: electrolyte	changes	
Urine NaCl	† with all diuretics (strength varies based on pote as a result.	ency of diuretic effect). Serum NaCl may decrease
Urine K <sup>+</sup>	† especially with loop and thiazide diuretics. Ser	um K+ may decrease as a result.
Blood pH	<ul> <li>↓ (acidemia): carbonic anhydrase inhibitors: ↓ H blockade prevents K<sup>+</sup> secretion and H<sup>+</sup> secretion all cells (via H<sup>+</sup>/K<sup>+</sup> exchanger) in exchange for I (alkalemia): loop diuretics and thiazides cause</li> <li>■ Volume contraction → ↑ AT II → ↑ Na<sup>+</sup>/H<sup>+</sup> e ("contraction alkalosis")</li> <li>■ K<sup>+</sup> loss leads to K<sup>+</sup> exiting all cells (via H<sup>+</sup>/K<sup>+</sup> e)</li> </ul>	n. Additionally, hyperkalemia leads to K <sup>+</sup> entering H <sup>+</sup> exiting cells. alkalemia through several mechanisms: xchange in PCT → ↑ HCO <sub>3</sub> <sup>-</sup> reabsorption

FAS1\_2019\_14-Renal.indd 609 11/7/19 5:42 PM

↑ with loop diuretics: ↓ paracellular Ca<sup>2+</sup> reabsorption → hypocalcemia.

→ alkalosis and "paradoxical aciduria"

↓ with thiazides: enhanced Ca<sup>2+</sup> reabsorption.

■ In low K<sup>+</sup> state, H<sup>+</sup> (rather than K<sup>+</sup>) is exchanged for Na<sup>+</sup> in cortical collecting tubule

### 610 SECTION III RENAL → RENAL—PHARMACOLOGY

Angiotensin- converting enzyme inhibitors	Captopril, enalapril, lisinopril, ramipril.	
MECHANISM	Inhibit ACE → ↓ AT II → ↓ GFR by preventing constriction of efferent arterioles. ↑ renin due to loss of negative feedback. Inhibition of ACE also prevents inactivation of bradykinin, a potent vasodilator.	
CLINICAL USE	Hypertension, HF (\dagger mortality), proteinuria, diabetic nephropathy. Prevent unfavorable heart remodeling as a result of chronic hypertension.	In chronic kidney disease (eg, diabetic nephropathy), ↓ intraglomerular pressure, slowing GBM thickening.
ADVERSE EFFECTS	Cough, Angioedema (both due to  † bradykinin; contraindicated in Cl esterase inhibitor deficiency), Teratogen (fetal renal malformations), † Creatinine (↓ GFR), Hyperkalemia, and Hypotension. Used with caution in bilateral renal artery stenosis because ACE inhibitors will further ↓ GFR  → renal failure.	Captopril's CATCHH.
Angiotensin II receptor Dlockers	Losartan, candesartan, valsartan.	
MECHANISM	Selectively block binding of angiotensin II to $AT_1$ receptor. Effects similar to ACE inhibitors, but ARBs do not increase bradykinin.	
CLINICAL USE	Hypertension, HF, proteinuria, or chronic kidney disease (eg, diabetic nephropathy) with intolerance to ACE inhibitors (eg, cough, angioedema).	
ADVERSE EFFECTS	Hyperkalemia, ↓ GFR, hypotension; teratogen.	
Aliskiren		
MECHANISM	Direct renin inhibitor, blocks conversion of angiotensinogen to angiotensin I. Aliskiren Kills Renin.	
CLINICAL USE	Hypertension.	
ADVERSE EFFECTS	Hyperkalemia, ↓ GFR, hypotension, angioedema taking ACE inhibitors or ARBs and contraindica	, , , , , , , , , , , , , , , , , , , ,

11/7/19 5:42 PM FAS1\_2019\_14-Renal.indd 610

#### HIGH-YIELD SYSTEMS

## Reproductive

"Artificial insemination is when the farmer does it to the cow instead of the bull."

Student essay

Make no mistake about why these babies are here - they are here to replace us.

—Jerry Seinfeld

"Whoever called it necking was a poor judge of anatomy."

—Groucho Marx

"See, the problem is that God gives men a brain and a penis, and only enough blood to run one at a time."

-Robin Williams

The reproductive system can be intimidating at first but is manageable once you organize the concepts into the pregnancy, endocrinologic, embryologic, and oncologic aspects of reproduction. Study the endocrine and reproductive chapters together, because mastery of the hypothalamic-pituitary-gonadal axis is key to answering questions on ovulation, menstruation, disorders of sexual development, contraception, and many pathologies.

Embryology is a nuanced subject that covers multiple organ systems. Approaching it from a clinical perspective will allow for better understanding. For instance, make the connection between the presentation of DiGeorge syndrome and the 3rd/4th pharyngeal pouch, and between the Müllerian/Wolffian systems and disorders of sexual development.

As for oncology, don't worry about remembering screening or treatment guidelines. It is more important to know how these cancers present (eg, signs and symptoms) and their associated labs, histopathology, and risk factors. In addition, some of the testicular and ovarian cancers have distinct patterns of hCG, AFP, LH, or FSH derangements that serve as helpful clues in exam questions.

<b>▶</b> Embryology	612
▶ Anatomy	624
▶ Physiology	629
▶ Pathology	638
▶ Pharmacology	655

FAS1\_2019\_15-Repro.indd 611 11/7/19 5:52 PM

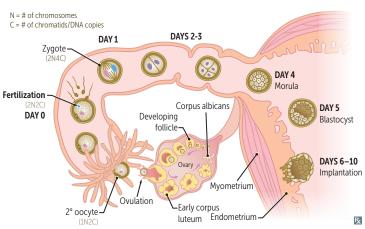
#### ▶ REPRODUCTIVE—EMBRYOLOGY

#### Important genes of embryogenesis

GENE	LOCATION	FUNCTION	NOTES
Sonic hedgehog (SHH) gene	Zone of polarizing activity at base of limb buds	Anterior-posterior axis patterning, CNS development	Mutations → holoprosencephaly
<i>Wnt</i> -7 gene	Apical ectodermal ridge at distal end of each limb	Dorsal-ventral axis patterning, limb development	
Fibroblast growth factor (FGF) gene	Apical ectodermal ridge	Limb lengthening (via mitosis of mesoderm)	"Look at that Fetus, Growing Fingers"
Homeobox ( <i>Hox</i> ) genes	Multiple	Segmental organization in cranial-caudal direction, transcription factor coding	Mutations → appendages in wrong locations. Isotretinoin → † Hox gene expression

#### **Early fetal development**

Early embryonic development



Within week 1	hCG secretion begins around the time of implantation of blastocyst.	Blasto <b>cyst</b> " <b>sticks</b> " at day <b>6</b> .
Within week 2	Bilaminar disc (epiblast, hypoblast).	2 weeks = 2 layers.
Within week 3	Gastrulation forms trilaminar embryonic disc.  Cells from epiblast invaginate → primitive streak → endoderm, mesoderm, ectoderm.  Notochord arises from midline mesoderm; overlying ectoderm becomes neural plate.	3 weeks = 3 layers.
Weeks 3–8 (embryonic period)	Neural tube formed by neuroectoderm and closes by week 4. Organogenesis.	Extremely susceptible to teratogens.
Week 4	Heart begins to beat. Upper and lower limb buds begin to form.	4 weeks = 4 limbs and 4 heart chambers.
Week 6	Fetal cardiac activity visible by transvaginal ultrasound.	
Week 8	Fetal movements start.	Gait at week 8.
Week 10	Genitalia have male/female characteristics.	Tenitalia.

FAS1\_2019\_15-Repro.indd 612 11/7/19 5:52 PM

#### **Embryologic derivatives**

Ectoderm		External/outer layer	
Surface ectoderm	Epidermis; adenohypophysis (from Rathke pouch); lens of eye; epithelial linings of oral cavity, sensory organs of ear, and olfactory epithelium; anal canal below the pectinate line; parotid, sweat, mammary glands.	Craniopharyngioma—benign Rathke pouch tumor with cholesterol crystals, calcifications	
Neural tube	Brain (neurohypophysis, CNS neurons, oligo- dendrocytes, astrocytes, ependymal cells, pineal gland), retina, spinal cord.	Neuroectoderm—think CNS.	
Neural crest	Melanocytes, Odontoblasts, Tracheal cartilage, Enterochromaffin cells, Leptomeninges (arachnoid, pia), PNS ganglia (cranial, dorsal root, autonomic), Adrenal medulla, Schwann cells, Spiral membrane (aorticopulmonary septum), Endocardial cushions (also derived partially from mesoderm), Skull bones.	MOTEL PASSES  Neural crest—think PNS and non-neural structures nearby.	
Muscle, bone, connective tissue, serous linings of body cavities (eg, peritoneum, pericardium, pleura), spleen (develops within foregut mesentery), cardiovascular structures, lymphatics, blood, wall of gut tube, upper vagina, kidneys, adrenal cortex, dermis, testes, ovaries, microglia.  Middle/"meat" layer. Mesodermal defects = V Vertebral defects Anal atresia Cardiac defects Tracheo-Esophageal fi		Mesodermal defects = VACTERL: Vertebral defects Anal atresia Cardiac defects Tracheo-Esophageal fistula	
Endoderm	Gut tube epithelium (including anal canal above the pectinate line), most of urethra and lower vagina (derived from urogenital sinus), luminal epithelial derivatives (eg, lungs, liver, gallbladder, pancreas, eustachian tube, thymus, parathyroid, thyroid follicular and parafollicular [C] cells).	"Enternal" layer.	

#### Types of errors in morphogenesis

Agenesis	Absent organ due to absent primordial tissue.	
Aplasia	Absent organ despite presence of primordial tissue.	
Hypoplasia	Incomplete organ development; primordial tissue present.	
Disruption	2° breakdown of previously normal tissue or structure (eg, amniotic band syndrome).	
Deformation	Extrinsic disruption (eg, multiple gestations → crowding → foot deformities); occurs after embryonic period.	
Malformation	Intrinsic disruption; occurs during embryonic period (weeks 3–8).	
Sequence	Abnormalities result from a single 1° embryologic event (eg, oligohydramnios → Potter sequence).	

FAS1\_2019\_15-Repro.indd 613 11/7/19 5:52 PM

Teratogens	Most susceptible in 3rd–8th weeks (embryonic pe 3, "all-or-none" effects. After week 8, growth and	
TERATOGEN	EFFECTS ON FETUS	NOTES
Medications		
ACE inhibitors	Renal failure, oligohydramnios, hypocalvaria.	
Alkylating agents	Absence of digits, multiple anomalies.	
Aminoglycosides	Ototoxicity.	A mean guy hit the baby in the ear.
Antiepileptic drugs	Neural tube defects, cardiac defects, cleft palate, skeletal abnormalities (eg, phalanx/nail hypoplasia, facial dysmorphism).	High-dose folate supplementation recommended. Most commonly valproate, carbamazepine, phenytoin, phenobarbital.
Diethylstilbestrol (DES)	Vaginal clear cell adenocarcinoma, congenital Müllerian anomalies.	
Fluoroquinolones	Cartilage damage.	
Folate antagonists	Neural tube defects.	Antiepileptics, trimethoprim, methotrexate.
Isotretinoin	Multiple severe birth defects.	Contraception mandatory. Iso <b>TERAT</b> inoin.
Lithium	Ebstein anomaly.	
Methimazole	Aplasia cutis congenita (congenital absence of skin, particularly on scalp).	
Tetracyclines	Discolored teeth, inhibited bone growth.	"Teethracyclines."
Thalidomide	Limb defects (phocomelia, micromelia— "flipper" limbs).	Limb defects with "tha-limb-domide."
Warfarin	Bone and cartilage deformities (stippled epiphyses, nasal and limb hypoplasia), optic nerve atrophy, fetal cerebral hemorrhage.	Do not wage warfare on the baby; keep it hepp with heparin (does not cross placenta).
Substance abuse		
Alcohol	Fetal alcohol syndrome.	
Cocaine	Low birth weight, preterm birth, IUGR, placental abruption.	Cocaine → vasoconstriction.
Smoking (nicotine, CO)	Low birth weight (leading cause in developed countries), preterm labor, placental problems, IUGR, SIDS, ADHD.	Nicotine → vasoconstriction. CO → impaired $O_2$ delivery.
Other		
lodine (lack or excess)	Congenital goiter or hypothyroidism (cretinism).	
Maternal diabetes	Caudal regression syndrome, cardiac defects (eg, VSD), neural tube defects, macrosomia, neonatal hypoglycemia (due to islet cell hyperplasia), polycythemia.	
Methylmercury	Neurotoxicity.	Highest in swordfish, shark, tilefish, king mackerel.
Vitamin A excess	Extremely high risk for spontaneous abortions and birth defects (cleft palate, cardiac).	
X-rays	Microcephaly, intellectual disability.	Minimized by lead shielding.

FAS1\_2019\_15-Repro.indd 614 11/7/19 5:52 PM

#### **Fetal alcohol** syndrome



One of the leading preventable causes of intellectual disability in the US. Newborns of mothers who consumed alcohol during any stage of pregnancy have † incidence of congenital abnormalities, including pre- and postnatal developmental retardation, microcephaly, facial abnormalities A (eg, smooth philtrum, thin vermillion border, small palpebral fissures), limb dislocation, heart defects. Heart-lung fistulas and holoprosencephaly in most severe form. One mechanism is due to impaired migration of neuronal and glial cells.

#### **Neonatal abstinence** syndrome

Complex disorder involving CNS, ANS, and GI systems. Secondary to maternal substance use/ abuse (most commonly opioids).

Universal screening for substance abuse is recommended in all pregnant patients.

Newborns may present with uncoordinated sucking reflexes, irritability, high-pitched crying, tremors, tachypnea, sneezing, diarrhea, and possibly seizures.

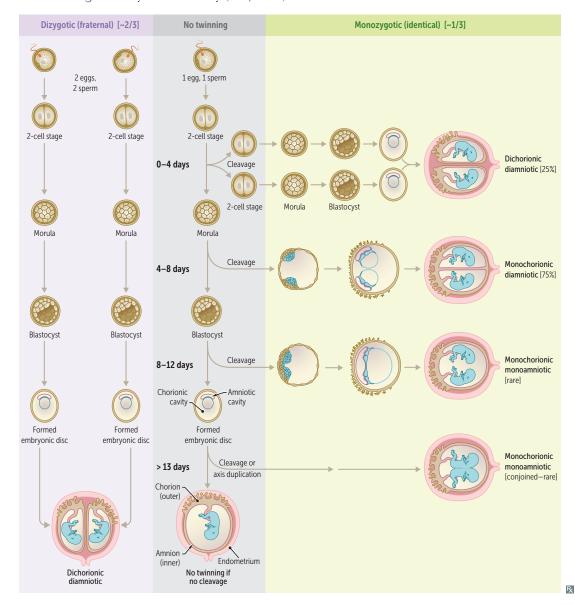
Treatment (for opiate abuse): methadone, morphine, buprenorphine.

FAS1\_2019\_15-Repro.indd 615 11/7/19 5:52 PM

#### **Twinning**

Dizygotic ("fraternal") twins arise from 2 eggs that are separately fertilized by 2 different sperm (always 2 zygotes) and will have 2 separate amniotic sacs and 2 separate placentas (chorions). Monozygotic ("identical") twins arise from 1 fertilized egg (1 egg + 1 sperm) that splits in early pregnancy. The timing of cleavage determines chorionicity (number of chorions) and amnionicity (number of amnions) (SCAB):

- Cleavage 0–4 days: Separate chorion and amnion
- Cleavage 4–8 days: shared Chorion
- Cleavage 8–12 days: shared Amnion
- Cleavage 13+ days: shared Body (conjoined)



FAS1\_2019\_15-Repro.indd 616 11/7/19 5:52 PM

#### **Placenta** 1° site of nutrient and gas exchange between mother and fetus. Fetal component Cytotrophoblast Inner layer of chorionic villi. Cytotrophoblast makes Cells. Syncytiotrophoblast Outer layer of chorionic villi; synthesizes and Syncytiotrophoblast synthesizes hormones. secretes hormones, eg, hCG (structurally Lacks MHC-I expression → ↓ chance of attack similar to LH; stimulates corpus luteum to by maternal immune system. secrete progesterone during first trimester). Maternal component **Decidua** basalis Derived from endometrium. Maternal blood in lacunae. circulation Endometrial artery Branch villus Umbilical vein-Maternal circulation (O<sub>2</sub> rich) Umbilical arteries H<sub>2</sub>O, electrolytes (O<sub>2</sub> poor) Nutrients Hormones lgG Drugs Fetal circulation Viruses CO<sub>2</sub> H<sub>2</sub>O Urea, waste products Hormones Syncytiotrophoblast Cytotrophoblast -Endothelial cell Amnion Chorionic plate Maternal blood Decidua basalis Ŗ

FAS1\_2019\_15-Repro.indd 617 11/7/19 5:52 PM

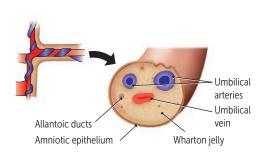
#### **REPRODUCTIVE** ▶ REPRODUCTIVE—EMBRYOLOGY

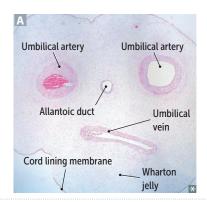
#### **Umbilical** cord

Two umbilical arteries return deoxygenated blood from fetal internal iliac arteries to placenta A.

One umbilical vein supplies oxygenated blood from placenta to fetus; drains into IVC via liver or via ductus venosus. Single umbilical artery (2-vessel cord) is associated with congenital and chromosomal anomalies.

Umbilical arteries and vein are derived from allantois.





#### **Urachus**

Allantois forms from hindgut and extends into urogenital sinus. Allantois becomes the urachus, a duct between fetal bladder and umbilicus. Failure of urachus to involute can lead to anomalies that may increase risk of infection and/or malignancy (eg, adenocarcinoma) if not treated. Obliterated urachus is represented by the median umbilical ligament after birth, which is covered by median umbilical fold of the peritoneum.

#### Patent urachus

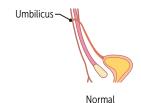
Total failure of urachus to obliterate → urine discharge from umbilicus.

#### **Urachal** cyst

Partial failure of urachus to obliterate; fluid-filled cavity lined with uroepithelium, between umbilicus and bladder. Cyst can become infected and present as painful mass below umbilicus.

### Vesicourachal diverticulum

Slight failure of urachus to obliterate → outpouching of bladder.









Vitelline duct

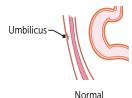
7th week—obliteration of vitelline duct (omphalomesenteric duct), which connects yolk sac to midgut lumen.

## Vitelline fistula Meckel diverticulum

Vitelline duct fails to close → meconium discharge from umbilicus.

Partial closure of vitelline duct, with patent portion attached to ileum (true diverticulum, white arrow in ■). May be asymptomatic. May have heterotopic gastric and/or pancreatic tissue → melena, hematochezia, abdominal pain.









Vitelline fistula

Meckel diverticulum 🛚 🗷

FAS1\_2019\_15-Repro.indd 618 11/7/19 5:52 PM

Aortic arch derivatives	Develop into arterial system.	
1st	Part of maxillary artery (branch of external carotid)	lst arch is maximal
2nd	Stapedial artery and hyoid artery	Second = Stapedial
3rd	Common Carotid artery and proximal part of internal Carotid artery	C is 3rd letter of alphabet
4th	On left, aortic arch; on right, proximal part of right subclavian artery	4th arch (4 limbs) = systemic
6th	Proximal part of pulmonary arteries and (on left only) ductus arteriosus	6th arch = pulmonary and the pulmonary-to- systemic shunt (ductus arteriosus)
	3rd 4th Right recurrent laryngeal nerve	4th Left recurrent laryngeal nerve loops around aortic arch distal

#### Pharyngeal apparatus

Composed of pharyngeal clefts, arches, pouches.

Pharyngeal clefts—derived from ectoderm. Also called pharyngeal grooves.

loops around right

subclavian artery

Truncus arteriosus

6 months postnatal

Pharyngeal arches—derived from mesoderm (muscles, arteries) and neural crest (bones, cartilage).

Pharyngeal pouches—derived from endoderm.

**CAP** covers outside to inside:

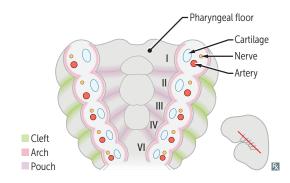
to ductus arteriosus

Clefts = ectoderm

Descending aorta

Arches = mesoderm + neural crest

Pouches = endoderm



### Pharyngeal cleft derivatives

1st cleft develops into external auditory meatus.

2nd through 4th clefts form temporary cervical sinuses, which are obliterated by proliferation of 2nd arch mesenchyme.

Persistent cervical sinus → pharyngeal cleft cyst within lateral neck, anterior to sternocleidomastoid muscle (does not move with swallowing, vs thyroglossal duct cyst).

FAS1\_2019\_15-Repro.indd 619 11/7/19 5:52 PM

#### **Pharyngeal arch derivatives**

ARCH	CARTILAGE	MUSCLES	NERVES <sup>a</sup>	NOTES
1st pharyngeal arch	Maxillary process  → Maxilla, zygoMatic bone  Mandibular process  → Meckel cartilage  → Mandible,  Malleus and incus,  sphenoMandibular  ligament	Muscles of Mastication (temporalis, Masseter, lateral and Medial pterygoids), Mylohyoid, anterior belly of digastric, tensor tympani, anterior 2/3 of tongue, tensor veli palatini	CN V <sub>3</sub> chew	Pierre Robin sequence— micrognathia, glossoptosis, cleft palate, airway obstruction  Treacher Collins syndrome—autosomal dominant neural crest dysfunction → craniofacial abnormalities (eg, zygomatic bone and mandibular hypoplasia), hearing loss, airway compromise
2nd pharyngeal arch	Reichert cartilage: Stapes, Styloid process, leSSer horn of hyoid, Stylohyoid ligament	Muscles of facial expression, Stapedius, Stylohyoid, platySma, posterior belly of digastric	CN VII (facial expression) smile	
3rd pharyngeal arch	Greater horn of hyoid	Stylopharyngeus (think of stylopharyngeus innervated by glossopharyngeal nerve)	CN IX (stylo- pharyngeus) swallow stylishly	
4th and 6th pharyngeal arches	Arytenoids, Cricoid, Corniculate, Cuneiform, Thyroid (used to sing and ACCCT)	4th arch: most pharyngeal constrictors; cricothyroid, levator veli palatini 6th arch: all intrinsic muscles of larynx except cricothyroid	4th arch: CN X (superior laryngeal branch) simply swallow 6th arch: CN X (recurrent/ inferior laryngeal branch) speak	Arches 3 and 4 form posterior 1/3 of tongue Arch 5 makes no major developmental contributions

<sup>&</sup>lt;sup>a</sup>Sensory and motor nerves are not pharyngeal arch derivatives. They grow into the arches and are derived from neural crest (sensory) and neuroectoderm (motor).

FAS1\_2019\_15-Repro.indd 620 11/7/19 5:52 PM

When at the restaurant of the golden arches, children tend to first chew (1), then smile (2), then swallow stylishly (3) or simply swallow (4), and then speak (6).

#### **Pharyngeal pouch derivatives**

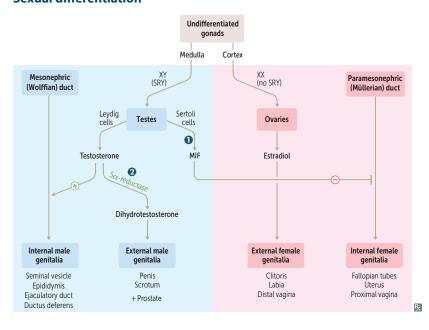
POUCH	DERIVATIVES	NOTES		MNEMONIC
1st pharyngeal pouch	Middle ear cavity, eustachian tube, mastoid air cells	lst pouch contribu endoderm-lined s of ear		Ear, tonsils, bottom-to-top: 1 (ear) 2 (tonsils)
2nd pharyngeal pouch	Epithelial lining of palatine tonsil			3 dorsal (bottom for inferior parathyroids) 3 ventral (to = thymus) 4 (top = superior parathyroids)
3rd pharyngeal pouch	Dorsal wings → inferior parathyroids Ventral wings → thymus	3rd pouch contribustructures (thymuright inferior para 3rd-pouch structur below 4th-pouch	us, left and athyroids) res end up	
4th pharyngeal pouch	Dorsal wings → superior parathyroids Ventral wings → ultimopharyngeal body			
	→ parafollicular (C) cells of thyroid			
Cleft lip and cleft		es, but often occur tog	gether.	
-	thyroid	naxillary and	gether.	

FAS1\_2019\_15-Repro.indd 621 11/7/19 5:52 PM

#### **Genital embryology**

Female	Default development. Mesonephric duct degenerates and paramesonephric duct develops.	Indifferent gonad
Male	SRY gene on Y chromosome—produces testisdetermining factor → testes development.  Sertoli cells secrete Müllerian inhibitory factor (MIF, also called antimullerian hormone) that suppresses development of paramesonephric ducts.	Mesonephros  Paramesonephric duct  Urogenital sinus
	Leydig cells secrete androgens that stimulate development of mesonephric ducts.	Testis-determining factor Androgens MIF  No androgens
Paramesonephric (Müllerian) duct	Develops into female internal structures— fallopian tubes, uterus, upper portion of vagina (lower portion from urogenital sinus). Male remnant is appendix testis.  Müllerian agenesis (Mayer-Rokitansky- Küster-Hauser syndrome)—may present as 1° amenorrhea (due to a lack of uterine development) in females with fully developed 2° sexual characteristics (functional ovaries).	Testis Ovary  Metanephric kidney  Oviduct  Urreter  Degenerated mesonephric durct
Mesonephric (Wolffian) duct	Develops into male internal structures (except prostate)—Seminal vesicles, Epididymis, Ejaculatory duct, Ductus deferens (SEED). Female remnant is Gartner duct.	Degenerated duct  Vas deferens Vagina
	i cinaic icililant is Garther duct.	R

#### **Sexual differentiation**



- ◆ Absence of Sertoli cells or lack of Müllerian inhibitory factor → develop both male and female internal genitalia and male external genitalia (streak gonads)
- 2 5α-reductase deficiency—inability to convert testosterone into DHT → male internal genitalia, ambiguous external genitalia until puberty (when ↑ testosterone levels cause masculinization)

#### In the testes:

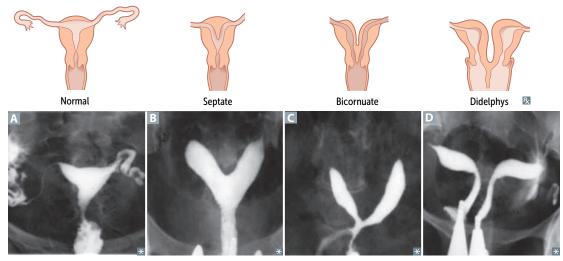
Leydig Leads to male (internal and external) sexual differentiation.

Sertoli Shuts down female (internal) sexual differentiation.

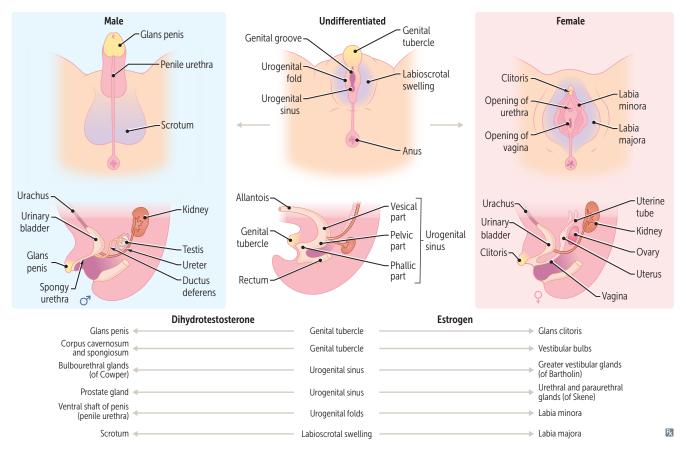
FAS1\_2019\_15-Repro.indd 622 11/7/19 5:52 PM

#### **Uterine (Müllerian duct) anomalies**

Septate uterus	Common anomaly vs normal uterus A. Incomplete resorption of septum B. ↓ fertility and early miscarriage/pregnancy loss. Treat with septoplasty.
Bicornuate uterus	Incomplete fusion of Müllerian ducts <b>C</b> . † risk of complicated pregnancy, early pregnancy loss, malpresentation, prematurity.
Uterus didelphys	Complete failure of fusion → double uterus, cervix, vagina D. Pregnancy possible.



#### Male/female genital homologs



FAS1\_2019\_15-Repro.indd 623 11/7/19 5:52 PM

#### **Congenital penile abnormalities**

#### **Hypospadias**



Abnormal opening of penile urethra on ventral surface of penis due to failure of urethral folds to fuse.

Hypospadias is more common than epispadias. Associated with inguinal hernia, cryptorchidism, chordee (downward or upward bending of penis).

#### Hypo is below.

Can be seen in  $5\alpha$ -reductase deficiency.

#### **E**pispadias



Abnormal opening of penile urethra on dorsal surface of penis due to faulty positioning of genital tubercle.

Exstrophy of the bladder is associated with Epispadias.

When you have **E**pispadias, you hit your **E**ye when you p**EE**.

#### **Descent of testes and ovaries**

	DESCRIPTION	MALE REMNANT	FEMALE REMNANT
Gubernaculum	Band of fibrous tissue	Anchors testes within scrotum	Ovarian ligament + round ligament of uterus
Processus vaginalis	Evagination of peritoneum	Forms tunica vaginalis Persistent patent processus vaginalis → hydrocele	Obliterated

#### ▶ REPRODUCTIVE—ANATOMY

#### **Gonadal drainage**

Venous drainage

Left ovary/testis → left gonadal vein → left renal vein → IVC.

Right ovary/testis → right gonadal vein → IVC.

Because the left spermatic vein enters the left renal vein at a 90° angle, flow is less laminar on left than on right → left venous pressure > right venous pressure → varicocele more common on the left.

Lymphatic drainage

Ovaries/testes → para-aortic lymph nodes.

Body of uterus/cervix/superior part of bladder

→ external iliac nodes.

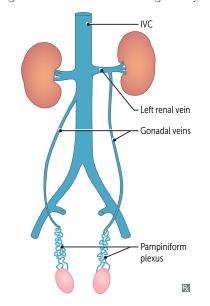
Prostate/cervix/corpus cavernosum/proximal vagina → internal iliac nodes.

Distal vagina/vulva/scrotum/distal anus

→ superficial inguinal nodes.

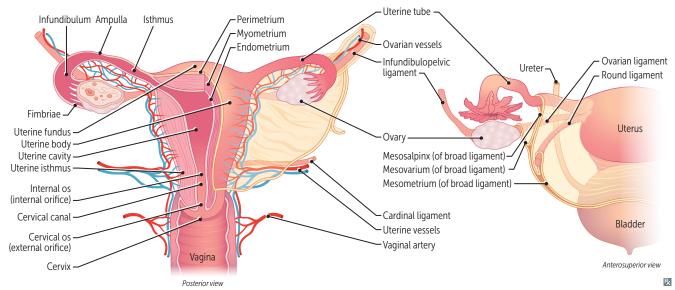
Glans penis → deep inguinal nodes.

"Left gonadal vein takes the Longest way."



FAS1\_2019\_15-Repro.indd 624 11/7/19 5:52 PM

#### **Female reproductive anatomy**



LIGAMENT	CONNECTS	STRUCTURES CONTAINED	NOTES
Infundibulopelvic (suspensory) ligament	Ovaries to lateral pelvic wall	Ovarian vessels	Ligate vessels during oophorectomy to avoid bleeding Ureter courses retroperitoneally, close to gonadal vessels → at risk of injury during ligation of ovarian vessels
Cardinal (transverse cervical) ligament	Cervix to side wall of pelvis	Uterine vessels	Ureter at risk of injury during ligation of uterine vessels in hysterectomy
Round ligament of the uterus	Uterine horn to labia majora		Derivative of gubernaculum. Travels through round inguinal canal; above the artery of Sampson
Broad ligament	Uterus, fallopian tubes, and ovaries to pelvic side wall	Ovaries, fallopian tubes, round ligaments of uterus	Fold of peritoneum that comprises the mesosalpinx, mesometrium, and mesovarium
Ovarian ligament	Medial pole of ovary to uterine horn		Derivative of gubernaculum Ovarian ligament latches to lateral uterus

#### **Adnexal torsion**

Twisting of ovary and fallopian tube around infundibulopelvic ligament and ovarian ligament → compression of ovarian vessels in infundibulopelvic ligament → blockage of lymphatic and venous outflow. Continued arterial perfusion → ovarian edema → complete blockage of arterial inflow → necrosis, local hemorrhage.

Associated with ovarian masses. Presents with acute pelvic pain, adnexal mass, nausea/vomiting.

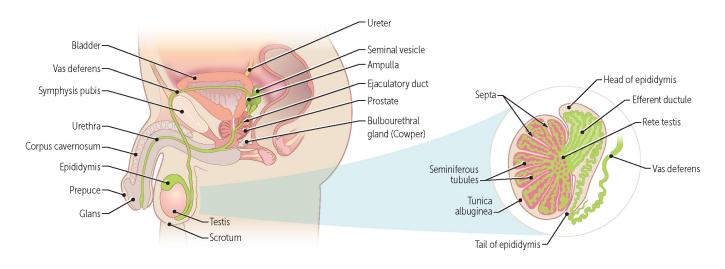
FAS1\_2019\_15-Repro.indd 625 11/7/19 5:52 PM

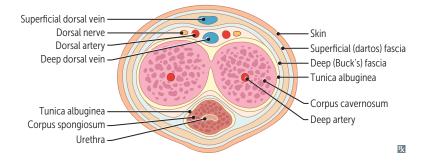
## Female reproductive epithelial histology



TISSUE	HISTOLOGY/NOTES
Vulva	Stratified squamous epithelium
Vagina	Stratified squamous epithelium, nonkeratinized
Ectocervix	Stratified squamous epithelium, nonkeratinized
Transformation zone	Squamocolumnar junction A (most common area for cervical cancer)
Endocervix	Simple columnar epithelium
Uterus	Simple columnar epithelium with long tubular glands in proliferative phase; coiled glands in secretory phase
Fallopian tube	Simple columnar epithelium, ciliated
Ovary, outer surface	Simple cuboidal epithelium (germinal epithelium covering surface of ovary)

#### Male reproductive anatomy





Pathway of sperm during ejaculation—

#### **SEVEN UP:**

Seminiferous tubules

**E**pididymis

Vas deferens

Ejaculatory ducts

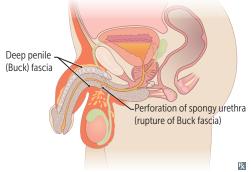
(Nothing)

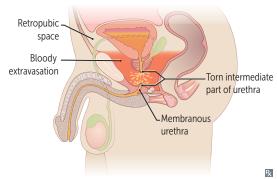
**U**rethra

Penis

FAS1\_2019\_15-Repro.indd 626 11/7/19 5:52 PM

Urethral injury	Occurs almost exclusively in men. Suspect if blood seen at urethral meatus. Urethral catheterization is relatively contraindicated.		
	Anterior urethral injury	Posterior urethral injury	
PART OF URETHRA	Bulbar (spongy) urethra	Membranous urethra	
MECHANISM	Perineal straddle injury	Pelvic fracture	
LOCATION OF URINE LEAK/BLOOD ACCUMULATION	Blood accumulates in scrotum  If Buck fascia is torn, urine escapes into perineal space	Urine leaks into retropubic space	
PRESENTATION	Blood at urethral meatus and scrotal hematoma	Blood at urethral meatus and high-riding prostate	





#### **Autonomic** innervation of male sexual response

Erection—Parasympathetic nervous system (pelvic splanchnic nerves, S2-S4):

- NO  $\rightarrow$  † cGMP  $\rightarrow$  smooth muscle relaxation  $\rightarrow$  vasodilation  $\rightarrow$  proerectile.
- Norepinephrine  $\rightarrow \uparrow [Ca^{2+}]_{in} \rightarrow smooth$ muscle contraction → vasoconstriction → antierectile.

Emission—Sympathetic nervous system (hypogastric nerve, T11-L2).

Expulsion—visceral and Somatic nerves (pudendal nerve).

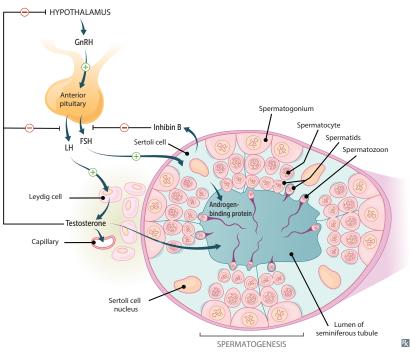
Point, Squeeze, and Shoot. S2, 3, 4 keep the penis off the floor.

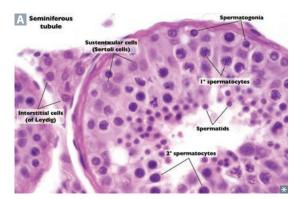
PDE-5 inhibitors (eg, sildenafil) → ↓ cGMP breakdown.

FAS1\_2019\_15-Repro.indd 627 11/7/19 5:52 PM

#### **Seminiferous tubules**

CELL	FUNCTION	LOCATION/NOTES
Spermatogonia	Maintain germ cell pool and produce 1° spermatocytes	Line seminiferous tubules A Germ cells
Sertoli cells	Secrete inhibin B → inhibit FSH  Secrete androgen-binding protein → maintain local levels of testosterone  Produce MIF	Line seminiferous tubules Non-germ cells Convert testosterone and androstenedione to estrogens via aromatase
	Tight junctions between adjacent Sertoli cells form blood-testis barrier → isolate gametes from autoimmune attack Support and nourish developing spermatozoa Regulate spermatogenesis	Sertoli cells are inSide Seminiferous tubules, Support Sperm Synthesis, and inhibit FSH Homolog of female granulosa cells
	Temperature sensitive; ↓ sperm production and ↓ inhibin B with ↑ temperature	† temperature seen in varicocele, cryptorchidism
Leydig cells	Secrete testosterone in the presence of LH; testosterone production unaffected by temperature	Interstitium Endocrine cells Homolog of female theca interna cells Leydies (ladies) dig testosterone





FAS1\_2019\_15-Repro.indd 628 11/7/19 5:52 PM

#### ▶ REPRODUCTIVE—PHYSIOLOGY

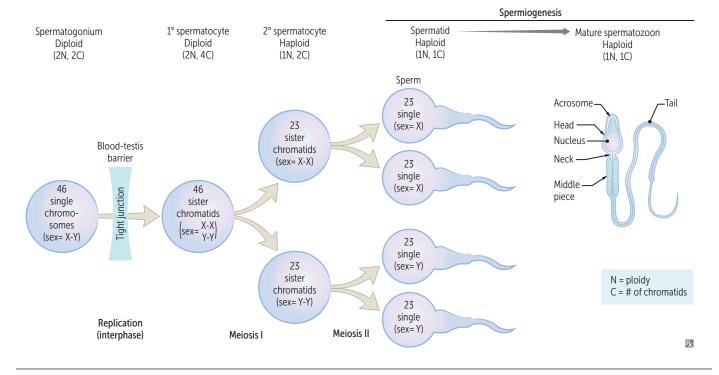
#### **Spermatogenesis**

Begins at puberty with spermatogonia. Full development takes 2 months. Occurs in seminiferous tubules. Produces spermatids that undergo spermiogenesis (loss of cytoplasmic contents, gain of acrosomal cap) to form mature spermatozoa.

"Conium" is going to be a sperm; "Zoon" is "Zooming" to egg.

Tail mobility impaired in ciliary dyskinesia/ Kartagener syndrome → infertility. Tail mobility normal in cystic fibrosis (in CF,

absent vas deferens → infertility).



FAS1\_2019\_15-Repro.indd 629 11/7/19 5:52 PM

### 630 SECTION III

#### REPRODUCTIVE → REPRODUCTIVE—PHYSIOLOGY

#### Estrogen

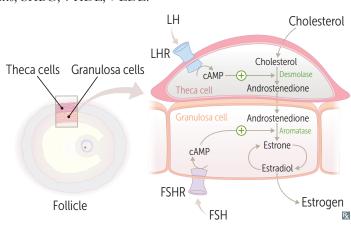
SOURCE	Ovary (17 $\beta$ -estradiol), placenta (estriol), adipose tissue (estrone via aromatization).
FUNCTION	Development of genitalia and breast, female fat distribution.
	Growth of follicle, endometrial proliferation,
	† myometrial excitability.
	Upregulation of estrogen, LH, and progesterone
	receptors; feedback inhibition of FSH and
	LH, then LH surge; stimulation of prolactin
	secretion.
	↑ transport proteins, SHBG; ↑ HDL; ↓ LDL.

Potency: estradiol > estrone > estriol.

#### Pregnancy:

- 50-fold ↑ in estradiol and estrone
- 1000-fold ↑ in estriol (indicator of fetal wellbeing)

Estrogen receptors expressed in cytoplasm; translocate to nucleus when bound by estrogen.



#### **Progesterone**

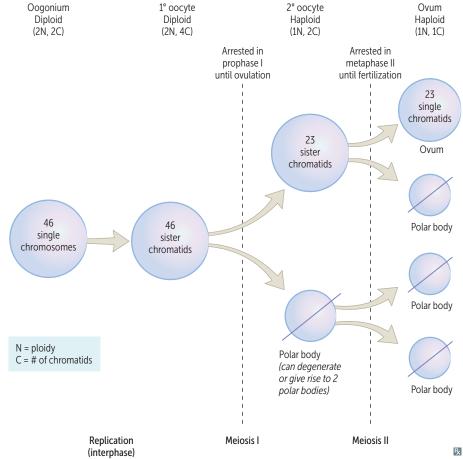
SOURCE	Corpus luteum, placenta, adrenal cortex, testes.	Fall in progesterone after delivery disinhib
FUNCTION	<ul> <li>During luteal phase, prepares uterus for implantation of fertilized egg:</li> <li>Stimulation of endometrial glandular secretions and spiral artery development</li> <li>Production of thick cervical mucus  inhibits sperm entry into uterus</li> <li>Prevention of endometrial hyperplasia</li> <li>† body temperature</li> <li>↓ estrogen receptor expression</li> <li>↓ gonadotropin (LH, FSH) secretion</li> <li>During pregnancy:</li> <li>Maintenance of pregnancy</li> <li>↓ myometrial excitability → ↓ contraction frequency and intensity</li> <li>↓ prolactin action on breasts</li> </ul>	prolactin → lactation. ↑ progesterone is indicative of ovulation.  Progesterone is pro-gestation.  Prolactin is pro-lactation.

FAS1\_2019\_15-Repro.indd 630 11/7/19 5:52 PM

#### **Oogenesis**

1° oocytes begin meiosis I during fetal life and complete meiosis I just prior to ovulation. Meiosis I is arrested in prOphase I for years until Ovulation (1° oocytes). Meiosis II is arrested in metaphase II until fertilization (2° oocytes). "An egg met a sperm."

If fertilization does not occur within 1 day, the 2° oocyte degenerates.



#### **Ovulation**

↑ estrogen, ↑ GnRH receptors on anterior pituitary. Estrogen surge then stimulates LH release → ovulation (rupture of follicle). ↑ temperature (progesterone induced).

Mittelschmerz—transient mid-cycle ovulatory pain ("Middle hurts"); classically associated with peritoneal irritation (eg, follicular swelling/rupture, fallopian tube contraction). Can mimic appendicitis.

FAS1\_2019\_15-Repro.indd 631 11/7/19 5:52 PM

#### **Menstrual cycle**

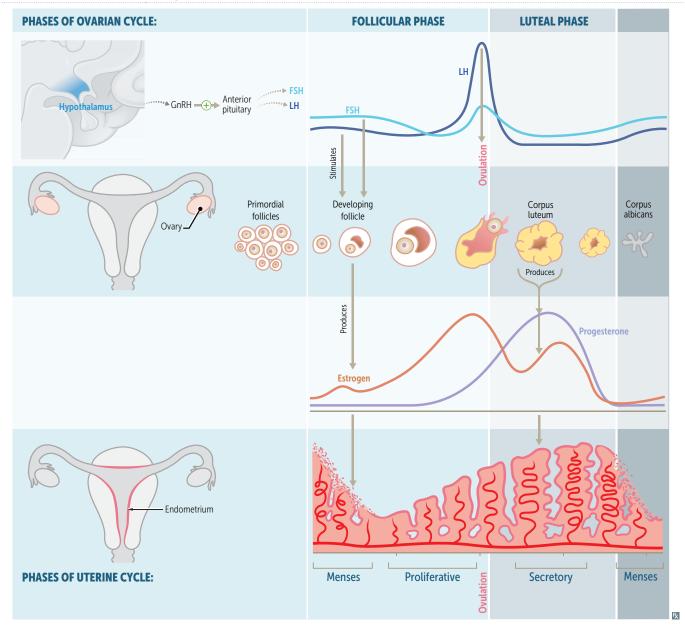
Follicular phase can vary in length. Luteal phase is 14 days. Ovulation day + 14 days = menstruation.

Follicular growth is fastest during 2nd week of the follicular phase.

Estrogen stimulates endometrial proliferation.

 $Progesterone\ maintains\ endometrium\ to\ support\ implantation.$ 

↓ progesterone → ↓ fertility.



FAS1\_2019\_15-Repro.indd 632 11/7/19 5:52 PM

### Abnormal uterine bleeding

Characterized as either heavy menstrual bleeding (AUB/HMB) or intermenstrual bleeding (AUB/IMB).

These are further subcategorized by **PALM-COEIN**:

- Structural causes (PALM): Polyp,
   Adenomyosis, Leiomyoma, or Malignancy/ hyperplasia
- Non-structural causes (COEIN):
   Coagulopathy, Ovulatory, Endometrial,
   Iatrogenic, Not yet classified

Terms such as dysfunctional uterine bleeding, menorrhagia, oligomenorrhea are no longer recommended.

#### **Pregnancy**

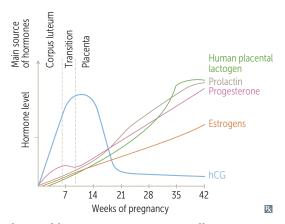
Fertilization most commonly occurs in upper end of fallopian tube (the ampulla). Occurs within 1 day of ovulation.

Implantation within the wall of the uterus occurs 6 days after fertilization. Syncytiotrophoblasts secrete hCG, which is detectable in blood 1 week after conception and on home test in urine 2 weeks after conception.

Gestational age—calculated from date of last menstrual period.

Physiologic adaptations in pregnancy:

- ↑ GFR → ↓ BUN and creatinine,
   ↓ glucosuria threshold
- ↑ cardiac output (↑ preload, ↓ afterload,
   ↑ HR → ↑ placental and uterus perfusion)
- Anemia (†† plasma, † RBCs)
- Hypercoagulability (to ↓ blood loss at delivery)
- Hyperventilation (eliminate fetal CO<sub>2</sub>)
- ↑ lipolysis and fat utilization (due to maternal hypoglycemia and insulin resistance) → preserves glucose and amino acids for utilization by the fetus



Placental hormone secretion generally increases over the course of pregnancy, but hCG peaks at 8–10 weeks.

#### **Human chorionic gonadotropin**

SOURCE

Syncytiotrophoblast of placenta.

FUNCTION

Maintains corpus luteum (and thus progesterone) for first 8–10 weeks of pregnancy by acting like LH (otherwise no luteal cell stimulation → abortion). After 8–10 weeks, placenta synthesizes its own estriol and progesterone and corpus luteum degenerates.

Used to detect pregnancy because it appears early in urine (see above).

Has identical  $\alpha$  subunit as LH, FSH, TSH (states of † hCG can cause hyperthyroidism).  $\beta$  subunit is unique (pregnancy tests detect  $\beta$  subunit). hCG is † in multiple gestations, hydatidiform moles, choriocarcinomas, and Down syndrome; hCG is ‡ in ectopic/failing pregnancy, Edwards syndrome, and Patau syndrome.

FAS1\_2019\_15-Repro.indd 633 11/7/19 5:52 PM

Human placental lactogen	Also called chorionic somatomammotropin.
SOURCE	Syncytiotrophoblast of placenta.
FUNCTION	Stimulates insulin production; overall † insulin resistance. Gestational diabetes can occur if maternal pancreatic function cannot overcome the insulin resistance.

#### **Apgar score**

	Score 2	Score 1	Score 0
Appearance	Pink	Extremities blue	Pale or blue
Pulse	≥ 100 bpm	< 100 bpm	No pulse
<b>G</b> rimace	Cries and pulls away	Grimaces or weak cry	No response to stimulation
Activity	Active movement	Arms, legs flexed	No movement
Respiration	Strong cry	Slow, irregular	No breathing

Assessment of newborn vital signs following delivery via a 10-point scale evaluated at 1 minute and 5 minutes. Apgar score is based on Appearance, Pulse, Grimace, Activity, and Respiration. Apgar scores < 7 may require further evaluation. If Apgar score remains low at later time points, there is † risk the child will develop long-term neurologic damage.

FAS1\_2019\_15-Repro.indd 634 11/7/19 5:52 PM

SECTION III

### Infant and child development

Milestone dates are ranges that have been approximated and vary by source. Children not meeting milestones may need assessment for potential developmental delay.

AGE	MOTOR	SOCIAL	VERBAL/COGNITIVE	
Infant	Parents	Start	Observing,	
0–12 mo	Primitive reflexes disappear— Moro (by 3 mo), rooting (by 4 mo), palmar (by 6 mo), Babinski (by 12 mo) Posture—lifts head up prone (by 1 mo), rolls and sits (by 6 mo), crawls (by 8 mo), stands (by 10 mo), walks (by 12–18 mo) Picks—passes toys hand to hand (by 6 mo), Pincer grasp (by 10 mo) Points to objects (by 12 mo)	Social smile (by 2 mo) Stranger anxiety (by 6 mo) Separation anxiety (by 9 mo)	Orients—first to voice (by 4 mo), then to name and gestures (by 9 mo) Object permanence (by 9 mo) Oratory—says "mama" and "dada" (by 10 mo)	
Toddler	Child	Rearing	Working,	
12–36 mo	Cruises, takes first steps (by 12 mo) Climbs stairs (by 18 mo) Cubes stacked—number = age (yr) × 3 Cutlery—feeds self with fork and spoon (by 20 mo) Kicks ball (by 24 mo)	Recreation—parallel play (by 24–36 mo) Rapprochement—moves away from and returns to mother (by 24 mo) Realization—core gender identity formed (by 36 mo)	Words—uses 50-200 words by 2 yr, uses 300+ words by 3 yr.	
Preschool	Don't	Forget, they're still	Learning!	
Drive—tricycle (3 wheels at 3 yr)  Drawings—copies line or circle, stick figure (by 4 yr)  Dexterity—hops on one foot (by 4 yr), uses buttons or zippers, grooms self (by 5 yr)		Freedom—comfortably spends part of day away from mother (by 3 yr) Friends—cooperative play, has imaginary friends (by 4 yr)	Language—understands 1000 words by 3 yr (3 zeros), uses complete sentences and prepositions (by 4 yr) Legends—can tell detailed stories (by 4 yr)	

#### Low birth weight

Defined as < 2500 g. Caused by prematurity or intrauterine growth restriction (IUGR). Associated with † risk of sudden infant death syndrome (SIDS) and with † overall mortality.

FAS1\_2019\_15-Repro.indd 635 11/7/19 5:52 PM 636 SECTION III

#### **REPRODUCTIVE** → REPRODUCTIVE—PHYSIOLOGY

#### Lactation

After parturition and delivery of placenta, rapid ↓ in progesterone disinhibits prolactin → initiation of lactation. Suckling is required to maintain milk production and ejection, since ↑ nerve stimulation → ↑ oxytocin and prolactin.

Prolactin—induces and maintains lactation and ↓ reproductive function.

Oxytocin—assists in milk letdown; also promotes uterine contractions.

Breast milk is the ideal nutrition for infants < 6 months old. Contains maternal immunoglobulins (conferring passive immunity; mostly IgA), macrophages, lymphocytes. Breast milk reduces infant infections and is associated with \$\ddot\$ risk for child to develop asthma, allergies, diabetes mellitus, and obesity. Guidelines recommend exclusively breastfed infants get vitamin D and possibly iron supplementation.

Breastfeeding ↓ maternal risk of breast and ovarian cancer and facilitates mother-child bonding.

#### Menopause

Diagnosed by amenorrhea for 12 months.

‡ estrogen production due to age-linked decline in number of ovarian follicles. Average age at onset is 51 years (earlier in smokers).

Usually preceded by 4–5 years of abnormal menstrual cycles. Source of estrogen (estrone) after menopause becomes peripheral conversion of androgens, ↑ androgens → hirsutism.

↑↑ FSH is specific for menopause (loss of negative feedback on FSH due to ↓ estrogen).

Hormonal changes: ↓ estrogen, ↑↑ FSH, ↑ LH (no surge), ↑ GnRH.

Causes HAVOCS: Hot flashes, Atrophy of the Vagina, Osteoporosis, Coronary artery disease, Sleep disturbances.

Menopause before age 40 suggests 1° ovarian insufficiency (premature ovarian failure); may occur in women who have received chemotherapy and/or radiation therapy.

#### **Androgens**

Testosterone, dihydrotestosterone (DHT), androstenedione.

#### SOURCE

DHT and testosterone (testis), **AnD**rostenedione (**AD**renal)

Potency: DHT > testosterone > androstenedione.

adipose tissue and testis).

#### FUNCTION

Testosterone:

- Differentiation of epididymis, vas deferens, seminal vesicles (internal genitalia, except prostate)
- Growth spurt: penis, seminal vesicles, sperm, muscle, RBCs
- Deepening of voice
- Closing of epiphyseal plates (via estrogen converted from testosterone)
- Libido

#### DHT:

- Early—differentiation of penis, scrotum, prostate
- Late—prostate growth, balding, sebaceous gland activity

Testosterone is converted to DHT by 5α-reductase, which is inhibited by finasteride. In the male, androgens are converted to estrogen by cytochrome P-450 aromatase (primarily in

Aromatase is the key enzyme in conversion of androgens to estrogen.

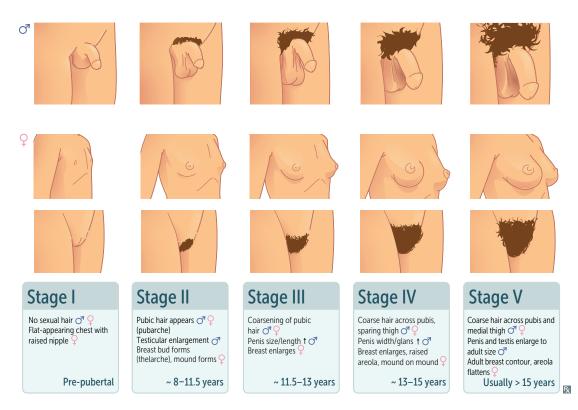
Androgenic steroid abuse—abuse of anabolic steroids to ↑ fat-free mass, muscle strength, and performance. Suspect in men who present with changes in behavior (eg, aggression), acne, gynecomastia, ↑ Hb and Hct, small testes (exogenous testosterone → hypothalamic-pituitary-gonadal axis inhibition

→ ↓ intratesticular testosterone → ↓ testicular size, ↓ sperm count, azoospermia). Women may present with virilization (eg, hirsutism, acne, breast atrophy, male pattern baldness).

FAS1\_2019\_15-Repro.indd 636 11/7/19 5:52 PM

#### **Tanner stages of sexual development**

Tanner stage is assigned independently to genitalia, pubic hair, and breast (eg, a person can have Tanner stage 2 genitalia, Tanner stage 3 pubic hair). Earliest detectable secondary sexual characteristic is breast bud development in girls, testicular enlargement in boys.



#### **Precocious puberty**

Appearance of 2° sexual characteristics (eg, adrenarche, thelarche, menarche) before age 8 years in girls and 9 years in boys. ↑ sex hormone exposure or production → ↑ linear growth, somatic and skeletal maturation (eg, premature closure of epiphyseal plates → short stature). Types include:

- Central precocious puberty († GnRH secretion): idiopathic (most common; early activation of hypothalamic-pituitary gonadal axis), CNS tumors.
- Peripheral precocious puberty (GnRH-independent; † sex hormone production or exposure to exogenous sex steroids): congenital adrenal hyperplasia, estrogen-secreting ovarian tumor (eg, granulosa cell tumor), Leydig cell tumor, McCune-Albright syndrome.

FAS1\_2019\_15-Repro.indd 637 11/7/19 5:52 PM

#### ▶ REPRODUCTIVE—PATHOLOGY

### Sex chromosome disorders

Aneuploidy most commonly due to meiotic nondisjunction.

#### Klinefelter syndrome



Male, 47,XXY.

Testicular atrophy, eunuchoid body shape, tall, long extremities, gynecomastia, female hair distribution A. May present with developmental delay. Presence of inactivated X chromosome (Barr body). Common cause of hypogonadism seen in infertility work-up.

Dysgenesis of seminiferous tubules

 $\rightarrow \downarrow$  inhibin B  $\rightarrow \uparrow$  FSH.

Abnormal Leydig cell function → ↓ testosterone → ↑ LH → ↑ estrogen.

**Turner syndrome** 



Female, 45,XO.

Short stature (associated with SHOX gene, preventable with growth hormone therapy), ovarian dysgenesis (streak ovary), shield chest **B**, bicuspid aortic valve, coarctation of the aorta (femoral < brachial pulse), lymphatic defects (result in webbed neck or cystic hygroma; lymphedema in feet, hands), horseshoe kidney, high-arched palate, shortened 4th metacarpals.

Most common cause of 1° amenorrhea. No Barr body.

Menopause before menarche.

↓ estrogen leads to ↑ LH, FSH.

Sex chromosome (X, or rarely Y) loss often due to nondisjunction during meiosis or mitosis.

Meiosis errors usually occur in paternal gametes

→ sperm missing the sex chromosome.

Mitosis errors occur after zygote formation → loss of sex chromosome in some but not all cells

→ mosaic karyotype (eg. 45,X/46XX).

(45,X/46,XY) mosaicism associated with increased risk for gonadoblastoma.

Pregnancy is possible in some cases (IVF, exogenous estradiol- $17\beta$  and progesterone).

#### **Double Y males**

47, XYY.

Phenotypically normal (usually undiagnosed), very tall. Normal fertility. May be associated with severe acne, learning disability, autism spectrum disorders.

Ovotesticular disorder 4
of sex development B

46,XX > 46,XY.

Both ovarian and testicular tissue present (ovotestis); ambiguous genitalia. Previously called true hermaphroditism.

FAS1\_2019\_15-Repro.indd 638 11/7/19 5:52 PM

Diagnosing disorders	Testoste	rone	LH	Diagnosis		
of sex hormones	1		t	Defective androgen receptor		
	<b>†</b>		1	Testosterone-secreting tumor, exogenous steroids		
	Ţ		1	Hypergonadotropic hypogonadism (1°)		
	ţ		ţ	Hypogonadotropic hypogonadism (2°)		
Other disorders of sex development	Disagreement between the phenotypic sex (external genitalia, influenced by hormonal levels) and the gonadal sex (testes vs ovaries, corresponds with Y chromosome). Includes the terms pseudohermaphrodite, hermaphrodite, and intersex.					
46,XX DSD	Ovaries present, but external genitalia are virilized or ambiguous. Due to excessive and inappropriate exposure to androgenic steroids during early gestation (eg, congenital adrenal hyperplasia or exogenous administration of androgens during pregnancy).					
46,XY DSD	Testes present, but external genitalia are female or ambiguous. Most common form is androgen insensitivity syndrome (testicular feminization).					
Disorders by physical	UTERUS	BREASTS	DISORDERS			
characteristics	$\oplus$	$\Theta$	Hypergonadotropic hypogonadism (eg, Turner syndrome, genetic mosaicism, pure gonadal dysgenesis) Hypogonadotropic hypogonadism (eg, CNS lesions, Kallmann syndrome)			
	$\Theta$	$\oplus$	Uterovaginal agenesis in genotypic female or androgen insensitivity in genotypic male			
	$\Theta$	$\ominus$	Male genotype	with insufficient production of testosterone		
Placental aromatase deficiency	Inability to synthesize estrogens from androgens. Masculinization of female (46,XX DSD) infants (ambiguous genitalia), † serum testosterone and androstenedione. Can present with maternal virilization during pregnancy (fetal androgens cross the placenta).					
Androgen insensitivity syndrome	Defect in androgen receptor resulting in normal-appearing female (46,XY DSD); female external genitalia with scant axillary and pubic hair, rudimentary vagina; uterus and fallopian tubes absent due to persistence of anti-Müllerian hormone from testes. Patients develop normal functioning testes (often found in labia majora; surgically removed to prevent malignancy). † testosterone, estrogen, LH (vs sex chromosome disorders).					
5α-reductase deficiency	Autosomal recessive; sex limited to genetic males (46,XY DSD). Inability to convert testosterone to DHT. Ambiguous genitalia until puberty, when † testosterone causes masculinization/† growth of external genitalia. Testosterone/estrogen levels are normal; LH is normal or †. Internal genitalia are normal.					
Kallmann syndrome	Failure to complete puberty; a form of hypogonadotropic hypogonadism. Defective migration of neurons and subsequent failure of olfactory bulbs to develop → ↓ synthesis of GnRH in the hypothalamus; hyposmia/anosmia; ↓ GnRH, FSH, LH, testosterone. Infertility (low sperm count in males; amenorrhea in females).					

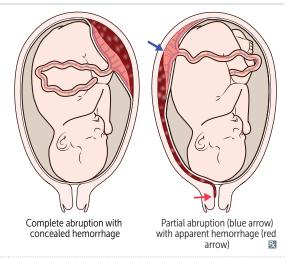
FAS1\_2019\_15-Repro.indd 639 11/7/19 5:52 PM

#### **Pregnancy complications**

#### Abruptio placentae

Premature separation (partial or complete) of placenta from uterine wall before delivery of infant. Risk factors: trauma (eg, motor vehicle accident), smoking, hypertension, preeclampsia, cocaine abuse.

Presentation: abrupt, painful bleeding (concealed or apparent) in third trimester; possible DIC (mediated by tissue factor activation), maternal shock, fetal distress. May be life threatening for mother and fetus.



### Morbidly adherent placenta

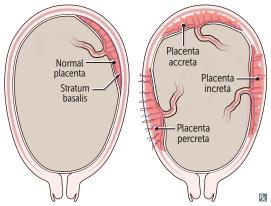
Defective decidual layer → abnormal attachment and separation after delivery. Risk factors: prior C-section or uterine surgery involving myometrium, inflammation, placenta previa, advanced maternal age, multiparity. Three types distinguishable by the depth of penetration:

Placenta **accreta**—placenta **attaches** to myometrium without penetrating it; most common type.

Placenta **increta**—placenta penetrates **into** myometrium.

Placenta percreta—placenta penetrates ("perforates") through myometrium and into uterine serosa (invades entire uterine wall); can result in placental attachment to rectum or bladder (can result in hematuria).

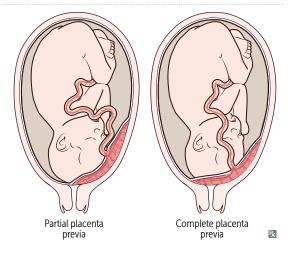
Presentation: often detected on ultrasound prior to delivery. No separation of placenta after delivery → postpartum bleeding (can cause Sheehan syndrome).



#### Placenta previa

Attachment of placenta over internal cervical os. Risk factors: multiparity, prior C-section. Associated with painless third-trimester bleeding. A "preview" of the placenta is visible through cervix.

Low-lying placenta (< 2 cm from internal cervical os, but not over it) is managed differently from placenta previa.

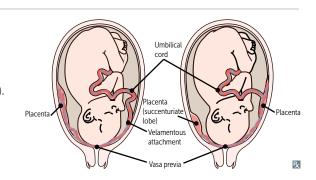


FAS1\_2019\_15-Repro.indd 640 11/7/19 5:52 PM

#### Pregnancy complications (continued)

#### Vasa previa

Fetal vessels run over, or in close proximity to, cervical os. May result in vessel rupture, exsanguination, fetal death. Presents with triad of membrane rupture, painless vaginal bleeding, fetal bradycardia (< 110 beats/min). Emergency C-section usually indicated. Frequently associated with velamentous umbilical cord insertion (cord inserts in chorioamniotic membrane rather than placenta → fetal vessels travel to placenta unprotected by Wharton jelly).



# Postpartum hemorrhage

Due to 4 T's: Tone (uterine atony; most common), Trauma (lacerations, incisions, uterine rupture), Thrombin (coagulopathy), Tissue (retained products of conception).

Treatment: uterine massage, oxytocin. If refractory, surgical ligation of uterine or internal iliac artery (will preserve fertility since ovarian arteries provide collateral circulation).

#### **Ectopic pregnancy**

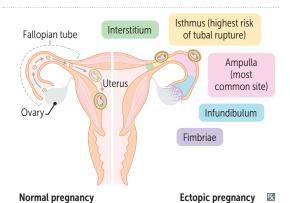


Implantation of fertilized ovum in a site other than the uterus, most often in ampulla of fallopian tube A. Suspect with history of amenorrhea, lower-than-expected rise in hCG based on dates, and sudden lower abdominal pain; confirm with ultrasound, which may show extraovarian adnexal mass. Often clinically mistaken for appendicitis.

Pain +/- bleeding.

#### Risk factors:

- Prior ectopic pregnancy
- History of infertility
- Salpingitis (PID)
- Ruptured appendix
- Prior tubal surgery
- Smoking
- Advanced maternal age



### **Amniotic fluid abnormalities**

#### **Polyhydramnios**

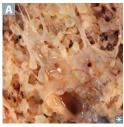
Too much amniotic fluid. Often idiopathic, but associated with fetal malformations (eg, esophageal/duodenal atresia, anencephaly; both result in inability to swallow amniotic fluid), maternal diabetes, fetal anemia, multiple gestations.

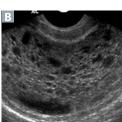
### Oligohydramnios

Too little amniotic fluid. Associated with placental insufficiency, bilateral renal agenesis, posterior urethral valves (in males) and resultant inability to excrete urine. Any profound oligohydramnios can cause Potter sequence.

FAS1\_2019\_15-Repro.indd 641 11/7/19 5:52 PM

#### **Hydatidiform mole**



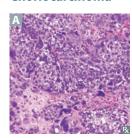


Cystic swelling of chorionic villi and proliferation of chorionic epithelium (only trophoblast). Presents with vaginal bleeding, emesis, uterine enlargement more than expected, pelvic pressure/pain. Associated with hCG-mediated sequelae: early preeclampsia (before 20 weeks), theca-lutein cysts, hyperemesis gravidarum, hyperthyroidism.

Treatment: dilation and curettage and methotrexate. Monitor hCG.

	Complete mole	Partial mole	
KARYOTYPE	46,XX; 46,XY	69,XXX; 69,XXY; 69,XYY	
COMPONENTS	Most commonly enucleated egg + single sperm (subsequently duplicates paternal DNA)	2 sperm + 1 egg	
HISTOLOGY	Hydropic villi, circumferential and diffuse trophoblastic proliferation	Only some villi are hydropic, focal/minimal trophoblastic proliferation	
FETAL PARTS	No	Yes (partial = fetal parts)	
STAINING FOR P57 PROTEIN	$\ominus$ (paternally imprinted)	⊕ (maternally expressed)	
UTERINE SIZE	†	<del>_</del>	
hCG	1111	†	
IMAGING	"Honeycombed" uterus or "clusters of grapes" A, "snowstorm" B on ultrasound	Fetal parts	
RISK OF INVASIVE MOLE	15–20%	< 5%	
RISK OF CHORIOCARCINOMA	2%	Rare	

#### Choriocarcinoma



Rare; can develop during or after pregnancy in mother or baby. Malignancy of trophoblastic tissue A (cytotrophoblasts, syncytiotrophoblasts); no chorionic villi present. † frequency of bilateral/multiple theca-lutein cysts. Presents with abnormal † hCG, shortness of breath, hemoptysis. Hematogenous spread to lungs → "cannonball" metastases B.

Treatment: methotrexate.



FAS1\_2019\_15-Repro.indd 642 11/7/19 5:52 PM

## **Hypertension in pregnancy**

Gestational hypertension	BP > 140/90 mm Hg after 20th week of gestation. No pre-existing hypertension. No proteinuria or end-organ damage.	Treatment: antihypertensives (Hydralazine, α-Methyldopa, Labetalol, Nifedipine), deliver at 37–39 weeks. Hypertensive Moms Love Nifedipine.		
Preeclampsia	New-onset hypertension with either proteinuria or end-organ dysfunction after 20th week of gestation (< 20 weeks suggests molar pregnancy).  Caused by abnormal placental spiral arteries → endothelial dysfunction, vasoconstriction, ischemia.  Incidence ↑ in patients with pre-existing hypertension, diabetes, chronic kidney disease, autoimmune disorders (eg, antiphospholipid antibody syndrome), age > 40 years.  Complications: placental abruption, coagulopathy, renal failure, pulmonary edema, uteroplacental insufficiency; may lead to eclampsia (+ seizures) and/or HELLP syndrome.	Treatment: antihypertensives, IV magnesium sulfate (to prevent seizure); definitive is delivery of fetus.  Proteinuria, Rising BP (new-onset HTN), End-organ dysfunction (eg, pulmonary edema).		
Eclampsia	Preeclampsia + maternal seizures. Maternal death due to stroke, intracranial hemorrhage, or ARDS.	Treatment: IV magnesium sulfate, antihypertensives, immediate delivery.		
HELLP syndrome  Hemolysis, Elevated Liver enzymes, Low Platelets. A manifestation of severe preeclampsia. Blood smear shows schistocytes. Can lead to DIC (due to release of tissue factor from injured placenta) and hepatic subcapsular hematomas → rupture → severe hypotension.		Treatment: immediate delivery.		
Incidence (US)—endometrial > ovarian > cervical; cervical cancer is more common worldwide due to lack of screening or HPV vaccination.  Prognosis: Cervical (best prognosis, diagnosed < 45 years old) > Endometrial (middleaged, about 55 years old) > Ovarian (worst prognosis, > 65 years).		CEOs often go from best to worst as they get older.		

FAS1\_2019\_15-Repro.indd 643 11/7/19 5:52 PM

### **Vulvar pathology**

Non-neoplastic	
Bartholin cyst and abscess	Due to blockage of Bartholin gland duct causing accumulation of gland fluid. May lead to abscess 2° to obstruction and inflammation A. Usually in reproductive-age females.
Lichen sclerosus	Thinning of epidermis with fibrosis/sclerosis of dermis. Presents with porcelain-white plaques with a red or violet border. Skin fragility with erosions can be observed <b>B</b> . Most common in postmenopausal women. Benign, but slightly increased risk for SCC.
Lichen simplex chronicus	Hyperplasia of vulvar squamous epithelium. Presents with leathery, thick vulvar skin with enhanced skin markings due to chronic rubbing or scratching. Benign, no risk of SCC.
Neoplastic	
Vulvar carcinoma	Carcinoma from squamous epithelial lining of vulva . Rare. Presents with leukoplakia, biopsy often required to distinguish carcinoma from other causes.  HPV-related vulvar carcinoma—associated with high-risk HPV types 16, 18. Risk factors: multiple partners, early coitarche. Usually in reproductive-age females.  Non-HPV vulvar carcinoma—usually from long-standing lichen sclerosus. Females > 70 years old.
Extramammary Paget disease	Intraepithelial adenocarcinoma. Carcinoma in situ, low risk of underlying carcinoma (vs Paget disease of the breast, which is always associated with underlying carcinoma). Presents with pruritus, erythema, crusting, ulcers D.









#### Imperforate hymen

Incomplete degeneration of the central portion of the hymen. Accumulation of vaginal mucus at birth → self-resolving bulge in introitus. If untreated, leads to 1° amenorrhea, cyclic abdominal pain, hematocolpos (accumulation of menstrual blood in vagina → bulging and bluish hymenal membrane).

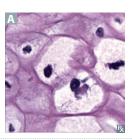
# **Vaginal tumors**

Vaginal squamous cell carcinoma	Usually 2° to cervical SCC; 1° vaginal carcinoma rare.
Clear cell adenocarcinoma	Affects women who had exposure to DES in utero.
Sarcoma botryoides	Embryonal rhabdomyosarcoma variant.  Affects girls < 4 years old; spindle-shaped cells; desmin ⊕.  Presents with clear, grape-like, polypoid mass emerging from vagina.

FAS1\_2019\_15-Repro.indd 644 11/7/19 5:52 PM

#### **Cervical pathology**

#### Dysplasia and carcinoma in situ



Disordered epithelial growth; begins at basal layer of squamocolumnar junction (transformation zone) and extends outward. Classified as CIN 1, CIN 2, or CIN 3 (severe, irreversible dysplasia or carcinoma in situ), depending on extent of dysplasia. Associated with HPV-16 and HPV-18, which produce both the E6 gene product (inhibits TP53) and E7 gene product (inhibits pRb) (6 before 7; P before R). Koilocytes A are pathognomonic of HPV infection. May progress slowly to invasive carcinoma if left untreated. Typically asymptomatic (detected with Pap smear) or presents as abnormal vaginal bleeding (often postcoital).

Risk factors: multiple sexual partners, HPV, smoking, early coitarche, DES exposure, immunocompromise (eg, HIV, transplant).

#### Invasive carcinoma

Often squamous cell carcinoma. Pap smear can detect cervical dysplasia before it progresses to invasive carcinoma. Diagnose via colposcopy and biopsy. Lateral invasion can block ureters → hydronephrosis → renal failure.

### **Primary ovarian** insufficiency

Also called premature ovarian failure.

Premature atresia of ovarian follicles in women of reproductive age. Most often idiopathic; associated with chromosomal abnormalities (especially in females < 30 years), autoimmunity. Need karyotype screening. Patients present with signs of menopause after puberty but before age 40. ↓ estrogen, † LH, † FSH.

#### Most common causes of anovulation

Pregnancy, polycystic ovarian syndrome, obesity, HPO axis abnormalities/immaturity, premature ovarian failure, hyperprolactinemia, thyroid disorders, eating disorders, competitive athletics, Cushing syndrome, adrenal insufficiency, chromosomal abnormalities (eg, Turner syndrome).

### **Functional** hypothalamic amenorrhea

Also called exercise-induced amenorrhea. Severe caloric restriction, † energy expenditure, and/or stress → functional disruption of pulsatile GnRH secretion → ↓ LH, FSH, estrogen. Pathogenesis includes ↓ leptin (due to ↓ fat) and ↑ cortisol (stress, excessive exercise).

Associated with eating disorders and "female athlete triad" (4 calorie availability/excessive exercise, ↓ bone mineral density, menstrual dysfunction).

### **Polycystic ovarian** syndrome



Hyperinsulinemia and/or insulin resistance hypothesized to alter hypothalamic hormonal feedback response → ↑ LH:FSH, ↑ androgens (eg, testosterone) from theca interna cells, ↓ rate of follicular maturation → unruptured follicles (cysts) + anovulation. Common cause of ↓ fertility in women. Enlarged, bilateral cystic ovaries A; presents with amenorrhea/oligomenorrhea, hirsutism, acne, ↓ fertility. Associated with obesity, acanthosis nigricans. ↑ risk of endometrial cancer 2° to

unopposed estrogen from repeated anovulatory cycles. Treatment: cycle regulation via weight reduction (\$\frac{1}{2}\$ peripheral estrone formation), OCPs (prevent endometrial hyperplasia due to unopposed estrogen); clomiphene (ovulation induction);

**Primary dysmenorrhea** Painful menses, caused by uterine contractions to ↓ blood loss → ischemic pain. Mediated by prostaglandins. Treatment: NSAIDs.

FAS1 2019 15-Repro.indd 645 11/7/19 5:52 PM

spironolactone, finasteride, flutamide to treat hirsutism.

#### **Ovarian cysts**

Follicular cyst	Distention of unruptured Graafian follicle. May be associated with hyperestrogenism, endometrial hyperplasia. Most common ovarian mass in young women.
Theca-lutein cyst	Often bilateral/multiple. Due to gonadotropin stimulation. Associated with choriocarcinoma and hydatidiform moles.

#### **Ovarian neoplasms**

Most common adnexal mass in women >55 years old. Present with abdominal distention, bowel obstruction, pleural effusion.

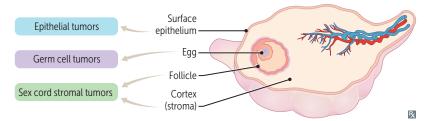
Risk † with advanced age, infertility, endometriosis, PCOS, genetic predisposition (eg, *BRCA1* or *BRCA2* mutations, Lynch syndrome, strong family history).

Risk ↓ with previous pregnancy, history of breastfeeding, OCPs, tubal ligation.

Epithelial tumors are typically serous (lined by serous epithelium natively found in fallopian tubes, and often bilateral) or mucinous (lined by mucinous epithelium natively found in cervix). Monitor response to therapy/relapse by measuring CA 125 levels (not good for screening).

Germ cell tumors can differentiate into somatic structures (eg, teratomas), or extra-embryonic structures (eg, yolk sac tumors), or can remain undifferentiated (eg, dysgerminoma).

Sex cord stromal tumors develop from embryonic sex cord (develops into theca and granulosa cells of follicle, Sertoli and Leydig cells of seminiferous tubules) and stromal (ovarian cortex) derivatives.

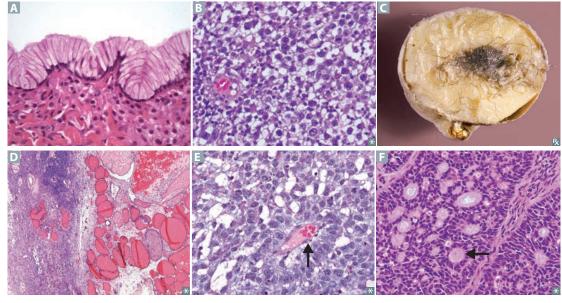


ТҮРЕ	MALIGNANT?	CHARACTERISTICS
Epithelial tumors		
Serous cystadenoma	Benign	Most common ovarian neoplasm.
Serous cystadenocarcinoma	Malignant	Most common malignant ovarian neoplasm. Psammoma bodies.
Mucinous cystadenoma	Benign	Multiloculated, large. Lined by mucus-secreting epithelium A.
Mucinous cystadenocarcinoma	Malignant	Rare. May be metastatic from appendiceal or GI tumors. Can result in pseudomyxoma peritonei (intraperitoneal accumulation of mucinous material).
Brenner tumor	Usually benign	Solid, pale yellow-tan tumor that appears encapsulated. "Coffee bean" nuclei on H&E stain.

FAS1\_2019\_15-Repro.indd 646 11/7/19 5:52 PM

## Ovarian neoplasms (continued)

•	•	
Germ cell tumors		
Dysgerminoma	Malignant	Most common in adolescents. Equivalent to male seminoma but rarer. Sheets of uniform "fried egg" cells <b>B</b> . Tumor markers: † hCG, LDH.
Mature cystic teratoma	Benign	Also called dermoid cyst. Most common ovarian tumor in young females.  Cystic mass with elements from all 3 germ layers (eg, teeth, hair, sebum)  May be painful 2° to ovarian enlargement or torsion. Monodermal form with thyroid tissue (struma ovarii ) may present with hyperthyroidism. Malignant transformation rare (usually to squamous cell carcinoma).
Immature teratoma	Malignant, aggressive	Contains fetal tissue, neuroectoderm. Commonly diagnosed before age 20. Typically represented by immature/embryonic-like neural tissue.
Yolk sac (endodermal sinus) tumor	Malignant, aggressive	Occur in ovaries and sacrococcygeal area in children. Yellow, friable (hemorrhagic) mass. 50% have Schiller-Duval bodies (resemble glomeruli, arrow in E). Tumor marker: † AFP.
Sex cord stromal tumors	5	
Thecoma	Benign	May produce estrogen. Usually presents as abnormal uterine bleeding in a postmenopausal woman.
Granulosa cell tumor	Malignant	Most common malignant sex cord stromal tumor. Predominantly women in their 50s. Often produces estrogen and/or progesterone and presents with postmenopausal bleeding, endometrial hyperplasia, sexual precocity (in preadolescents), breast tenderness. Histology shows Call-Exner bodies (granulosa cells arranged haphazardly around collections of eosinophilic fluid, resembling primordial follicles; arrow in F). "Give Granny a Call!"
Sertoli-Leydig cell tumor	Benign	Small, grey to yellow-brown mass. Resembles testicular histology with tubules/ cords lined by pink Sertoli cells. May produce androgens → virilization (eg, hirsutism, male pattern baldness, clitoral enlargement).
Fibromas	Benign	Bundles of spindle-shaped fibroblasts. Meigs syndrome—triad of ovarian fibroma, ascites, pleural effusion. "Pulling" sensation in groin.
	-	



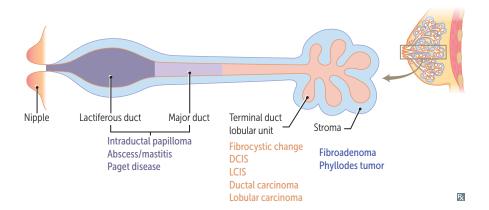
FAS1\_2019\_15-Repro.indd 647 11/7/19 5:52 PM

### **Uterine conditions**

Non-neoplastic uterine	e conditions
Adenomyosis	Extension of endometrial tissue (glandular) into uterine myometrium. Caused by hyperplasia of basal layer of endometrium. Presents with dysmenorrhea, AUB/HMB, and uniformly enlarged, soft, globular uterus. Treatment: GnRH agonists, hysterectomy, excision of an organized adenomyoma.
Asherman syndrome	Adhesions and/or fibrosis of the endometrium. Presents with ↓ fertility, recurrent pregnancy loss, AUB, pelvic pain. Often associated with dilation and curettage of intrauterine cavity.
Endometrial hyperplasia	Abnormal endometrial gland proliferation usually stimulated by excess estrogen. † risk for endometrial carcinoma (especially with nuclear atypia). Presents as postmenopausal vaginal bleeding. † risk with anovulatory cycles, hormone replacement therapy, PCOS, granulosa cell tumors.
Endometriosis	Endometrium-like glands/stroma outside endometrial cavity, most commonly in the ovary (frequently bilateral), pelvis, peritoneum (yellow-brown "powder burn" lesions). In ovary, appears as endometrioma (blood-filled "chocolate cysts" [oval structures above and below asterisks in A]). May be due to retrograde flow, metaplastic transformation of multipotent cells, transportation of endometrial tissue via lymphatic system. Characterized by cyclic pelvic pain, bleeding, dysmenorrhea, dyspareunia, dyschezia (pain with defecation), infertility; normal-sized uterus. Treatment: NSAIDs, OCPs, progestins, GnRH agonists, danazol, laparoscopic removal.
Endometritis	Inflammation of endometrium <b>B</b> associated with retained products of conception following delivery, miscarriage, abortion, or with foreign body (eg, IUD). Retained material is nidus for bacteria from vagina or GI tract. Chronic endometritis shows plasma cells on histology. Treatment: gentamicin + clindamycin +/– ampicillin.
Uterine neoplasms	
Endometrial carcinoma	Most common gynecologic malignancy . Presents with irregular vaginal bleeding. Two types: Endometrioid—most cases caused by unopposed estrogen exposure due to obesity, but also associated with early menarche, late menopause, nulliparity. Histology shows abnormally arranged endometrial glands. Early pathogenic events include loss of PTEN or mismatch repair proteins. Serous—associated with endometrial atrophy in postmenopausal women. Aggressive. Psammoma bodies often seen on histology. Characterized by formation of papillae and tufts.
Leiomyoma (fibroid)	Most common tumor in females. Often presents with multiple discrete tumors □. ↑ incidence in African Americans. Benign smooth muscle tumor; malignant transformation to leiomyosarcoma is rare. Estrogen sensitive; tumor size ↑ with pregnancy and ↓ with menopause. Peak occurrence at 20-40 years of age. May be asymptomatic, cause AUB, or result in miscarriage. Severe bleeding may lead to iron deficiency anemia. Whorled pattern of smooth muscle bundles with well-demarcated borders on histology ■.
Leiomyosarcoma	Malignant proliferation of smooth muscle arising from myometrium; arises de novo (not from leiomyomas), usually in postmenopausal women. Exam shows single lesion with areas of necrosis.
**	E E

FAS1\_2019\_15-Repro.indd 648 11/7/19 5:52 PM

#### **Breast pathology**



#### **Benign breast diseases**

#### Fibrocystic changes

Most common in premenopausal women 20-50 years old. Present with premenstrual breast pain or lumps; often bilateral and multifocal. Nonproliferative lesions include simple cysts (fluid-filled duct dilation, blue dome), papillary apocrine change/metaplasia, stromal fibrosis. Risk of cancer is usually not increased. Subtypes include:

- Sclerosing adenosis—acini and stromal fibrosis, associated with calcifications. Slight † risk for cancer.
- Epithelial hyperplasia—cells in terminal ductal or lobular epithelium. † risk of carcinoma with atypical cells.

# Inflammatory processes

Fat necrosis—benign, usually painless, lump due to injury to breast tissue. Calcified oil cyst on mammography; necrotic fat and giant cells on biopsy. Up to 50% of patients may not report trauma. Lactational mastitis—occurs during breastfeeding, † risk of bacterial infection through cracks in nipple. S aureus is most common pathogen. Treat with antibiotics and continue breastfeeding.

#### **Benign tumors**

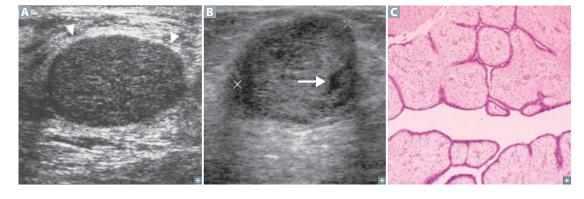
Fibroadenoma—most common in women < 35 years old. Small, well-defined, mobile mass A. Tumor composed of fibrous tissue and glands. † size and tenderness with † estrogen (eg, pregnancy, prior to menstruation). Risk of cancer is usually not increased.

Intraductal papilloma—small fibroepithelial tumor within lactiferous ducts, typically beneath areola. Most common cause of nipple discharge (serous or bloody). Slight † risk for cancer.

Phyllodes tumor—large mass **B** of connective tissue and cysts with "leaf-like" lobulations **C**. Most common in 5th decade. Some may become malignant.

#### **Gynecomastia**

Breast enlargement in males due to † estrogen compared with androgen activity. Physiologic in newborn, pubertal, and elderly males, but may persist after puberty. Other causes include cirrhosis, hypogonadism (eg, Klinefelter syndrome), testicular tumors, and drugs (Spironolactone, Hormones, Cimetidine, Finasteride, Ketoconazole: "Some Hormones Create Funny Knockers").



FAS1\_2019\_15-Repro.indd 649 11/7/19 5:52 PM

#### **Breast cancer**



Commonly postmenopausal. Often presents as a palpable hard mass A most often in the upper outer quadrant. Invasive cancer can become fixed to pectoral muscles, deep fascia, Cooper ligaments, and overlying skin → nipple retraction/skin dimpling.

Usually arises from terminal duct lobular unit. Amplification/overexpression of estrogen/ progesterone receptors or c-erbB2 (HER2, an EGF receptor) is common; triple negative

Risk factors in women: † age; history of atypical hyperplasia; family history of breast cancer; race (Caucasians at highest risk, African Americans at ↑ risk for triple ⊖ breast cancer); BRCA1/BRCA2 mutations; † estrogen exposure (eg, nulliparity); postmenopausal obesity (adipose tissue converts androstenedione to estrone); † total number of menstrual cycles; absence of breastfeeding; later age of first pregnancy; alcohol intake. In men: BRCA2 mutation, Klinefelter syndrome.

	$(ER \ominus, PR \ominus, and HER2/neu \ominus)$ form more aggressive.	Axillary lymph node metastasis most important prognostic factor in early-stage disease.	
ТҮРЕ	CHARACTERISTICS	NOTES	
Noninvasive carcinomas			
Ductal carcinoma in situ	Fills ductal lumen (black arrow in B indicates neoplastic cells in duct; blue arrow shows engorged blood vessel). Arises from ductal atypia. Often seen early as microcalcifications on mammography.	Early malignancy without basement membrane penetration. Usually does not produce a mass.  Comedocarcinoma—Subtype of DCIS. Cells have high-grade nuclei with extensive central necrosis C and dystrophic calcification.	
Paget disease	Extension of underlying DCIS/invasive breast cancer up the lactiferous ducts and into the contiguous skin of nipple → eczematous patches over nipple and areolar skin □.	Paget cells = intraepithelial adenocarcinoma cells.	
Lobular carcinoma in situ	↓ E-cadherin expression. No mass or calcifications → incidental biopsy finding.	† risk of cancer in either breast (vs DCIS, same breast and quadrant).	
Invasive carcinomas <sup>a</sup>			
Invasive ductal	Firm, fibrous, "rock-hard" mass with sharp margins and small, glandular, duct-like cells in desmoplastic stroma.		
Invasive lobular	↓ E-cadherin expression → orderly row of cells ("single file" • and no duct formation. Often lacks desmoplastic response.	Often bilateral with multiple lesions in the same location.  Lines of cells = Lobular.	
Medullary	Large, anaplastic cells growing in sheets with associated lymphocytes and plasma cells.	Well-circumscribed tumor can mimic fibroadenoma.	
Inflammatory	Dermal lymphatic space invasion → breast pain with warm, swollen, erythematous skin around exaggerated hair follicles, peau d'orange <b>F</b> .	Poor prognosis (50% survival at 5 years). Often mistaken for mastitis or Paget disease. Usually lacks a palpable mass.	
B		E F	

<sup>a</sup>All types of invasive breast carcinoma can be either of tubular subtype (well-differentiated tubules that lack myoepithelium) or mucinous subtype (abundant extracellular mucin, seen in older women).

FAS1\_2019\_15-Repro.indd 650 11/7/19 5:52 PM

#### **Penile pathology**

#### Peyronie disease



Abnormal curvature of penis A due to fibrous plaque within tunica albuginea. Associated with erectile dysfunction. Can cause pain, anxiety. Consider surgical repair or treatment with collagenase injections once curvature stabilizes. Distinct from penile fracture (rupture of corpora cavernosa due to forced bending).

### Ischemic priapism

Painful sustained erection lasting > 4 hours. Associated with sickle cell disease (sickled RBCs block venous drainage of corpus cavernosum vascular channels), medications (eg, sildenafil, trazodone). Treat immediately with corporal aspiration, intracavernosal phenylephrine, or surgical decompression to prevent ischemia.

# Squamous cell carcinoma



Seen in the US, but more common in Asia, Africa, South America. Precursor in situ lesions:

Bowen disease (in penile shaft, presents as leukoplakia "white plaque"), erythroplasia of Queyrat (carcinoma in situ of the glans B, presents as erythroplakia "red plaque"). Bowenoid papulosis (carcinoma in situ of unclear malignant potential, presenting as reddish papules). Associated with uncircumcised males and HPV.

#### Cryptorchidism



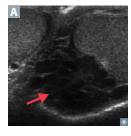
Descent failure of one ⚠ or both testes; impaired spermatogenesis (since sperm develop best at temperatures < 37°C); can have normal testosterone levels (Leydig cells are mostly unaffected by temperature); associated with ↑ risk of germ cell tumors. Prematurity ↑ risk of cryptorchidism. ↓ inhibin B, ↑ FSH, ↑ LH; testosterone ↓ in bilateral cryptorchidism, normal in unilateral. Most cases resolve spontaneously; otherwise, orchiopexy performed before 2 years of age.

#### **Testicular torsion**

Rotation of testicle around spermatic cord and vascular pedicle. Commonly presents in males 12–18 years old. May occur after an inciting event (eg, trauma) or spontaneously. Characterized by acute, severe pain, high-riding testis, and absent cremasteric reflex.

Treatment: surgical correction (orchiopexy) within 6 hours, manual detorsion if surgical option unavailable in timeframe. If testis is not viable, orchiectomy. Orchiopexy, when performed, should be bilateral because the contralateral testis is at risk for subsequent torsion.

#### **Varicocele**



Dilated veins in pampiniform plexus due to † venous pressure; most common cause of scrotal enlargement in adult males; most often on left side because of † resistance to flow from left gonadal vein drainage into left renal vein; can cause infertility because of † temperature; diagnosed by standing clinical exam/Valsalva maneuver (distension on inspection and "bag of worms" on palpation; augmented by Valsalva) or ultrasound A; does not transilluminate. Treatment: consider surgical ligation or embolization if associated with pain or infertility.

FAS1\_2019\_15-Repro.indd 651 11/7/19 5:52 PM

# tumors

**Extragonadal germ cell** Arise in midline locations. In adults, most commonly in retroperitoneum, mediastinum, pineal, and suprasellar regions. In infants and young children, sacrococcygeal teratomas are most common.

#### **Scrotal masses**

Benign scrotal lesions present as testicular masses that can be transilluminated (vs solid testicular tumors).

#### **Congenital hydrocele**



Common cause of scrotal swelling A in infants, due to incomplete obliteration of processus vaginalis. Most spontaneously resolve within l year.

Transilluminating swelling.

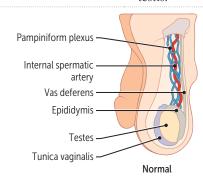
#### **Acquired hydrocele**

Scrotal fluid collection usually 2° to infection, trauma, tumor. If bloody → hematocele.

#### Spermatocele

Cyst due to dilated epididymal duct or rete testis.

Paratesticular fluctuant nodule.



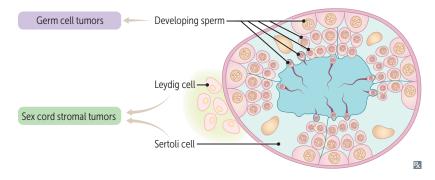








**Testicular tumors** 



Germ cell tumors account for ~ 95% of all testicular tumors. Arise from germ cells that produce sperm. Most often occur in young men. Risk factors: cryptorchidism, Klinefelter syndrome. Can present as a mixed germ cell tumor. Do not transilluminate. Usually not biopsied (risk of seeding scrotum), removed via radical orchiectomy.

Sex cord stromal tumors develop from embryonic sex cord (develops into Sertoli and Leydig cells of seminiferous tubules, theca and granulosa cells of follicle) derivatives. 5% of all testicular tumors. Mostly benign.

FAS1\_2019\_15-Repro.indd 652 11/7/19 5:52 PM

## **Testicular tumors (continued)**

	,	
Germ cell tumors		
Seminoma	Malignant	Painless, homogenous testicular enlargement. Most common testicular tumor. Analogous to ovarian dysgerminoma. Does not occur in infancy Large cells in lobules with watery cytoplasm and "fried egg" appearance on histology, † placental ALP (PALP). Highly radiosensitive. Late metastasis, excellent prognosis.
Teratoma	May be malignant	Unlike in females, <mark>M</mark> ature teratoma in adult <b>M</b> ales may be <b>M</b> alignant. Benign in children.
Embryonal carcinoma	Malignant	Painful, hemorrhagic mass with necrosis. Often glandular/papillary morphology. "Pure" embryonal carcinoma is rare; most commonly mixed with other tumor types. May present with metastases. May be associated with † hCG and normal AFP levels when pure († AFP when mixed). Worse prognosis than seminoma.
Yolk sac (endodermal sinus) tumor	Malignant, aggressive	Yellow, mucinous. Analogous to ovarian yolk sac tumor. Schiller-Duval bodies resemble primitive glomeruli. † AFP is highly characteristic. Most common testicular tumor in boys < 3 years old.
Choriocarcinoma	Malignant	Disordered syncytiotrophoblastic and cytotrophoblastic elements. Hematogenous metastases to lungs and brain. † hCG, may produce gynecomastia, symptoms of hyperthyroidism (α-subunit of hCG is identical to LH, FSH, TSH).
Non-germ cell tumors		
Sertoli cell tumor	Mostly benign	Androblastoma from sex cord stroma.
Leydig cell tumor	Mostly benign	Golden brown color; contains Reinke crystals (eosinophilic cytoplasmic inclusions). Produces androgens or estrogens → gynecomastia in men, precocious puberty in boys.
Testicular lymphoma	Malignant, aggressive	Most common testicular cancer in older men. Not a 1° cancer; arises from metastatic lymphoma to testes.

### Hormone levels in germ cell tumors

	SEMINOMA	YOLK SAC TUMOR	CHORIOCARCINOMA	TERATOMA	EMBRYONAL CARCINOMA
PALP	†	_	_	_	_
AFP	_	<b>†</b> †	_	_	−/↑ (when mixed)
β- <b>hCG</b>	<b>_/↑</b>	<b>_/</b> ↑	<b>†</b> †	<del>-</del>	<b>†</b>

11/7/19 5:52 PM FAS1\_2019\_15-Repro.indd 653

# 654

#### **SECTION III**

#### **REPRODUCTIVE** ▶ REPRODUCTIVE—PATHOLOGY

# **Epididymitis and orchitis**

Most common causes:

- C trachomatis and N gonorrhoeae (young men)
- E coli and Pseudomonas (elderly, associated with UTI and BPH)
- Autoimmune (eg, granulomas involving seminiferous tubules)

#### **Epididymitis**

Inflammation of epididymis. Presents with localized pain and tenderness over posterior testis. 

Prehn sign (pain relief with scrotal elevation). May progress to involve testis.

#### **Orchitis**

Inflammation of testis. Presents with testicular pain and swelling. Mumps orchitis † infertility risk. Rare in boys < 10 years old.

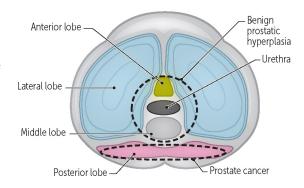
# Benign prostatic hyperplasia

Common in men > 50 years old. Characterized by smooth, elastic, firm nodular enlargement (hyperplasia not hypertrophy) of periurethral (lateral and middle) lobes, which compress the urethra into a vertical slit. Not premalignant. Often presents with † frequency of urination, nocturia, difficulty starting and stopping urine

nocturia, difficulty starting and stopping urine stream, dysuria. May lead to distention and hypertrophy of bladder, hydronephrosis, UTIs.

† free prostate-specific antigen (PSA).

Treatment:  $\alpha_1$ -antagonists (terazosin, tamsulosin), which cause relaxation of smooth muscle;  $5\alpha$ -reductase inhibitors (eg, finasteride); PDE-5 inhibitors (eg, tadalafil); surgical resection (eg, TURP, ablation).



#### **Prostatitis**

Characterized by dysuria, frequency, urgency, low back pain. Warm, tender, enlarged prostate. Acute bacterial prostatitis—in older men most common bacterium is *E coli*; in young men consider *C trachomatis*, *N gonorrhoeae*.

Chronic prostatitis—either bacterial or nonbacterial (eg, 2° to previous infection, nerve problems, chemical irritation).

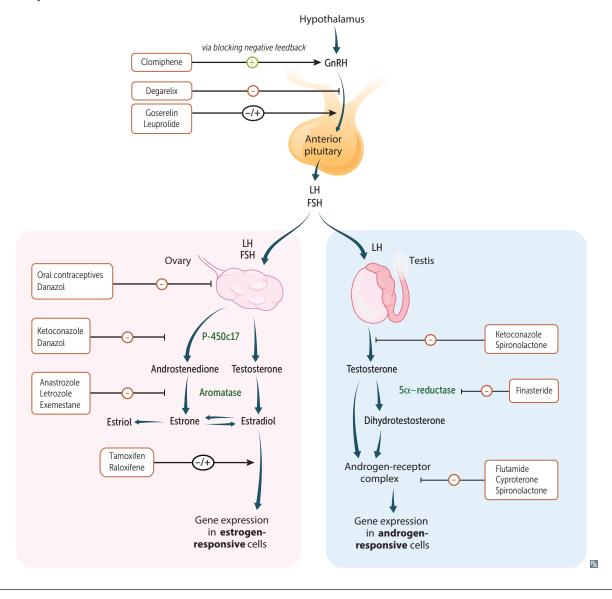
# Prostatic adenocarcinoma

Common in men > 50 years old. Arises most often from posterior lobe (peripheral zone) of prostate gland and is most frequently diagnosed by † PSA and subsequent needle core biopsies. Prostatic acid phosphatase (PAP) and PSA are useful tumor markers († total PSA, with ‡ fraction of free PSA). Osteoblastic metastases in bone may develop in late stages, as indicated by lower back pain and † serum ALP and PSA. Metastasis to the spine often occurs via Batson (vertebral) venous plexus.

FAS1\_2019\_15-Repro.indd 654 11/7/19 5:52 PM

## ► REPRODUCTIVE—PHARMACOLOGY

#### **Control of reproductive hormones**



FAS1\_2019\_15-Repro.indd 655 11/7/19 5:52 PM

Goserelin, leu	prol	ide
----------------	------	-----

MECHANISM	GnRH analogs. When used in pulsatile fashion act as GnRH agonists. When used in continuous fashion first transiently act as GnRH agonists (tumor flare), but subsequently act as GnRH antagonists (downregulate GnRH receptor in pituitary → ↓ FSH and ↓ LH).	oe used in <mark>lieu</mark> of GnRH.	
CLINICAL USE	Uterine fibroids, endometriosis, precocious puberty, prostate cancer, infertility.		
ADVERSE EFFECTS	Hypogonadism, ↓ libido, erectile dysfunction, nausea, vomiting.		
Degarelix			
MECHANISM	GnRH antagonist. No start-up flare.		
CLINICAL USE	Prostate cancer.		
ADVERSE EFFECTS	Hot flashes, liver toxicity.		
Estrogens	Ethinyl estradiol, DES, mestranol.		
MECHANISM	Bind estrogen receptors.		
CLINICAL USE	Hypogonadism or ovarian failure, menstrual abnormalities (combined OCPs), hormone replacement therapy in postmenopausal women.		
ADVERSE EFFECTS	↑ risk of endometrial cancer (when given without progesterone), bleeding in postmenopausal women, clear cell adenocarcinoma of vagina in females exposed to DES in utero, ↑ risk of thrombi. Contraindications—ER ⊕ breast cancer, history of DVTs, tobacco use in women > 35 years old.		
Selective estrogen rece	eptor modulators		
Clomiphene	Antagonist at estrogen receptors in hypothalamus. Prevents normal feedback inhibition and † release of LH and FSH from pituitary, which stimulates ovulation. Used to treat infertility due to anovulation (eg, PCOS). May cause hot flashes, ovarian enlargement, multiple simultaneous pregnancies, visual disturbances.		
Tamoxifen	Antagonist at breast; agonist at bone, uterus; ↑ risk of thromboembolic events (especially with smoking) and endometrial cancer. Used to treat and prevent recurrence of ER/PR ⊕ breast cancer.		
Raloxifene	Antagonist at breast, uterus; agonist at bone; † risk of thromboembolic events (especially with smoking) but no increased risk of endometrial cancer (vs tamoxifen); used primarily to treat osteoporosis.		
Aromatase inhibitors	Anastrozole, letrozole, exemestane.		
MECHANISM	Inhibit peripheral conversion of androgens to estrogen.		
CLINICAL USE	$\mathrm{ER} \oplus \mathrm{breast}$ cancer in postmenopausal women.		

11/7/19 5:52 PM FAS1\_2019\_15-Repro.indd 656

Hormone replacement therapy	Used for relief or prevention of menopausal symptoms (eg, hot flashes, vaginal atrophy), osteoporosis († estrogen, ↓ osteoclast activity).  Unopposed estrogen replacement therapy † risk of endometrial cancer, progesterone/progestin is added. Possible increased cardiovascular risk.	
Progestins	Levonorgestrel, medroxyprogesterone, etonogestrel, norethindrone, megestrol.	
MECHANISM	Bind progesterone receptors, ↓ growth and ↑ vascularization of endometrium, thicken cervical mucus.	
CLINICAL USE	Contraception (forms include pill, intrauterine device, implant, depot injection), endometrial cancer, abnormal uterine bleeding. Progestin challenge: presence of withdrawal bleeding excludes anatomic defects (eg, Asherman syndrome) and chronic anovulation without estrogen.	
Antiprogestins	Mifepristone, ulipristal.	
MECHANISM	Competitive inhibitors of progestins at progesterone receptors.	
CLINICAL USE	Termination of pregnancy (mifepristone with misoprostol); emergency contraception (ulipristal).	
Combined	Progestins and ethinyl estradiol; forms include pill, patch, vaginal ring.	
contraception	Estrogen and progestins inhibit LH/FSH and thus prevent estrogen surge. No estrogen surge → no LH surge → no ovulation.	
	Progestins cause thickening of cervical mucus, thereby limiting access of sperm to uterus.  Progestins also inhibit endometrial proliferation → endometrium is less suitable to the implantation of an embryo.	
	Adverse effects: breakthrough menstrual bleeding, breast tenderness, VTE, hepatic adenomas. Contraindications: smokers > 35 years old († risk of cardiovascular events), patients with † risk of cardiovascular disease (including history of venous thromboembolism, coronary artery disease, stroke), migraine (especially with aura), breast cancer, liver disease.	
Copper intrauterine dev	vice	
MECHANISM	Produces local inflammatory reaction toxic to sperm and ova, preventing fertilization and implantation; hormone free.	
CLINICAL USE	Long-acting reversible contraception. Most effective emergency contraception.	
ADVERSE EFFECTS	Heavier or longer menses, dysmenorrhea. Risk of PID with insertion (contraindicated in active pelvic infection).	
Tocolytics	Medications that relax the uterus; include terbutaline ( $\beta_2$ -agonist action), nifedipine ( $Ca^{2+}$ channel blocker), indomethacin (NSAID). Used to $\downarrow$ contraction frequency in preterm labor and allow time for administration of steroids (to promote fetal lung maturity) or transfer to appropriate medical center with obstetrical care.	

FAS1\_2019\_15-Repro.indd 657 11/7/19 5:52 PM

# **REPRODUCTIVE** ► REPRODUCTIVE—PHARMACOLOGY

MECHANISM	Synthetic androgen that acts as partial agonist a	t androgen receptors.
CLINICAL USE	Endometriosis, hereditary angioedema.	
ADVERSE EFFECTS	Weight gain, edema, acne, hirsutism, masculinization, ↓ HDL levels, hepatotoxicity, idiopathic intracranial hypertension.	
Testosterone, methy	ltestosterone	
MECHANISM	Agonists at androgen receptors.	
CLINICAL USE	Treat hypogonadism and promote development promote recovery after burn or injury.	of 2° sex characteristics; stimulate anabolism to
ADVERSE EFFECTS		tosterone in males by inhibiting release of LH (via ure closure of epiphyseal plates. † LDL, ↓ HDL.
Antiandrogens		
Finasteride	5α-reductase inhibitor (\$\frac{1}{2}\$ conversion of testosterone to DHT). Used for BPH and male-pattern baldness. Adverse effects: gynecomastia and sexual dysfunction.	Testosterone $\xrightarrow{5\alpha\text{-reductase}}$ DHT (more potent).
Flutamide, bicalutamide, apalutamide, enzalutamide	Nonsteroidal competitive inhibitors at androgen receptors. Used for prostate carcinoma.	
Ketoconazole	Inhibits steroid synthesis (inhibits 17,20 desmolase/17α-hydroxylase).	Used in PCOS to reduce androgenic symptoms.
Spironolactone	Inhibits steroid binding, 17,20 desmolase/17 $lpha$ -hydroxylase.	Both can cause gynecomastia and amenorrhea
Tamsulosin	$\alpha_{_{\! 1}}$ -antagonist used to treat BPH by inhibiting sm receptors (found on prostate) vs vascular $\alpha_{_{1B}}$ rec	
Minoxidil		
MECHANISM	Direct arteriolar vasodilator.	
CLINICAL USE	Androgenetic alopecia (pattern baldness), severe refractory hypertension.	

FAS1\_2019\_15-Repro.indd 658 11/7/19 5:52 PM

# HIGH-YIELD SYSTEMS

# Respiratory

"There's so much pollution in the air now that if it weren't for our lungs, there'd be no place to put it all."

-Robert Orben

"Freedom is the oxygen of the soul."

-Moshe Dayan

"Whenever I feel blue, I start breathing again."

-L. Frank Baum

"Life is not the amount of breaths you take; it's the moments that take your breath away."

-Will Smith, Hitch

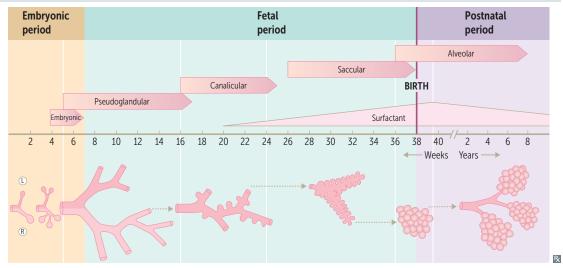
Group key respiratory, cardiovascular, and renal concepts together for study whenever possible. Know obstructive vs restrictive lung disorders,  $\dot{V}\dot{Q}$  mismatch, lung volumes, mechanics of respiration, and hemoglobin physiology. Lung cancers and other causes of lung masses are high yield. Be comfortable reading basic chest x-rays, CT scans, and PFTs.

▶ Embryology 660
▶ Anatomy 662
▶ Physiology 664
▶ Pathology 671
▶ Pharmacology 686

FAS1\_2019\_16-Respiratory.indd 659 11/8/19 7:33 AM

# ▶ RESPIRATORY—EMBRYOLOGY

Lung development	Occurs in five stages. Initial development includes development of lung bud from distal end of respiratory diverticulum during week 4. Every Pulmonologist Can See Alveoli.		
STAGE	STRUCTURAL DEVELOPMENT	NOTES	
Embryonic (weeks 4–7)	Lung bud → trachea → bronchial buds → mainstem bronchi → secondary (lobar) bronchi → tertiary (segmental) bronchi.	Errors at this stage can lead to tracheoesophageal fistula.	
Pseudoglandular (weeks 5–17)	Endodermal tubules → terminal bronchioles. Surrounded by modest capillary network.	Respiration impossible, incompatible with life.	
Canalicular (weeks 16–25)	Terminal bronchioles → respiratory bronchioles → alveolar ducts. Surrounded by prominent capillary network.	Airways increase in diameter. Respiration capable at 25 weeks. Pneumocytes develop starting at 20 weeks.	
Saccular (week 26-birth)	Alveolar ducts → terminal sacs. Terminal sacs separated by 1° septae.		
Alveolar (week 36–8 years)	Terminal sacs → adult alveoli (due to 2° septation).  In utero, "breathing" occurs via aspiration and expulsion of amniotic fluid → ↑ vascular resistance through gestation.  At birth, fluid gets replaced with air → ↓ in pulmonary vascular resistance.	At birth: 20–70 million alveoli. By 8 years: 300–400 million alveoli.	



### **Congenital lung malformations**

Pulmonary hypoplasia	<b>a</b> Poorly developed bronchial tree with abnormal histology. Associated with congenital diaphragmatic hernia (usually left-sided), bilateral renal agenesis (Potter sequence).	
Bronchogenic cysts	Caused by abnormal budding of the foregut and dilation of terminal or large bronchi. Discrete, round, sharply defined, fluid-filled densities on CXR (air-filled if infected). Generally asymptomatic but can drain poorly, causing airway compression and/or recurrent respiratory infections.	

FAS1\_2019\_16-Respiratory.indd 660 11/8/19 7:33 AM

#### **Club cells**

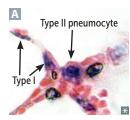
Nonciliated; low columnar/cuboidal with secretory granules. Located in bronchioles. Degrade toxins; secrete component of surfactant; act as reserve cells.

#### **Alveolar cell types**

### Type I pneumocytes

Squamous. 97% of alveolar surfaces. Thinly line the alveoli (two black arrows in A) for optimal gas exchange.

#### Type II pneumocytes



Cuboidal and clustered A.

#### 2 functions:

- 1. Serve as stem cell precursors for 2 cell types (type I and type II cells); proliferate during lung damage.
- Secrete surfactant from lamellar bodies (arrowheads in B)

Surfactant— ↓ alveolar surface tension, ↓ alveolar collapse, ↓ lung recoil, and ↑ compliance.

Composed of multiple lecithins, mainly dipalmitoylphosphatidylcholine (DPPC). Synthesis begins ~week 20 of gestation and achieves mature levels ~week 35. Corticosteroids important for fetal surfactant synthesis and lung development.

Ca Nur

**Alveolar macrophages** 

Phagocytose foreign materials; release cytokines and alveolar proteases. Hemosiderin-laden macrophages ("HF cells") may be found in the setting of pulmonary edema or alveolar hemorrhage.

# Neonatal respiratory distress syndrome



Surfactant deficiency → ↑ surface tension → alveolar collapse ("ground-glass" appearance of lung fields) A.

Risk factors: prematurity, maternal diabetes (due to † fetal insulin), C-section delivery (‡ release of fetal glucocorticoids; less stressful than vaginal delivery).

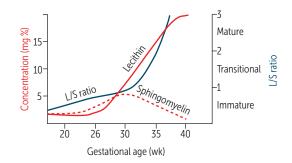
Treatment: maternal steroids before birth; exogenous surfactant for infant.

Therapeutic supplemental O<sub>2</sub> can result in Retinopathy of prematurity, Intraventricular hemorrhage, Bronchopulmonary dysplasia (RIB).

Collapsing pressure  $(P) = \frac{2 \text{ (surface tension)}}{\text{radius}}$ 

Law of Laplace—Alveoli have ↑ tendency to collapse on expiration as radius ↓.

Screening tests for fetal lung maturity: lecithinsphingomyelin (L/S) ratio in amniotic fluid (≥ 2 is healthy; < 1.5 predictive of NRDS), foam stability index, surfactant-albumin ratio. Persistently low O₂ tension → risk of PDA.



FAS1\_2019\_16-Respiratory.indd 661 11/8/19 7:33 AM

#### ► RESPIRATORY — ANATOMY

#### **Respiratory tree**

#### **Conducting zone**

Large airways consist of nose, pharynx, larynx, trachea, and bronchi. Airway resistance highest in the large- to medium-sized bronchi. Small airways consist of bronchioles that further divide into terminal bronchioles (large numbers in parallel → least airway resistance).

Warms, humidifies, and filters air but does not participate in gas exchange → "anatomic dead space." Cartilage and goblet cells extend to the end of bronchi.

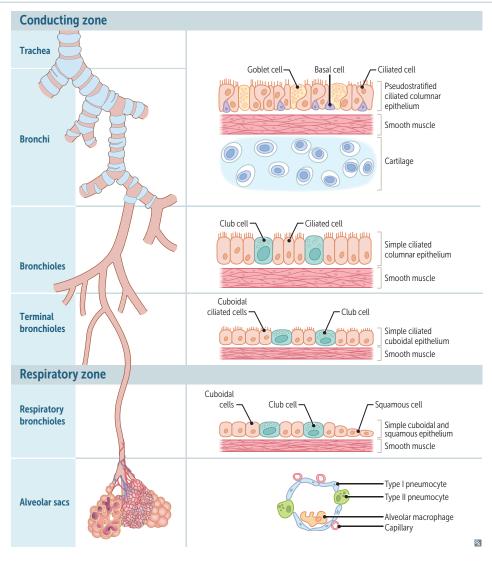
Pseudostratified ciliated columnar cells primarily make up epithelium of bronchus and extend to beginning of terminal bronchioles, then transition to cuboidal cells. Clear mucus and debris from lungs (mucociliary escalator).

Airway smooth muscle cells extend to end of terminal bronchioles (sparse beyond this point).

#### **Respiratory zone**

Lung parenchyma; consists of respiratory bronchioles, alveolar ducts, and alveoli. Participates in gas exchange.

Mostly cuboidal cells in respiratory bronchioles, then simple squamous cells up to alveoli. Cilia terminate in respiratory bronchioles. Alveolar macrophages clear debris and participate in immune response.



FAS1\_2019\_16-Respiratory.indd 662 11/8/19 7:34 AM

#### **Lung anatomy**

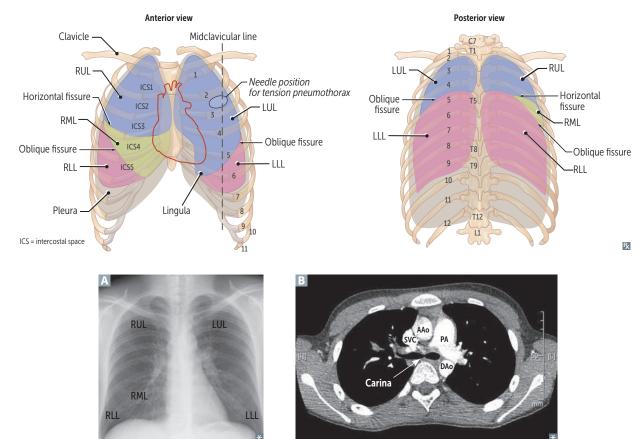


Right lung has 3 lobes; Left has Less Lobes (2) and Lingula (homolog of right middle lobe). Instead of a middle lobe, left lung has a space occupied by the heart A.

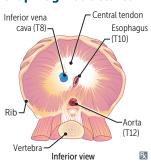
Relation of the pulmonary artery to the bronchus at each lung hilum is described by RALS—Right Anterior; Left Superior. Carina is posterior to ascending aorta and anteromedial to descending aorta B.

Right lung is a more common site for inhaled foreign bodies because right main stem bronchus is wider, more vertical, and shorter than the left. If you aspirate a peanut:

- While supine—usually enters superior segment of right lower lobe.
- While lying on right side—usually enters right upper lobe.
- While upright—usually enters right lower lobe.



#### **Diaphragm structures**



Structures perforating diaphragm:

- At T8: IVC, right phrenic nerve
- At T10: esophagus, vagus (CN 10; 2 trunks)
- At T12: aorta (red), thoracic duct (white), azygos vein (blue) ("At T-1-2 it's the red, white, and blue")

Diaphragm is innervated by C3, 4, and 5 (phrenic nerve). Pain from diaphragm irritation (eg, air, blood, or pus in peritoneal cavity) can be referred to shoulder (C5) and trapezius ridge (C3, 4).

Number of letters = T level:

T8: vena cava (IVC)

T10: (O)esophagus

T12: aortic hiatus

I ate (8) ten eggs at twelve.

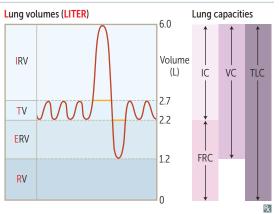
C3, 4, 5 keeps the diaphragm alive. Other bifurcations:

- The common carotid bifourcates at C4.
- The trachea bifourcates at T4.
- The abdominal aorta bifourcates at L4.

FAS1\_2019\_16-Respiratory.indd 663 11/8/19 7:34 AM

## ▶ RESPIRATORY—PHYSIOLOGY

Lung volumes	Note: a <b>capacity</b> is a sum of ≥ 2 physiologic <b>volume</b>	nes.
Inspiratory reserve volume	Air that can still be breathed in after normal inspiration	Lun
Tidal volume	Air that moves into lung with each quiet inspiration, typically 500 mL	I
Expiratory reserve volume	Air that can still be breathed out after normal expiration	7
Residual volume	Air in lung after maximal expiration; RV and any lung capacity that includes RV cannot be measured by spirometry	E
Inspiratory capacity	IRV + TV Air that can be breathed in after normal exhalation	··· F
Functional residual capacity	RV + ERV Volume of gas in lungs after normal expiration	
Vital capacity	TV + IRV + ERV  Maximum volume of gas that can be expired  after a maximal inspiration	
Total lung capacity	IRV + TV + ERV + RV Volume of gas present in lungs after a maximal inspiration	



# Determination of physiologic dead space

 $V_{D} = V_{T} \times \frac{\mathbf{Paco}_{2} - \mathbf{PEco}_{2}}{\mathbf{Paco}_{2}}$ 

V<sub>D</sub> = physiologic dead space = anatomic dead space of conducting airways plus alveolar dead space; apex of healthy lung is largest contributor of alveolar dead space. Volume of inspired air that does not take part in gas exchange.

 $V_T$  = tidal volume.  $Paco_2$  = arterial  $Pco_2$ .  $Peco_2$  = expired air  $Pco_2$ . Taco, Paco, Paco, Paco (refers to order of variables in equation)

Physiologic dead space—approximately equivalent to anatomic dead space in normal lungs. May be greater than anatomic dead space in lung diseases with  $\dot{V}/\dot{Q}$  defects.

# Ventilation

Minute ventilation	Total volume of gas entering lungs per minute $V_{\rm E} = V_{\rm T} \times RR$	Normal values: Respiratory rate (RR) = 12–20 breaths/min
Alveolar ventilation	Volume of gas that reaches alveoli each minute $V_{\rm A} = (V_{\rm T} - V_{\rm D}) \times RR$	$V_{\rm T} = 500 \text{ mL/breath}$ $V_{\rm D} = 150 \text{ mL/breath}$

FAS1\_2019\_16-Respiratory.indd 664 11/8/19 7:34 AM

#### Lung and chest wall

### **Elastic recoil**

Tendency for lungs to collapse inward and chest wall to spring outward.

At FRC, airway and alveolar pressures equal atmospheric pressure (called zero), and intrapleural pressure is negative (preventing atelectasis). The inward pull of the lung is balanced by the outward pull of the chest wall. System pressure is atmospheric. Pulmonary vascular resistance (PVR) is at a minimum.

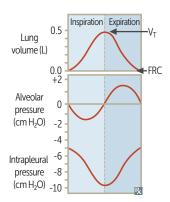
#### Compliance

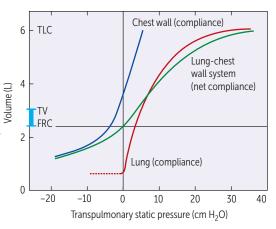
Change in lung volume for a change in pressure  $(\Delta V/\Delta P)$ . Inversely proportional to wall stiffness and increased by surfactant.

- † compliance = lung easier to fill (eg, emphysema, aging)
- I compliance = lung harder to fill (eg, pulmonary fibrosis, pneumonia, ARDS, pulmonary edema)

### Hysteresis

Lung inflation follows a different pressurevolume curve than lung deflation due to need to overcome surface tension forces in inflation.



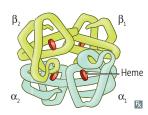


# Respiratory system changes in the elderly

Aging is associated with progressive  $\mbox{\ensuremath{\mbox{\sc i}}}$  in lung function. TLC remains the same.

INCREASED	DECREASED
Lung compliance (loss of elastic recoil)	Chest wall compliance († chest wall stiffness)
RV	FVC and ${\rm FEV}_{\scriptscriptstyle 1}$
Ÿ/Q mismatch	Respiratory muscle strength (can impair cough)
A-a gradient	Ventilatory response to hypoxia/hypercapnia

#### Hemoglobin



Normal adult hemoglobin (Hb) is composed of 4 polypeptide subunits (2  $\alpha$  and 2  $\beta$ ) and exists in 2 forms:

- Deoxygenated form has low affinity for O<sub>2</sub>, thus promoting release/unloading of O<sub>2</sub>.
- Oxygenated form has high affinity for O<sub>2</sub> (300×). Hb exhibits positive cooperativity and positive allostery.

Hemoglobin acts as buffer for H<sup>+</sup> ions. Myoglobin is composed of a single polypeptide chain associated with one heme moiety. Higher affinity for oxygen than Hb.

FAS1\_2019\_16-Respiratory.indd 665 11/8/19 7:34 AM

# Oxygen content of blood

 $O_2$  content =  $(1.34 \times Hb \times Sao_2) + (0.003 \times Pao_2)$ Hb = hemoglobin concentration;  $Sao_2$  = arterial  $O_2$  saturation  $Pao_2$  = partial pressure of  $O_2$  in arterial blood

Normally 1 g Hb can bind 1.34 mL O<sub>2</sub>; normal Hb amount in blood is 15 g/dL.

O<sub>2</sub>, binding capacity  $\approx 20$  mL O<sub>2</sub>/dL of blood.

With  $\downarrow$  Hb there is  $\downarrow$  O<sub>2</sub> content of arterial blood, but no change in O<sub>2</sub> saturation and Pao<sub>2</sub>.

 $O_2$  delivery to tissues = cardiac output  $\times O_2$  content of blood.

	Hb CONCENTRATION	% O <sub>2</sub> SAT OF Hb	DISSOLVED O <sub>2</sub> (Pao <sub>2</sub> )	TOTAL O <sub>2</sub> CONTENT
CO poisoning	Normal	↓ (CO competes with O <sub>2</sub> )	Normal	1
Anemia	<b>†</b>	Normal	Normal	<b>†</b>
Polycythemia	†	Normal	Normal	<b>†</b>

### Methemoglobin

Iron in Hb is normally in a reduced state (ferrous Fe<sup>2+</sup>; "just the 2 of us").

Oxidized form of Hb (ferric, Fe³+) does not bind O₂ as readily as Fe²+, but has ↑ affinity for cyanide → tissue hypoxia from ↓ O₂ saturation and ↓ O₂ content.

Methemoglobinemia may present with cyanosis and chocolate-colored blood.

Nitrites (eg, from dietary intake or polluted/ high-altitude water sources) and benzocaine cause poisoning by oxidizing Fe<sup>2+</sup> to Fe<sup>3+</sup>. **Meth**emoglobinemia can be treated with

methylene blue and vitamin C.

# Oxygen-hemoglobin dissociation curve

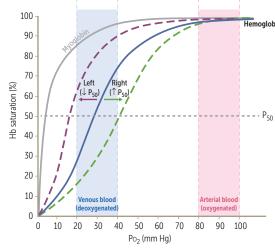
ODC has sigmoidal shape due to positive cooperativity (ie, tetrameric Hb molecule can bind 4 O<sub>2</sub> molecules and has higher affinity for each subsequent O<sub>2</sub> molecule bound). Myoglobin is monomeric and thus does not show positive cooperativity; curve lacks sigmoidal appearance.

Shifting ODC to the right  $\rightarrow \downarrow$  Hb affinity for O<sub>2</sub> (facilitates unloading of O<sub>2</sub> to tissue)  $\rightarrow \uparrow$  P<sub>50</sub> (higher Po<sub>2</sub> required to maintain 50% saturation).

Shifting ODC to the left  $\rightarrow \downarrow O_2$  unloading

- → renal hypoxia → † EPO synthesis
- → compensatory erythrocytosis.

Fetal Hb (2  $\alpha$  and 2  $\gamma$  subunits) has higher affinity for O<sub>2</sub> than adult Hb (due to  $\downarrow$  affinity for 2,3-BPG)  $\rightarrow$  dissociation curve is shifted left, driving diffusion of O<sub>2</sub> across the placenta from mother to fetus.



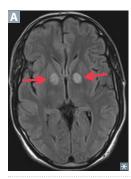
Left shift $(\downarrow O_2 \text{ unloading to tissue})$ Left = Lower	Right shift  (↑ O <sub>2</sub> unloading to tissues)  ACE BATs right handed
↓ H <sup>+</sup> (↑ pH, base) ↓ Pco <sub>2</sub> ↓ 2,3-BPG ↓ Temperature ↑ CO ↑ MetHb ↑ HbF	↑H <sup>+</sup> (↓ pH, Acid) ↑Pco <sub>2</sub> Exercise ↑2,3-BPG High Altitude ↑ Temperature

ľχ

FAS1\_2019\_16-Respiratory.indd 666 11/8/19 7:34 AM

#### **Cyanide vs carbon** Both inhibit aerobic metabolism via inhibition of complex IV (cytochrome c oxidase) → hypoxia monoxide poisoning that does not fully correct with supplemental O<sub>2</sub> and † anaerobic metabolism. Both can lead to pink or cherry red skin (usually postmortem finding), seizures, and coma. Cyanide Carbon monoxide SOURCE Byproduct of synthetic product combustion, Odorless gas from fires, car exhaust, or gas ingestion of amygdalin (cyanogenic glucoside heaters. found in apricot seeds) or cyanide. TREATMENT Hydroxocobalamin (binds cyanide 100% O<sub>2</sub>, hyperbaric O<sub>2</sub>. → cyanocobalamin → renal excretion). Nitrites (oxidize Hb → methemoglobin → binds cyanide → cyanomethemoglobin → less toxicity). Sodium thiosulfate († cyanide conversion to thiocyanate → renal excretion).

#### SIGNS/SYMPTOMS



Breath has bitter almond odor; cardiovascular collapse.

Headache, dizziness.

Multiple individuals may be involved (eg, family with similar symptoms in winter).

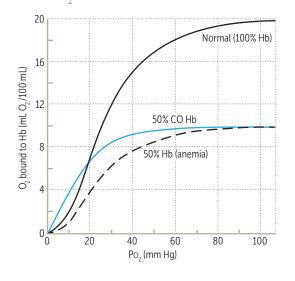
Classically associated with bilateral globus pallidus lesions on MRI A, although rarely seen with cyanide toxicity as well.

EFFECT ON OXYGEN-HEMOGLOBIN DISSOCIATION CURVE

Curve normal; oxygen saturation may appear normal initially.

Left shift in curve  $\rightarrow \uparrow$  affinity for  $O_2 \rightarrow \downarrow O_2$  unloading in tissues.

Binds competitively to Hb with 200× greater affinity than O<sub>2</sub> to form carboxyhemoglobin → ↓ %O<sub>2</sub> saturation of Hb.



FAS1\_2019\_16-Respiratory.indd 667 11/8/19 7:34 AM

SECTION III

#### **RESPIRATORY** ▶ RESPIRATORY—PHYSIOLOGY

#### **Pulmonary circulation**

Normally a low-resistance, high-compliance system. A ↓ in PAO<sub>2</sub> causes a hypoxic vasoconstriction that shifts blood away from poorly ventilated regions of lung to well-ventilated regions of lung.

Perfusion limited— $O_2$  (normal health),  $CO_2$ ,  $N_2O$ . Gas equilibrates early along the length of the capillary. Exchange can be † only if blood flow †.

Diffusion limited—O<sub>2</sub> (emphysema, fibrosis, exercise), CO. Gas does not equilibrate by the time blood reaches the end of the capillary.

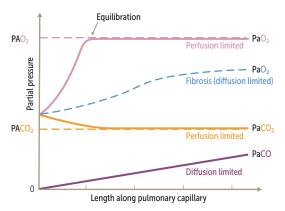
A consequence of pulmonary hypertension is cor pulmonale and subsequent right ventricular failure.

Diffusion: 
$$\dot{V}_{gas} = A \times D_k \times \frac{P_1 - P_2}{\Delta_v}$$
 where

A = area,  $\Delta_x$  = alveolar wall thickness,  $D_k$  = diffusion coefficient of gas,  $P_1 - P_2$ = difference in partial pressures.

- A ↓ in emphysema.
- $\Delta_x$  † in pulmonary fibrosis.

DLCO is the extent to which CO passes from air sacs of lungs into blood.



Ŗ

11/8/19 7:34 AM

Pa = partial pressure of gas in pulmonary capillary blood PA = partial pressure of gas in alveolar air

# Pulmonary vascular resistance

$$PVR = \frac{P_{pulm \ artery} - P_{L \ atrium}}{O}$$

Remember:  $\Delta P = Q \times R$ , so  $R = \Delta P / Q$ 

$$R = \frac{8\eta l}{\pi r^4}$$

 $P_{\text{pulm artery}} = \text{pressure in pulmonary artery}$  $P_{\text{Latrium}} \approx \text{pulmonary capillary wedge pressure}$ 

Q = cardiac output (flow)

R = resistance

 $\eta$  = viscosity of blood

l = vessel length

r = vessel radius

# Alveolar gas equation

$$PAO_2 = PIO_2 - \frac{PacO_2}{R}$$

$$\approx 150 \text{ mm Hg}^{a} - \frac{\text{Paco}_{2}}{0.8}$$

<sup>a</sup>At sea level breathing room air

PAO<sub>2</sub> = alveolar PO<sub>2</sub> (mm Hg)

 $PIO_2 = PO_2$  in inspired air (mm Hg)

Paco<sub>2</sub> = arterial Pco<sub>2</sub> (mm Hg) R = respiratory quotient = CO<sub>2</sub> produced/

O<sub>2</sub> consumed

A-a gradient = PAO<sub>2</sub> - PaO<sub>2</sub>. Normal A-a gradient estimated as (age/4) + 4 (eg, for a person <40 years old, gradient should be <14).

FAS1\_2019\_16-Respiratory.indd 668

#### **Oxygen deprivation**

Hypoxia (↓ O <sub>2</sub> delivery to tissue)	Hypoxemia (↓ Pao₂)	Ischemia (loss of blood flow)
↓ cardiac output	Normal A-a gradient	Impeded arterial flow
Hypoxemia	<ul> <li>High altitude</li> </ul>	↓ venous drainage
Ischemia	<ul> <li>Hypoventilation (eg, opioid use,</li> </ul>	
Anemia	obesity hypoventilation syndrome)	
CO poisoning	↑ A-a gradient	
	<ul> <li>V/Q mismatch</li> </ul>	
	<ul> <li>Diffusion limitation (eg, fibrosis)</li> </ul>	
	<ul> <li>Right-to-left shunt</li> </ul>	

# Ventilation/perfusion mismatch

Ideally, ventilation is matched to perfusion (ie,  $\dot{V} | \dot{Q} = 1$ ) for adequate gas exchange.

Lung zones:

- $\dot{V}/\dot{Q}$  at apex of lung = 3 (wasted ventilation)
- V/Q at base of lung = 0.6 (wasted perfusion)

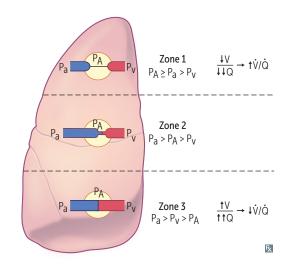
  Both ventilation and perfusion are greater at the base of the lung than at the apex of the lung.

  With exercise (↑ cardiac output), there is vasodilation of apical capillaries → V/Q ratio approaches 1.

Certain organisms that thrive in high  $O_2$  (eg, TB) flourish in the apex.

 $\dot{V}/\dot{Q} = 0$  = "oirway" obstruction (shunt). In shunt, 100% O<sub>2</sub> does not improve Pao<sub>2</sub> (eg, foreign body aspiration).

V/Q = ∞ = blood flow obstruction (physiologic dead space). Assuming < 100% dead space, 100% O<sub>2</sub> improves Pao<sub>2</sub> (eg, pulmonary embolus).



FAS1\_2019\_16-Respiratory.indd 669 11/8/19 7:34 AM

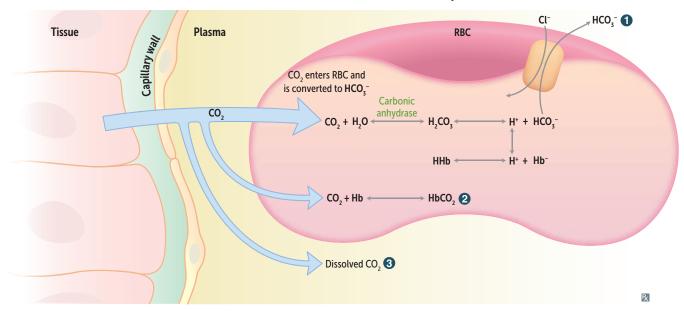
# Carbon dioxide transport

CO<sub>2</sub> is transported from tissues to lungs in 3 forms:

- 1 HCO<sub>3</sub>- (70%).
- 2 Carbaminohemoglobin or HbCO<sub>2</sub> (21–25%). CO<sub>2</sub> bound to Hb at N-terminus of globin (not heme). CO<sub>2</sub> favors deoxygenated form (O<sub>2</sub> unloaded).
- **3** Dissolved CO<sub>2</sub> (5–9%).

In lungs, oxygenation of Hb promotes dissociation of H $^+$  from Hb. This shifts equilibrium toward CO $_2$  formation; therefore, CO $_2$  is released from RBCs (Haldane effect). In peripheral tissue, † H $^+$  from tissue metabolism shifts curve to right, unloading O $_2$  (Bohr effect).

Majority of blood CO<sub>2</sub> is carried as HCO<sub>3</sub><sup>-</sup> in the plasma.



# Response to high altitude

↓ atmospheric oxygen (PiO<sub>2</sub>) → ↓ Pao<sub>2</sub> → ↑ ventilation → ↓ Paco<sub>2</sub> → respiratory alkalosis → altitude sickness.

Chronic † in ventilation.

↑ erythropoietin → ↑ Het and Hb (due to chronic hypoxia).

† 2,3-BPG (binds to Hb causing rightward shift of the ODC so that Hb releases more O<sub>2</sub>).

Cellular changes († mitochondria).

† renal excretion of HCO<sub>3</sub><sup>-</sup> to compensate for respiratory alkalosis (can augment with acetazolamide).

Chronic hypoxic pulmonary vasoconstriction results in pulmonary hypertension and RVH.

#### Response to exercise

† CO, production.

† O, consumption.

Right shift of ODC.

† ventilation rate to meet O, demand.

V/Q ratio from apex to base becomes more uniform.

† pulmonary blood flow due to † cardiac output.

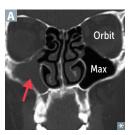
↓ pH during strenuous exercise (2° to lactic acidosis).

No change in Pao, and Paco₂, but † in venous CO₂ content and ↓ in venous O₂ content.

FAS1\_2019\_16-Respiratory.indd 670 11/8/19 7:34 AM

#### ▶ RESPIRATORY—PATHOLOGY

#### **Rhinosinusitis**



Obstruction of sinus drainage into nasal cavity  $\rightarrow$  inflammation and pain over affected area. Typically affects maxillary sinuses, which drain against gravity due to ostia located superomedially (red arrow points to fluid-filled right maxillary sinus in A).

Superior meatus—drains sphenoid, posterior ethmoid; middle meatus—drains frontal, maxillary, and anterior ethmoid; inferior meatus—drains nasolacrimal duct.

Most common acute cause is viral URI; may lead to superimposed bacterial infection, most commonly *H influenzae*, *S pneumoniae*, *M catarrhalis*.

Paranasal sinus infections may extend to the orbits, cavernous sinus, and brain, causing complications (eg, orbital cellulitis, cavernous sinus syndrome, meningitis).

#### **Epistaxis**

Nose bleed. Most commonly occurs in anterior segment of nostril (Kiesselbach plexus). Life-threatening hemorrhages occur in posterior segment (sphenopalatine artery, a branch of maxillary artery). Common causes include foreign body, trauma, allergic rhinitis, and nasal angiofibromas (common in adolescent males).

Kiesselbach drives his Lexus with his LEGS: superior Labial artery, anterior and posterior Ethmoidal arteries, Greater palatine artery, Sphenopalatine artery.

#### Head and neck cancer

Mostly squamous cell carcinoma. Risk factors include tobacco, alcohol, HPV-16 (oropharyngeal), EBV (nasopharyngeal). Field cancerization: carcinogen damages wide mucosal area → multiple tumors that develop independently after exposure.

# Deep venous thrombosis



Blood clot within a deep vein → swelling, redness A, warmth, pain. Predisposed by Virchow triad (SHE):

- Stasis (eg, post-op, long drive/flight)
- Hypercoagulability (eg, defect in coagulation cascade proteins, such as factor V Leiden; oral contraceptive use; pregnancy)
- Endothelial damage (exposed collagen triggers clotting cascade)

Most pulmonary emboli arise from proximal deep veins of lower extremity.

D-dimer lab test used clinically to rule out DVT in low-to-moderate risk patients (high sensitivity, low specificity).

Imaging test of choice is compression ultrasound with Doppler.

Use unfractionated heparin or low-molecular weight heparins (eg, enoxaparin) for prophylaxis and acute management.

Use oral anticoagulants (eg, rivaroxaban, apixaban) for treatment and long-term prevention.

FAS1\_2019\_16-Respiratory.indd 671 11/8/19 7:34 AM

neurologic abnormalities, petechial rash.

#### **Pulmonary emboli**

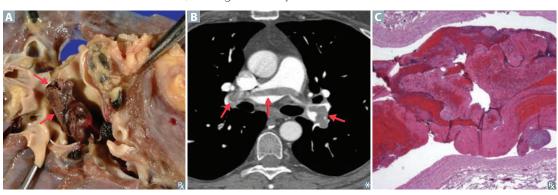
V/Q mismatch, hypoxemia, respiratory alkalosis. Sudden-onset dyspnea, pleuritic chest pain, tachypnea, tachycardia. Large emboli or saddle embolus ♠ may cause sudden death due to electromechanical dissociation (pulseless electrical activity). CT pulmonary angiography is imaging test of choice for PE (look for filling defects) ▶ May have S1Q3T3 abnormality on ECG. Lines of Zahn ☑ are interdigitating areas of pink (platelets, fibrin) and red (RBCs) found only in

thrombi formed before death; help distinguish pre- and postmortem thrombi.

Types: Fat, Air, Thrombus, Bacteria, Amniotic fluid, Tumor. An embolus moves like a FAT BAT.

Fat emboli—associated with long bone fractures and liposuction; classic triad of hypoxemia,

Air emboli—nitrogen bubbles precipitate in ascending divers (caisson disease/decompression sickness); treat with hyperbaric O<sub>2</sub>; or, can be iatrogenic 2° to invasive procedures (eg, central line placement). Amniotic fluid emboli—typically occurs during labor or postpartum, but can be due to uterine trauma. Can lead to DIC. Rare, but high mortality.



#### **Mediastinal pathology**

Normal mediastinum contains heart, thymus, lymph nodes, esophagus, and aorta.

#### **Mediastinal masses**

Some pathologies (eg, lymphoma, lung cancer, abscess) can occur in any compartment, but there are common associations:

- Anterior—4T's: Thyroid (substernal goiter), Thymic neoplasm, Teratoma, "Terrible" lymphoma.
- Middle—esophageal carcinoma, metastases, hiatal hernia, bronchogenic cysts.
- Posterior—neurogenic tumor (eg, neurofibroma), multiple myeloma.

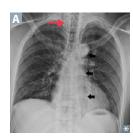
#### Mediastinitis

Inflammation of mediastinal tissues. Commonly due to postoperative complications of cardiothoracic procedures (≤ 14 days), esophageal perforation, or contiguous spread of odontogenic/retropharyngeal infection.

Chronic mediastinitis—also known as fibrosing mediastinitis; due to † proliferation of connective tissue in mediastinum. *Histoplasma capsulatum* is common cause.

Clinical features: fever, tachycardia, leukocytosis, chest pain, and sternal wound drainage.

#### **Pneumomediastinum**



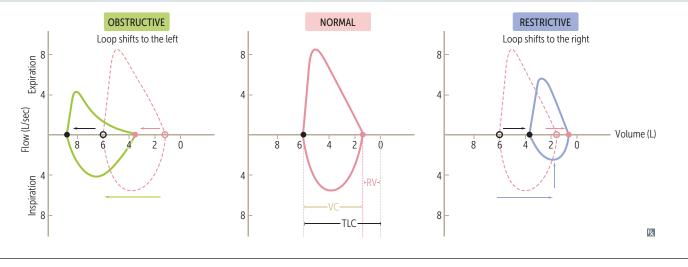
Presence of gas (usually air) in the mediastinum (black arrows show air around the aorta, red arrow shows air dissecting into the neck A). Can either be spontaneous (due to rupture of pulmonary bleb) or 2° (eg, trauma, iatrogenic, Boerhaave syndrome).

Ruptured alveoli allow tracking of air into the mediastinum via peribronchial and perivascular sheaths. Clinical features: chest pain, dyspnea, voice change, subcutaneous emphysema,  $\oplus$  Hamman sign (crepitus on cardiac auscultation).

FAS1\_2019\_16-Respiratory.indd 672 11/8/19 7:34 AM

## Flow-volume loops

FLOW-VOLUME PARAMETER	Obstructive lung disease	Restrictive lung disease
RV	†	<b>↓</b>
FRC	<b>†</b>	<b>↓</b>
TLC	†	↓
FEV <sub>1</sub>	<b>‡</b> ‡	<b>↓</b>
FVC	<b>↓</b>	↓
FEV <sub>1</sub> /FVC	<b>\</b>	Normal or †
	FEV <sub>1</sub> decreased more than FVC	FEV <sub>1</sub> decreased proportionately to FVC



11/8/19 7:34 AM FAS1\_2019\_16-Respiratory.indd 673

# Obstructive lung diseases

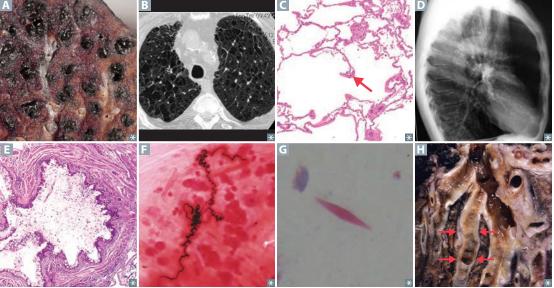
Obstruction of air flow  $\rightarrow$  air trapping in lungs. Airways close prematurely at high lung volumes  $\rightarrow$  † FRC, † RV, † TLC. PFTs: ‡‡ FEV<sub>1</sub>, ‡ FVC  $\rightarrow$  ‡ FEV<sub>1</sub>/FVC ratio (hallmark),  $\dot{V}\dot{Q}$  mismatch. Chronic hypoxic pulmonary vasoconstriction can lead to cor pulmonale. Chronic obstructive pulmonary disease (COPD) includes chronic bronchitis and emphysema. "FRiCkin' RV needs some increased TLC, but it's hard with COPD!"

ТҮРЕ	PRESENTATION	PATHOLOGY	OTHER
Chronic bronchitis ("blue bloater")	Findings: wheezing, crackles, cyanosis (hypoxemia due to shunting), dyspnea, CO <sub>2</sub> retention, 2° polycythemia.	Hypertrophy and hyperplasia of mucus-secreting glands in bronchi → Reid index (thickness of mucosal gland layer to thickness of wall between epithelium and cartilage) > 50%. DLCO usually normal.	Diagnostic criteria: productive cough for ≥ 3 months in a year for > 2 consecutive years.
Emphysema ("pink puffer")  Normal  Centriacinar emphysema  Panacinar emphysema	Findings: barrel-shaped chest , exhalation through pursed lips (increases airway pressure and prevents airway collapse).	Centriacinar—affects respiratory bronchioles while sparing distal alveoli, associated with smoking A  B. Frequently in upper lobes (smoke rises up).  Panacinar—affects respiratory bronchioles and alveoli, associated with α₁-antitrypsin deficiency. Frequently in lower lobes.  Enlargement of air spaces ↓ recoil, ↑ compliance, ↓ DLCO from destruction of alveolar walls (arrow in C) and ↓ blood volume in pulmonary capillaries.  Imbalance of proteases and antiproteases → ↑ elastase activity → ↑ loss of elastic fibers → ↑ lung compliance.	CXR: † AP diameter, flattened diaphragm, † lung field lucency.
Asthma	Findings: cough, wheezing, tachypnea, dyspnea, hypoxemia, ↓ inspiratory/ expiratory ratio, pulsus paradoxus, mucus plugging ■.  Triggers: viral URIs, allergens, stress.	Hyperresponsive bronchi → reversible bronchoconstriction.  Smooth muscle hypertrophy and hyperplasia, Curschmann spirals  (shed epithelium forms whorled mucous plugs), and Charcot-Leyden crystals  (eosinophilic, hexagonal, double-pointed crystals formed from breakdown of eosinophils in sputum). DLCO normal or ↑.	Type I hypersensitivity reaction.  Diagnosis supported by spirometry and methacholine challenge.  NSAID-exacerbated respiratory disease is a combination of COX inhibition (leukotriene overproduction → airway constriction), chronic sinusitis with nasal polyps, and asthma symptoms.

FAS1\_2019\_16-Respiratory.indd 674 11/8/19 7:34 AM

#### **Obstructive lung diseases (continued)**

ТҮРЕ	PRESENTATION	PATHOLOGY	OTHER
Bronchiectasis	Findings: purulent sputum, recurrent infections (most often <i>P aeruginosa</i> ), hemoptysis, digital clubbing.	Chronic necrotizing infection of bronchi or obstruction  → permanently dilated airways.	Associated with bronchial obstruction, poor ciliary motility (eg, smoking, Kartagener syndrome), cystic fibrosis H, allergic bronchopulmonary aspergillosis.
A D D			



# Restrictive lung diseases



Restricted lung expansion causes \$\frac{1}{2}\$ lung volumes (\$\frac{1}{2}\$ FVC and TLC). PFTs: \$\frac{1}{2}\$ FEV\_1/FVC ratio. Patient presents with short, shallow breaths.

### Types:

- Poor breathing mechanics (extrapulmonary, normal D<sub>LCO</sub>, normal A-a gradient):
  - Poor muscular effort—polio, myasthenia gravis, Guillain-Barré syndrome
  - Poor structural apparatus—scoliosis, morbid obesity
- Interstitial lung diseases (pulmonary,  $\downarrow$  D<sub>LCO</sub>,  $\uparrow$  A-a gradient):
  - Pneumoconioses (eg, coal workers' pneumoconiosis, silicosis, asbestosis)
  - Sarcoidosis: bilateral hilar lymphadenopathy, noncaseating granulomas; ↑ ACE and Ca<sup>2+</sup>
  - Idiopathic pulmonary fibrosis (repeated cycles of lung injury and wound healing with
     † collagen deposition, "honeycomb" lung appearance [red arrows in A], traction
     bronchiectasis [blue arrow in A] and digital clubbing).
  - Granulomatosis with polyangiitis (Wegener)
  - Pulmonary Langerhans cell histiocytosis (eosinophilic granuloma)
  - Hypersensitivity pneumonitis
  - Drug toxicity (eg, bleomycin, busulfan, amiodarone, methotrexate)

Hypersensitivity pneumonitis—mixed type III/IV hypersensitivity reaction to environmental antigen. Causes dyspnea, cough, chest tightness, fever, headache. Often seen in farmers and those exposed to birds. Reversible in early stages if stimulus is avoided.

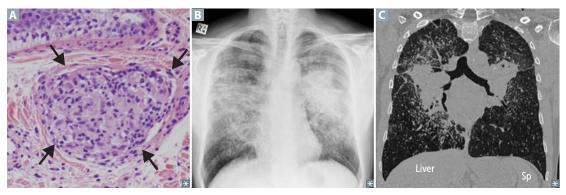
FAS1\_2019\_16-Respiratory.indd 675 11/8/19 7:34 AM

#### **Sarcoidosis**

Characterized by immune-mediated, widespread noncaseating granulomas A, elevated serum ACE levels, and elevated CD4/CD8 ratio in bronchoalveolar lavage fluid. More common in African-American females. Often asymptomatic except for enlarged lymph nodes. CXR shows bilateral adenopathy and coarse reticular opacities B; CT of the chest better demonstrates the extensive hilar and mediastinal adenopathy .

Associated with **Bell palsy**, **U**veitis, **G**ranulomas (noncaseating epithelioid, containing microscopic Schaumann and asteroid bodies), **L**upus pernio (skin lesions on face resembling lupus), **I**nterstitial fibrosis (restrictive lung disease), **E**rythema nodosum, **R**heumatoid arthritis-like arthropathy, hypercalcemia (due to † lα-hydroxylase–mediated vitamin D activation in macrophages). A **facial droop** is **UGLIER**.

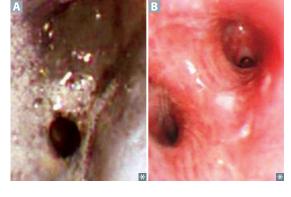
Treatment: steroids (if symptomatic).



# Inhalation injury and sequelae

Complication of inhalation of noxious stimuli (eg, smoke). Caused by heat, particulates (< 1 µm diameter), or irritants (eg, NH<sub>3</sub>) → chemical tracheobronchitis, edema, pneumonia, ARDS. Many patients present 2° to burns, CO inhalation, cyanide poisoning, or arsenic poisoning. Singed nasal hairs or soot in oropharynx common on exam.

Bronchoscopy shows severe edema, congestion of bronchus, and soot deposition (A, 18 hours after inhalation injury; B, resolution at 11 days after injury).



FAS1\_2019\_16-Respiratory.indd 676 11/8/19 7:34 AM

DECDIDATABLE		
RESPIRATORY	▶ RESPIRATORY—	-PATHOLOGY

Pneumoconioses	Asbestos is from the roof (was common in insula Silica and coal are from the base (earth), but affective the coal are from the base (earth).	
Asbestosis	Associated with shipbuilding, roofing, plumbing. "Ivory white," calcified, supradiaphragmatic A and pleural plaques are pathognomonic of asbestosis.  Risk of bronchogenic carcinoma > risk of mesothelioma. † risk of Caplan syndrome (rheumatoid arthritis and pneumoconioses with intrapulmonary nodules).	Affects lower lobes. Asbestos (ferruginous) bodies are golden-brown fusiform rods resembling dumbbells C, found in alveolar sputum sample, visualized using Prussian blue stain, often obtained by bronchoalveolar lavage.  † risk of pleural effusions.
Berylliosis	Associated with exposure to beryllium in aerospace and manufacturing industries. Granulomatous (noncaseating)  on histology and therefore occasionally responsive to steroids. † risk of cancer and cor pulmonale.	Affects upper lobes.
Coal workers' pneumoconiosis	Prolonged coal dust exposure → macrophages laden with carbon → inflammation and fibrosis.  Also known as black lung disease. ↑ risk of Caplan syndrome.	Affects upper lobes.  Small, rounded nodular opacities seen on imaging.  Anthracosis—asymptomatic condition found in many urban dwellers exposed to sooty air.
Silicosis	Associated with sandblasting, foundries, mines. Macrophages respond to silica and release fibrogenic factors, leading to fibrosis. It is thought that silica may disrupt phagolysosomes and impair macrophages, increasing susceptibility to TB. † risk of cancer, cor pulmonale, and Caplan syndrome.	Affects upper lobes.  "Eggshell" calcification of hilar lymph nodes on CXR.  The silly egg sandwich I found is mine!
	A B B C C C C C C C C C C C C C C C C C	C D

FAS1\_2019\_16-Respiratory.indd 677 11/8/19 7:34 AM

## **RESPIRATORY** ▶ RESPIRATORY—PATHOLOGY

## Mesothelioma



Malignancy of the pleura associated with asbestosis. May result in hemorrhagic pleural effusion (exudative), pleural thickening A.

Psammoma bodies seen on histology. Calretinin and cytokeratin 5/6 ⊕ in almost all mesotheliomas, ⊝ in most carcinomas. Smoking not a risk factor.

## **Acute respiratory distress syndrome**

	· · · · · · · · · · · · · · · · · · ·
PATHOPHYSIOLOGY	Alveolar insult → release of pro-inflammatory cytokines → neutrophil recruitment, activation, and release of toxic mediators (eg, reactive oxygen species, proteases, etc) → capillary endothelial damage and ↑ vessel permeability → leakage of protein-rich fluid into alveoli → formation of intra-alveolar hyaline membranes (arrows in A) and noncardiogenic pulmonary edema (normal PCWP).  Loss of surfactant also contributes to alveolar collapse.
CAUSES	Sepsis (most common), aspiration, pneumonia, trauma, pancreatitis.
DIAGNOSIS	Diagnosis of exclusion with the following criteria (ARDS):  Abnormal chest X-ray (bilateral lung opacities)  Respiratory failure within 1 week of alveolar insult  Decreased Pao <sub>3</sub> /Fio <sub>3</sub> (ratio < 300, hypoxemia due to † intrapulmonary shunting and diffusion

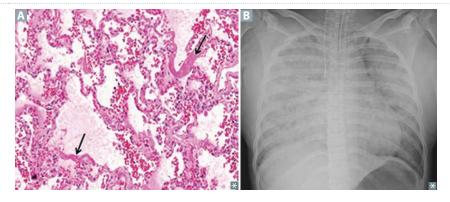
Decreased Pao<sub>2</sub>/Fio<sub>2</sub> (ratio < 300, hypoxemia due to † intrapulmonary shunting and diffusion abnormalities)</li>

• Symptoms of respiratory failure are not due to HF/fluid overload

CONSEQUENCES Impaired gas exchange, ↓ lung compliance; pulmonary hypertension.

MANAGEMENT Treat the underlying cause.

Mechanical ventilation: ↓ tidal volume, ↑ PEEP.



FAS1\_2019\_16-Respiratory.indd 678 11/8/19 7:34 AM

Sleep apnea	Repeated cessation of breathing > 10 seconds during sleep → disrupted sleep → daytime somnolence. Diagnosis confirmed by sleep study.  Nocturnal hypoxia → systemic/pulmonary hypertension, arrhythmias (atrial fibrillation/flutter), sudden death.	
Obstructive sleep apnea	Hypoxia → ↑ EPO release → ↑ erythropoiesis.  Respiratory effort against airway obstruction. Normal Pao <sub>2</sub> during the day. Associated with obesity, loud snoring, daytime sleepiness. Caused by excess parapharyngeal tissue in adults, adenotonsillar hypertrophy in children. Treatment: weight loss, CPAP, dental devices.	
Central sleep apnea	Impaired respiratory effort due to CNS injury/toxicity, HF, opioids. May be associated with Cheyne-Stokes respirations (oscillations between apnea and hyperpnea). Think 3 C's: Congest HF, CNS toxicity, Cheyne-Stokes respirations. Treat with positive airway pressure.	
Obesity hypoventilation syndrome	Obesity (BMI ≥ 30 kg/m²) → hypoventilation → ↑ Paco <sub>2</sub> during waking hours (retention); ↓ Pao <sub>2</sub> and ↑ Paco <sub>2</sub> during sleep. Also known as Pickwickian syndrome.	
Pulmonary hypertension	Normal mean pulmonary artery pressure = 10–14 mm Hg; pulmonary hypertension ≥ 25 mm Hg at rest. Results in arteriosclerosis, medial hypertrophy, intimal fibrosis of pulmonary arteries, plexiform lesions. Course: severe respiratory distress → cyanosis and RVH → death from decompensated cor pulmonale.	
Pulmonary arterial hypertension	Often idiopathic. Heritable PAH can be due to an inactivating mutation in <i>BMPR2</i> gene (normally inhibits vascular smooth muscle proliferation); poor prognosis. Pulmonary vasculature endothelial dysfunction results in † vasoconstrictors (eg, endothelin) and ↓ vasodilators (eg, NO and prostacyclins).  Other causes include drugs (eg, amphetamines, cocaine), connective tissue disease, HIV infection, portal hypertension, congenital heart disease, schistosomiasis.	
Left heart disease	Causes include systolic/diastolic dysfunction and valvular disease.	
Lung diseases or hypoxia	Destruction of lung parenchyma (eg, COPD), lung inflammation/fibrosis (eg, interstitial lung diseases), hypoxemic vasoconstriction (eg, obstructive sleep apnea, living in high altitude).	
Chronic thromboembolic	Recurrent microthrombi → ↓ cross-sectional area of pulmonary vascular bed.	
Multifactorial	Causes include hematologic, systemic, and metabolic disorders, along with compression of the pulmonary vasculature by a tumor.	

11/8/19 7:34 AM FAS1\_2019\_16-Respiratory.indd 679

## Physical findings in select lung diseases

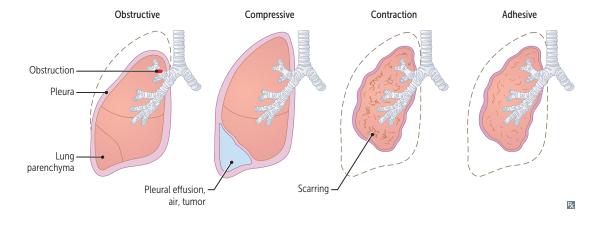
ABNORMALITY	BREATH SOUNDS	PERCUSSION	FREMITUS	TRACHEAL DEVIATION
Pleural effusion	1	Dull	1	None if small Away from side of lesion if large
Atelectasis	ļ	Dull	<b>†</b>	Toward side of lesion
Simple pneumothorax	ļ	Hyperresonant	<b>†</b>	None
Tension pneumothorax	1	Hyperresonant	ţ	Away from side of lesion
Consolidation (lobar pneumonia, pulmonary edema)	Bronchial breath sounds; late inspiratory crackles, egophony, whispered pectoriloquy	Dull	<b>†</b>	None

## **Atelectasis**



Alveolar collapse (right upper lobe collapse against mediastinum in A). Multiple causes:

- Obstructive—airway obstruction prevents new air from reaching distal airways, old air is resorbed (eg, foreign body, mucous plug, tumor)
- Compressive—external compression on lung decreases lung volumes (eg, space-occupying lesion, pleural effusion)
- Contraction (cicatrization)—scarring of lung parenchyma that distorts alveoli (eg, sarcoidosis)
- Adhesive—due to lack of surfactant (eg, NRDS in premature babies)



FAS1\_2019\_16-Respiratory.indd 680 11/8/19 7:34 AM

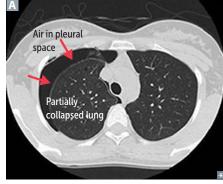
Pleural effusions	Excess accumulation of fluid ⚠ between pleural layers → restricted lung expansion during inspiration. Can be treated with thoracentesis to remove/reduce fluid ▶.		
Lymphatic	Also known as chylothorax. Due to thoracic duct injury from trauma or malignancy. Milky-appearing fluid; † triglycerides.		
Exudate	† protein content (> 2.9 g/dL), cloudy (cellular). Due to malignancy, inflammation/infection (eg, pneumonia, collagen vascular disease), trauma (occurs in states of † vascular permeability). Must be drained due to risk of infection.		
Transudate	↓ protein content (< 2.5 g/dL), clear (hypocellular). Due to ↑ hydrostatic pressure (eg, HF, Na <sup>+</sup> retention) or ↓ oncotic pressure (eg, nephrotic syndrome, cirrhosis).		
	Normal	Exudate	Transudate
	Hydrostatic pressure		Increased hydrostatic pressure
	Colloid osmotic pressure	 Fluid and protein leakage	Decreased colloid osmotic pressure
	♥ Plasma proteins		↓   Fluid leakage ■
	Pretreatment	Pretreatment ** Post-treatment	Post-treatment **

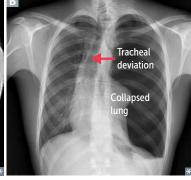
11/8/19 7:34 AM FAS1\_2019\_16-Respiratory.indd 681

682 SECTION III

# **RESPIRATORY** → RESPIRATORY—PATHOLOGY

Pneumothorax	Accumulation of air in pleural space ⚠. Dyspnea, uneven chest expansion. Chest pain, ↓ tactile fremitus, hyperresonance, and diminished breath sounds, all on the affected side.
Primary spontaneous pneumothorax	Due to rupture of apical subpleural bleb or cysts. Occurs most frequently in tall, thin, young males and smokers.
Secondary spontaneous pneumothorax	Due to diseased lung (eg, bullae in emphysema, infections), mechanical ventilation with use of high pressures → barotrauma.
Traumatic pneumothorax	Caused by blunt (eg, rib fracture), penetrating (eg, gunshot), or iatrogenic (eg, central line placement, lung biopsy, barotrauma due to mechanical ventilation) trauma.
Tension pneumothorax	Can be from any of the above. Air enters pleural space but cannot exit. Increasing trapped air  → tension pneumothorax. Trachea deviates away from affected lung B. May lead to increased intrathoracic pressure → mediastinal displacement → kinking of IVC → ↓ venous return  → ↓ cardiac output. Needs immediate needle decompression and chest tube placement.





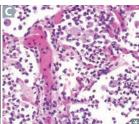
FAS1\_2019\_16-Respiratory.indd 682 11/8/19 7:34 AM

## **Pneumonia**

ТҮРЕ	TYPICAL ORGANISMS	CHARACTERISTICS
Lobar pneumonia	S pneumoniae most frequently, also Legionella, Klebsiella	Intra-alveolar exudate → consolidation A; may involve entire lobe B or the whole lung.
Bronchopneumonia	S pneumoniae, S aureus, H influenzae, Klebsiella	Acute inflammatory infiltrates <b>C</b> from bronchioles into adjacent alveoli; patchy distribution involving ≥ 1 lobe <b>D</b> .
Interstitial (atypical) pneumonia	Mycoplasma, Chlamydophila pneumoniae, Chlamydophila psittaci, Legionella, viruses (RSV, CMV, influenza, adenovirus)	Diffuse patchy inflammation localized to interstitial areas at alveolar walls; CXR shows bilateral multifocal opacities <b>E</b> . Generally follows a more indolent course ("walking" pneumonia).
Cryptogenic organizing pneumonia	Etiology unknown. Secondary organizing pneumonia is caused by chronic inflammatory diseases (eg, rheumatoid arthritis) or medication side effects (eg, amiodarone).	Formerly known as bronchiolitis obliterans organizing pneumonia (BOOP). Noninfectious pneumonia characterized by inflammation of bronchioles and surrounding structure.











## **Natural history of lobar pneumonia**

	Congestion	Red hepatization	Gray hepatization	Resolution
DAYS	1–2	3–4	5–7	8+
FINDINGS	Red-purple, partial consolidation of parenchyma Exudate with mostly bacteria	Red-brown consolidation Exudate with fibrin, bacteria, RBCs, WBCs Reversible	Uniformly gray Exudate full of WBCs, lysed RBCs, and fibrin	Enzymatic digestion of exudate by macrophages

11/8/19 7:34 AM FAS1\_2019\_16-Respiratory.indd 683

## **Lung cancer**

Leading cause of cancer death.

Presentation: cough, hemoptysis, bronchial obstruction, wheezing, pneumonic "coin" lesion on CXR or noncalcified nodule on CT. Sites of metastases from lung cancer: Liver (jaundice, hepatomegaly), Adrenals, Bone (pathologic fracture), Brain; "Lung 'mets' Love Affective Boneheads and Brainiacs." In the lung, metastases (usually multiple lesions) are more common than 1° neoplasms. Most often from breast, colon,

**SPHERE** of complications:

Superior vena cava/thoracic outlet syndromes

Pancoast tumor

Horner syndrome

Endocrine (paraneoplastic)

Recurrent laryngeal nerve compression (hoarseness)

Effusions (pleural or pericardial)

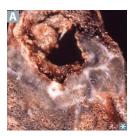
Risk factors include smoking, secondhand smoke, radon, asbestos, family history.

Squamous and Small cell carcinomas are Sentral (central) and often caused by Smoking.

		d bladder cancer. (central) and often caus	ed by <b>S</b> moking.
ТҮРЕ	LOCATION	CHARACTERISTICS	HISTOLOGY
Small cell			
Small cell (oat cell) carcinoma	Central	Undifferentiated → very aggressive.  May produce ACTH (Cushing syndrome), ADH (SIADH), or Antibodies against presynaptic Ca²+ channels (Lambert-Eaton myasthenic syndrome) or neurons (paraneoplastic myelitis, encephalitis, subacute cerebellar degeneration). Amplification of <i>myc</i> oncogenes common. Managed with chemotherapy +/- radiation.	Neoplasm of neuroendocrine Kulchitsky cells → small dark blue cells A. Chromogranin A ⊕, neuron-specific enolase ⊕, synaptophysin ⊕.
Non-small cell			
Adenocarcinoma	Peripheral	Most common 1° lung cancer. More common in women than men, most likely to arise in nonsmokers. Activating mutations include <i>KRAS</i> , <i>EGFR</i> , and <i>ALK</i> . Associated with hypertrophic osteoarthropathy (clubbing). Bronchioloalveolar subtype (adenocarcinoma in situ): CXR often shows hazy infiltrates similar to pneumonia; better prognosis.	Glandular pattern on histology, often stains mucin ⊕ B.  Bronchioloalveolar subtype: grows along alveolar septa → apparent "thickening" of alveolar walls. Tall, columnar cells containing mucus.
Squamous cell carcinoma	Central	Hilar mass C arising from bronchus; Cavitation; Cigarettes; hyperCalcemia (produces PTHrP).	Keratin pearls <b>D</b> and intercellular bridges.
Large cell carcinoma	Peripheral	Highly anaplastic undifferentiated tumor; poor prognosis. Less responsive to chemotherapy; removed surgically. Strong association with smoking.	Pleomorphic giant cells <b>E</b> .
Bronchial carcinoid tumor	Central or peripheral	Excellent prognosis; metastasis rare. Symptoms due to mass effect or carcinoid syndrome (flushing, diarrhea, wheezing).	Nests of neuroendocrine cells; chromogranin $A \oplus$ .
A	B.		E T

FAS1\_2019\_16-Respiratory.indd 684 11/8/19 7:34 AM

## **Lung abscess**





Localized collection of pus within parenchyma A. Caused by aspiration of oropharyngeal contents (especially in patients predisposed to loss of consciousness [eg, alcoholics, epileptics]) or bronchial obstruction (eg, cancer).

Air-fluid levels **B** often seen on CXR; presence suggests cavitation. Due to anaerobes (eg, Bacteroides, Fusobacterium, Peptostreptococcus) or S aureus. Treatment: antibiotics, drainage, or surgery.

Lung abscess 2° to aspiration is most often found in right lung. Location depends on patient's position during aspiration: RLL if upright, RUL or RML if recumbent.

## **Pancoast tumor**



Also known as superior sulcus tumor. Carcinoma that occurs in the apex of lung A may cause Pancoast syndrome by invading/compressing local structures.

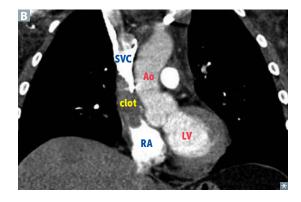
Compression of locoregional structures may cause array of findings:

- Recurrent laryngeal nerve → hoarseness
- Stellate ganglion → Horner syndrome (ipsilateral ptosis, miosis, anhidrosis)
- Superior vena cava → SVC syndrome
- Brachiocephalic vein → brachiocephalic syndrome (unilateral symptoms)
- Brachial plexus → sensorimotor deficits
- Phrenic nerve → hemidiaphragm paralysis (hemidiaphragm elevation on CXR)

## Superior vena cava syndrome



An obstruction of the SVC that impairs blood drainage from the head ("facial plethora"; note blanching after fingertip pressure in A), neck (jugular venous distention), and upper extremities (edema). Commonly caused by malignancy (eg, mediastinal mass, Pancoast tumor) and thrombosis from indwelling catheters B. Medical emergency. Can raise intracranial pressure (if obstruction is severe) → headaches, dizziness, ↑ risk of aneurysm/ rupture of intracranial arteries.



FAS1\_2019\_16-Respiratory.indd 685 11/8/19 7:34 AM **RESPIRATORY** ► RESPIRATORY—PHARMACOLOGY

Histamine-1 blockers	Reversible inhibitors of H <sub>1</sub> histamine receptors.		
First generation	Diphenhydramine, dimenhydrinate, chlorpheniramine, doxylamine.	Names usually contain "-en/-ine" or "-en/-ate."	
CLINICAL USE	Allergy, motion sickness, sleep aid.		
ADVERSE EFFECTS	Sedation, antimuscarinic, anti-α-adrenergic.		
Second generation	Loratadine, fexofenadine, desloratadine, cetirizine.	Names usually end in "-adine."	
CLINICAL USE	Allergy.		
ADVERSE EFFECTS	Far less sedating than 1st generation because of ↓ entry into CNS.		
Guaifenesin	Expectorant—thins respiratory secretions; does n	not suppress cough reflex.	
V-acetylcysteine	Mucolytic—liquifies mucus in chronic bronchop disulfide bonds. Also used as an antidote for acc	oulmonary diseases (eg, COPD, CF) by disrupting etaminophen overdose.	
Dextromethorphan	effect when used in excess. Naloxone can be gi	ptors). Synthetic codeine analog. Has mild opioid ven for overdose. Mild abuse potential. May cause	
	serotonin syndrome if combined with other ser	otonergic agents.	
Pseudoephedrine, phe		otonergic agents.	
Pseudoephedrine, phe		otonergic agents.	
	nylephrine		
	nylephrine α-adrenergic agonists. Reduce hyperemia, edema (used as nasal decong	gestants); open obstructed eustachian tubes.	
MECHANISM  CLINICAL USE  ADVERSE EFFECTS	nylephrine α-adrenergic agonists. Reduce hyperemia, edema (used as nasal decong Hypertension. Rebound congestion if used more anxiety (pseudoephedrine).		
MECHANISM CLINICAL USE ADVERSE EFFECTS Pulmonary hypertension	nylephrine α-adrenergic agonists. Reduce hyperemia, edema (used as nasal decong Hypertension. Rebound congestion if used more anxiety (pseudoephedrine).	gestants); open obstructed eustachian tubes. than 4–6 days. Can also cause CNS stimulation,	
MECHANISM CLINICAL USE ADVERSE EFFECTS  Pulmonary hypertension DRUG Endothelin receptor antagonists	nylephrine α-adrenergic agonists. Reduce hyperemia, edema (used as nasal decong Hypertension. Rebound congestion if used more anxiety (pseudoephedrine).  on drugs  MECHANISM  Competitively antagonizes endothelin-1 receptors → ↓ pulmonary vascular resistance.	gestants); open obstructed eustachian tubes.  e than 4–6 days. Can also cause CNS stimulation.  CLINICAL NOTES  Hepatotoxic (monitor LFTs).  Example: bosentan.	
MECHANISM  CLINICAL USE  ADVERSE EFFECTS  Pulmonary hypertension  DRUG  Endothelin receptor	nylephrine α-adrenergic agonists. Reduce hyperemia, edema (used as nasal decong Hypertension. Rebound congestion if used more anxiety (pseudoephedrine).  on drugs  MECHANISM Competitively antagonizes endothelin-1	gestants); open obstructed eustachian tubes.  e than 4–6 days. Can also cause CNS stimulation.  CLINICAL NOTES  Hepatotoxic (monitor LFTs).	

FAS1\_2019\_16-Respiratory.indd 686 11/8/19 7:34 AM

Asthma drugs	Bronchoconstriction is mediated by (1) inflammatory processes and (2) parasympathetic tone; therapy is directed at these 2 pathways.		
$\beta_2$ -agonists	$\label{eq:balance} \begin{tabular}{ll} \textbf{Albuterol}-\text{relaxes bronchial smooth muscle (short acting $\beta_2$-agonist). For acute exacerbations. Can cause tremor, arrhythmia. \\ \textbf{Salmeterol, formoterol}-\text{long-acting agents for prophylaxis. Can cause tremor, arrhythmia.} \\ \end{tabular}$		
Inhaled corticosteroids	Fluticasone, budesonide—inhibit the synthesis of virtually all cytokines. Inactivate NF-κB, the transcription factor that induces production of TNF-α and other inflammatory agents. Ist-line therapy for chronic asthma. Use a spacer or rinse mouth after use to prevent oral thrush.		
Muscarinic antagonists	<b>Tiotropium, ipratropium</b> —competitively block muscarinic receptors, preventing bronchoconstriction. Also used for COPD. Tiotropium is long acting.		
Anti <mark>leu</mark> kotrienes	Montelukast, zafirlukast—block leukotriene receptors (CysLT1). Especially good for aspirin-induced and exercise-induced asthma.  Zileuton—5-lipoxygenase pathway inhibitor. Blocks conversion of arachidonic acid to leukotrienes. Hepatotoxic.		
Anti-IgE monoclonal therapy	Omalizumab—binds mostly unbound serum IgE and blocks binding to FcεRI. Used in allergic asthma with † IgE levels resistant to inhaled steroids and long-acting β <sub>2</sub> -agonists.	Antigen and IgE — Omalizumab on mast cells  — Steroids Chromones	
Methylxanthines	Theophylline—likely causes bronchodilation by inhibiting phosphodiesterase → ↑ cAMP levels due to ↓ cAMP hydrolysis. Limited use due to narrow therapeutic index (cardiotoxicity, neurotoxicity); metabolized by cytochrome P-450. Blocks actions of adenosine.	Mediators (leukotrienes, histamine, interleukins, etc)  β-agonists Theophylline Muscarinic  Steroids Antileukotrienes	
Chromones	<b>Cromolyn</b> —prevents mast cell degranulation. Prevents acute asthma symptoms. Rarely used.	antagonists  Anti-IL-5  monoclonal antibodies	
Anti-IL-5 monoclonal therapy	Prevents eosinophil differentiation, maturation, activation, and survival mediated by IL-5 stimulation. For maintenance therapy in severe eosinophilic asthma.  Mepolizumab, reslizumab—against IL-5.  Benralizumab—against IL-5 receptor α.  ATP  Bronchodilation  AC  ATP  Bronchodilation	Early response: bronchoconstriction  Symptoms  Late response: inflammation  Bronchial hyperreactivity	
ACP Muscarini antagonis	Bronchial tone  PDE  Theophylline  Adenosine  Theophylline		

11/8/19 7:34 AM FAS1\_2019\_16-Respiratory.indd 687

688 SECTION II

**RESPIRATORY** ► RESPIRATORY—PHARMACOLOGY

► NOTES	

FAS1\_2019\_16-Respiratory.indd 688 11/8/19 7:34 AM

# HIGH-YIELD SYSTEMS

# **Rapid Review**

"Study without thought is vain: thought without study is dangerous."

-Confucius

"It is better, of course, to know useless things than to know nothing."

—Lucius Annaeus Seneca

"For every complex problem there is an answer that is clear, simple, and wrong."

-H. L. Mencken

The following tables represent a collection of high-yield associations between diseases and their clinical findings, treatments, and key associations. They can be quickly reviewed in the days before the exam.

▶ Classic Presentations	690
Classic Labs/ Findings	695
Classic/Relevant Treatments	699
▶ Key Associations	702
▶ Equation Review	707
Easily Confused Medications	709

689

FAS1\_2019\_17\_Rapid Rev.indd 689 11/7/19 6:09 PM

## **RAPID REVIEW** ► CLASSIC PRESENTATIONS

#### ► CLASSIC PRESENTATIONS CLINICAL PRESENTATION DIAGNOSIS/DISEASE PAGE Gout, intellectual disability, self-mutilating behavior in a Lesch-Nyhan syndrome (HGPRT deficiency, X-linked 37 boy recessive) 49 Situs inversus, chronic sinusitis, bronchiectasis, infertility Kartagener syndrome (dynein arm defect affecting cilia) Blue sclera Osteogenesis imperfecta (type I collagen defect) 51 Ehlers-Danlos syndrome (type V collagen defect, type III 51 Elastic skin, hypermobility of joints, † bleeding tendency collagen defect seen in vascular subtype of ED) Arachnodactyly, lens dislocation (upward and temporal), Marfan syndrome (fibrillin defect) 52 aortic dissection, hyperflexible joints Café-au-lait spots (unilateral), polyostotic fibrous McCune-Albright syndrome (G<sub>s</sub>-protein activating 57 dysplasia, precocious puberty, multiple endocrine mutation) abnormalities Calf pseudohypertrophy Muscular dystrophy (most commonly Duchenne, due to 61 X-linked recessive frameshift mutation of dystrophin gene) Child uses arms to stand up from squat Duchenne muscular dystrophy (Gowers sign) 61 Becker muscular dystrophy (X-linked non-frameshift 61 Slow, progressive muscle weakness in boys deletions in dystrophin; less severe than Duchenne) Infant with cleft lip/palate, microcephaly or Patau syndrome (trisomy 13) 63 holoprosencephaly, polydactyly, cutis aplasia Infant with microcephaly, rocker-bottom feet, clenched 63 Edwards syndrome (trisomy 18) hands, and structural heart defect Single palmar crease Down syndrome 63 Dilated cardiomyopathy, edema, alcoholism or Wet beriberi (thiamine [vitamin B<sub>1</sub>] deficiency) 66 malnutrition Dermatitis, dementia, diarrhea Pellagra (niacin [vitamin B<sub>3</sub>] deficiency) 67 Swollen gums, mucosal bleeding, poor wound healing, Scurvy (vitamin C deficiency: can't hydroxylate proline/ 69 petechiae lysine for collagen synthesis) Chronic exercise intolerance with myalgia, fatigue, McArdle disease (skeletal muscle glycogen phosphorylase 87 painful cramps, myoglobinuria deficiency) Cori disease (debranching enzyme deficiency) or Von 87 Infant with hypoglycemia, hepatomegaly Gierke disease (glucose-6-phosphatase deficiency, more Myopathy (infantile hypertrophic cardiomyopathy), 87 Pompe disease (lysosomal $\alpha$ -1,4-glucosidase deficiency) exercise intolerance "Cherry-red spots" on macula Tay-Sachs (ganglioside accumulation) or Niemann-Pick 88 (sphingomyelin accumulation), central retinal artery occlusion Hepatosplenomegaly, pancytopenia, osteoporosis, Gaucher disease (glucocerebrosidase [β-glucosidase] 88 avascular necrosis of femoral head, bone crises deficiency) Achilles tendon xanthoma Familial hypercholesterolemia ( LDL receptor signaling) 94 Anaphylaxis following blood transfusion IgA deficiency 116 Male child, recurrent infections, no mature B cells Bruton disease (X-linked agammaglobulinemia) 116

FAS1\_2019\_17\_Rapid Rev.indd 690 11/7/19 6:09 PM

CLINICAL PRESENTATION	DIAGNOSIS/DISEASE	PAGE
Recurrent cold (noninflamed) abscesses, eczema, high serum IgE, † eosinophils	Hyper-IgE syndrome (Job syndrome: neutrophil chemotaxis abnormality)	116
"Strawberry tongue"	Scarlet fever Kawasaki disease	136, 314
Abdominal pain, diarrhea, leukocytosis, recent antibiotic use	Clostridium difficile infection	138
Back pain, fever, night sweats	Pott disease (vertebral TB)	140
Adrenal hemorrhage, hypotension, DIC	Waterhouse-Friderichsen syndrome (meningococcemia)	142, 349
Red "currant jelly" sputum in alcoholic or diabetic patients	Klebsiella pneumoniae pneumonia	145
Large rash with bull's-eye appearance	Erythema migrans from <i>Ixodes</i> tick bite (Lyme disease: <i>Borrelia</i> )	146
Ulcerated genital lesion	Nonpainful, indurated: chancre (1° syphilis, <i>Treponema pallidum</i> ) Painful, with exudate: chancroid ( <i>Haemophilus ducreyi</i> )	147, 184
Pupil accommodates but doesn't react	Neurosyphilis (Argyll Robertson pupil)	147
Smooth, moist, painless, wart-like white lesions on genitals	Condylomata lata (2° syphilis)	147
Fever, chills, headache, myalgia following antibiotic treatment for syphilis	Jarisch-Herxheimer reaction (rapid lysis of spirochetes results in endotoxin-like release)	148
Dog or cat bite resulting in infection	Pasteurella multocida (cellulitis at inoculation site)	149
Rash on palms and soles	Coxsackie A, 2° syphilis, Rocky Mountain spotted fever	150
Black eschar on face of patient with diabetic ketoacidosis	Mucor or Rhizopus fungal infection	153
Chorioretinitis, hydrocephalus, intracranial calcifications	Congenital toxoplasmosis	156
Child with fever later develops red rash on face that spreads to body	Erythema infectiosum/fifth disease ("slapped cheeks" appearance, caused by parvovirus B19)	164
Fever, cough, conjunctivitis, coryza, diffuse rash	Measles	170
Small, irregular red spots on buccal/lingual mucosa with blue-white centers	Koplik spots (measles [rubeola] virus)	170
Bounding pulses, wide pulse pressure, diastolic heart murmur, head bobbing	Aortic regurgitation	291
Systolic ejection murmur (crescendo-decrescendo)	Aortic stenosis	291
Continuous "machine-like" heart murmur	PDA (close with indomethacin; keep open with PGE analogs)	291
Chest pain on exertion	Angina (stable: with moderate exertion; unstable: with minimal exertion or at rest)	304
Chest pain with ST depressions on ECG	Angina (⊖ troponins) or NSTEMI (⊕ troponins)	304
Chest pain, pericardial effusion/friction rub, persistent fever following MI	Dressler syndrome (autoimmune-mediated post-MI fibrinous pericarditis, 2 weeks to several months after acute episode)	307
Painful, raised red lesions on pads of fingers/toes	Osler nodes (infective endocarditis, immune complex deposition)	311

# 692 SECTION III RAPID REVIEW → CLASSIC PRESENTATIONS

CLINICAL PRESENTATION	DIAGNOSIS/DISEASE	PAGE
Painless erythematous lesions on palms and soles	Janeway lesions (infective endocarditis, septic emboli/ microabscesses)	311
Splinter hemorrhages in fingernails	Bacterial endocarditis	311
Retinal hemorrhages with pale centers	Roth spots (bacterial endocarditis)	311
Distant heart sounds, distended neck veins, hypotension	Beck triad of cardiac tamponade	310
Cervical lymphadenopathy, desquamating rash, coronary aneurysms, red conjunctivae and tongue, hand-foot changes	Kawasaki disease (mucocutaneous lymph node syndrome, treat with IVIG and aspirin)	314
Palpable purpura on buttocks/legs, joint pain, abdominal pain (child), hematuria	Immunoglobulin A vasculitis (Henoch-Schönlein purpura, affects skin and kidneys)	315
Telangiectasias, recurrent epistaxis, skin discoloration, arteriovenous malformations, GI bleeding, hematuria	Hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu syndrome)	316
Skin hyperpigmentation, hypotension, fatigue	$1^{\circ}$ adrenocortical insufficiency → ↑ ACTH, ↑ α-MSH (eg, Addison disease)	349
Cutaneous flushing, diarrhea, bronchospasm	Carcinoid syndrome (right-sided cardiac valvular lesions, † 5-HIAA)	352
Cold intolerance, weight gain, brittle hair	Hypothyroidism	341
Cutaneous/dermal edema due to deposition of mucopolysaccharides in connective tissue	Myxedema (caused by hypothyroidism, Graves disease [pretibial])	340
Facial muscle spasm upon tapping	Chvostek sign (hypocalcemia)	344
No lactation postpartum, absent menstruation, cold intolerance	Sheehan syndrome (postpartum hemorrhage leading to pituitary infarction)	339
Deep, labored breathing/hyperventilation	Diabetic ketoacidosis (Kussmaul respirations)	347
Pancreatic, pituitary, parathyroid tumors	MEN 1 (autosomal dominant)	351
Thyroid tumors, pheochromocytoma, ganglioneuromatosis, Marfanoid habitus	MEN 2B (autosomal dominant RET mutation)	351
Thyroid and parathyroid tumors, pheochromocytoma	MEN 2A (autosomal dominant RET mutation)	351
Jaundice, palpable distended non-tender gallbladder	Courvoisier sign (distal malignant obstruction of biliary tree)	398
Vomiting blood following gastroesophageal lacerations	Mallory-Weiss syndrome (alcoholic and bulimic patients)	377
Dysphagia (esophageal webs), glossitis, iron deficiency anemia	Plummer-Vinson syndrome (may progress to esophageal squamous cell carcinoma)	377
Enlarged, hard left supraclavicular node	Virchow node (abdominal metastasis)	379
Arthralgias, adenopathy, cardiac and neurological symptoms, diarrhea	Whipple disease (Tropheryma whipplei)	381
Severe RLQ pain with palpation of LLQ	Rovsing sign (acute appendicitis)	383
Severe RLQ pain with deep tenderness	McBurney sign (acute appendicitis)	383
Hamartomatous GI polyps, hyperpigmented macules on mouth, feet, hands, genitalia	Peutz-Jeghers syndrome (inherited, benign polyposis can cause bowel obstruction; † cancer risk, mainly GI)	387
Multiple colon polyps, osteomas/soft tissue tumors, impacted/supernumerary teeth	Gardner syndrome (subtype of FAP)	387
Abdominal pain, ascites, hepatomegaly	Budd-Chiari syndrome (posthepatic venous thrombosis)	392

CLINICAL PRESENTATION	DIAGNOSIS/DISEASE	PAGE
Severe jaundice in neonate	Crigler-Najjar syndrome (congenital unconjugated hyperbilirubinemia)	394
Golden brown rings around peripheral cornea	Wilson disease (Kayser-Fleischer rings due to copper accumulation)	395
Fat, female, forty, fertile	Cholelithiasis (gallstones)	396
Painless jaundice	Cancer of the pancreatic head obstructing bile duct	398
Bluish line on gingiva	Burton line (lead poisoning)	419
Short stature, café-au-lait spots, thumb/radial defects, † incidence of tumors/leukemia, aplastic anemia	Fanconi anemia (genetic loss of DNA crosslink repair; often progresses to AML)	421
Red/pink urine, fragile RBCs	Paroxysmal nocturnal hemoglobinuria	422
Painful blue fingers/toes, hemolytic anemia	Cold agglutinin disease (autoimmune hemolytic anemia caused by <i>Mycoplasma pneumoniae</i> , infectious mononucleosis, CLL)	423
Petechiae, mucosal bleeding, prolonged bleeding time	Platelet disorders (eg, Glanzmann thrombasthenia, Bernard Soulier, HUS, TTP, ITP)	427
Fever, night sweats, weight loss	B symptoms of malignancy	429
Skin patches/plaques, Pautrier microabscesses, atypical T cells	Mycosis fungoides (cutaneous T-cell lymphoma) or Sézary syndrome (mycosis fungoides + malignant T cells in blood)	430
WBCs that look "smudged"	CLL	432
Neonate with arm paralysis following difficult birth, arm in "waiter's tip" position	Erb-Duchenne palsy (superior trunk [C5–C6] brachial plexus injury)	448
Anterior drawer sign ⊕	Anterior cruciate ligament injury	454
Bone pain, bone enlargement, arthritis	Osteitis deformans (Paget disease of bone, † osteoblastic and osteoclastic activity)	463
Swollen, hard, painful finger joints in an elderly individual, pain worse with activity	Osteoarthritis (osteophytes on PIP [Bouchard nodes], DIP [Heberden nodes])	466
Sudden swollen/painful big toe joint, tophi	Gout/podagra (hyperuricemia)	467
Dry eyes, dry mouth, arthritis	Sjögren syndrome (autoimmune destruction of exocrine glands)	468
Urethritis, conjunctivitis, arthritis in a male	Reactive arthritis associated with HLA-B27	469
"Butterfly" facial rash and Raynaud phenomenon in a young female	Systemic lupus erythematosus	470
Painful fingers/toes changing color from white to blue to red with cold or stress	Raynaud phenomenon (vasospasm in extremities)	472
Anticentromere antibodies	Scleroderma (CREST)	473
Dark purple skin/mouth nodules in a patient with AIDS	Kaposi sarcoma, associated with HHV-8	478
Anti-desmoglein (anti-desmosome) antibodies	Pemphigus vulgaris (blistering)	480
Pruritic, purple, polygonal planar papules and plaques (6 P's)	Lichen planus	482
↑ AFP in amniotic fluid/maternal serum	Dating error, anencephaly, spina bifida (open neural tube defects)	491
Ataxia, nystagmus, vertigo, dysarthria	Cerebellar lesion	499

FAS1\_2019\_17\_Rapid Rev.indd 693 11/7/19 6:09 PM

# 694 SECTION III RAPID REVIEW > CLASSIC PRESENTATIONS

CLINICAL PRESENTATION	DIAGNOSIS/DISEASE	PAGE
Toe extension/fanning upon plantar scrape	Babinski sign (UMN lesion)	510
Hyperphagia, hypersexuality, hyperorality	Klüver-Bucy syndrome (bilateral amygdala lesion)	511
Resting tremor, athetosis, chorea	Basal ganglia lesion	511
Lucid interval after traumatic brain injury	Epidural hematoma (middle meningeal artery rupture)	513
"Worst headache of my life"	Subarachnoid hemorrhage	513
Resting tremor, rigidity, akinesia, postural instability, shuffling gait	Parkinson disease (loss of dopaminergic neurons in substantia nigra pars compacta)	520
Chorea, dementia, caudate degeneration	Huntington disease (autosomal dominant CAG repeat expansion)	520
Nystagmus, intention tremor, scanning speech, bilateral internuclear ophthalmoplegia	Multiple sclerosis	523
Rapidly progressive limb weakness that ascends following GI/upper respiratory infection	Guillain-Barré syndrome (acute inflammatory demyelinating polyradiculopathy subtype)	524
Café-au-lait spots, Lisch nodules (iris hamartoma), cutaneous neurofibromas, pheochromocytomas, optic gliomas	Neurofibromatosis type I	525
Vascular birthmark (port-wine stain) of the face	Nevus flammeus (benign, but associated with Sturge-Weber syndrome)	525
Renal cell carcinoma (bilateral), hemangioblastomas, angiomatosis, pheochromocytoma	von Hippel-Lindau disease (dominant tumor suppressor gene mutation)	525
Bilateral vestibular schwannomas	Neurofibromatosis type 2	525
Hyperreflexia, hypertonia, Babinski sign present	UMN damage	529
Hyporeflexia, hypotonia, atrophy, fasciculations	LMN damage	529
Spastic weakness, sensory loss, bowel/bladder dysfunction	Spinal cord lesion	530
Unilateral facial drooping involving forehead	LMN facial nerve (CN VII) palsy; UMN lesions spare the forehead	532
Episodic vertigo, tinnitus, hearing loss	Ménière disease	534
Ptosis, miosis, anhidrosis	Horner syndrome (sympathetic chain lesion)	540
Conjugate horizontal gaze palsy, horizontal diplopia	Internuclear ophthalmoplegia (damage to MLF; may be unilateral or bilateral)	543
Polyuria, renal tubular acidosis type II, growth failure, electrolyte imbalances, hypophosphatemic rickets	Fanconi syndrome (multiple combined dysfunction of the proximal convoluted tubule)	586
Athlete with polycythemia	2° to erythropoietin injection	589
Periorbital and/or peripheral edema, proteinuria (> 3.5g/day), hypoalbuminemia, hypercholesterolemia	Nephrotic syndrome	597
Hereditary nephritis, sensorineural hearing loss, retinopathy, lens dislocation	Alport syndrome (mutation in collagen IV)	596
Streak ovaries, congenital heart disease, horseshoe kidney, cystic hygroma at birth, short stature, webbed neck, lymphedema	Turner syndrome (45,XO)	638
Red, itchy, swollen rash of nipple/areola	Paget disease of the breast (sign of underlying neoplasm)	650

CLINICAL PRESENTATION	DIAGNOSIS/DISEASE	PAGE
Fibrous plaques in tunica albuginea of penis with abnormal curvature	Peyronie disease (connective tissue disorder)	651
Hypoxemia, polycythemia, hypercapnia	Chronic bronchitis (hyperplasia of mucous cells, "blue bloater")	674
Pink complexion, dyspnea, hyperventilation	Emphysema ("pink puffer," centriacinar [smoking] or panacinar [ $\alpha_l$ -antitrypsin deficiency])	674
Bilateral hilar adenopathy, uveitis	Sarcoidosis (noncaseating granulomas)	676

#### ► CLASSIC LABS/FINDINGS LAB/DIAGNOSTIC FINDING DIAGNOSIS/DISEASE PAGE ↓ AFP in amniotic fluid/maternal serum Down syndrome, Edwards syndrome 63 Large granules in phagocytes, immunodeficiency Chédiak-Higashi disease (congenital failure of 117 phagolysosome formation) Recurrent infections, eczema, thrombocytopenia Wiskott-Aldrich syndrome 117 Sensitive: S pneumoniae; resistant: viridans streptococci 134 Optochin sensitivity (S mutans, S sanguis) Sensitive: S epidermidis; resistant: S saprophyticus 134 Novobiocin response Sensitive: S pyogenes (group A); resistant: S agalactiae 134 Bacitracin response (group B) Streptococcus bovis bacteremia Colon cancer 137 Branching gram ⊕ rods with sulfur granules Actinomyces israelii 139 Hilar lymphadenopathy, peripheral granulomatous lesion Ghon complex (1° TB: Mycobacterium bacilli) 140 in middle or lower lung lobes (can calcify) "Thumb sign" on lateral neck x-ray Epiglottitis (Haemophilus influenzae) 142 "Clue cells" (Gardnerella vaginalis) 148 Bacteria-covered vaginal epithelial cells Cardiomegaly with apical atrophy Chagas disease (*Trypanosoma cruzi*) 158 **EBV** 165 Atypical lymphocytes Enlarged cells with intranuclear inclusion bodies "Owl eye" appearance of CMV 165 Heterophile antibodies Infectious mononucleosis (EBV) 165 Intranuclear eosinophilic droplet-like bodies Cowdry type A bodies (HSV or VZV) 166 Eosinophilic globule in liver Councilman body (viral hepatitis, yellow fever), represents 168 hepatocyte undergoing apoptosis 170 "Steeple" sign on frontal CXR Croup (parainfluenza virus) Eosinophilic inclusion bodies in cytoplasm of Negri bodies of rabies 171 hippocampal and cerebellar neurons Ring-enhancing brain lesion on CT/MRI in AIDS Toxoplasma gondii, CNS lymphoma 177 211 Psammoma bodies Meningiomas, papillary thyroid carcinoma, mesothelioma, papillary serous carcinoma of the endometrium and ovary

FAS1\_2019\_17\_Rapid Rev.indd 695 11/7/19 6:09 PM

# 696 SECTION III RAPID REVIEW > CLASSIC LABS/FINDINGS

"Delta wave" on ECC, short PR interval, supraventricular bypasses AV node) "Boots-haped" heart on x-ray Terralogy of Fallot (due to RVII) 298 Rib notching (inferior surface, on x-ray) 199 Heart nodules (granulomatous) 299 Heart nodules (granulomatous) 290 Electrical alternants (alternating amplitude on ECC) 291 Antineutrophil cytoplasmic antibodies (ANCAs) 391 Antineutrophil cytoplasmic antibodies (ANCAs) 392 Antineutrophil cytoplasmic antibodies (ANCAs) 393 Antineutrophil cytoplasmic antibodies (ANCAs) 394 Electrical alternants (alternating amplitude on ECC) 395 Antineutrophil cytoplasmic antibodies (ANCAs) 396 Antineutrophil cytoplasmic antibodies (ANCAs) 397 Electrical alternants (alternating amplitude on ECC) 398 Enlarged thyroid cells with ground-glass nuclei with central clearing 499 Enlarged thyroid cells with ground-glass nuclei with central clearing 490 Mucin-filled cell with peripheral nucleus 490 Anti-transglutaminase/anti-gliadin/anti-endomysial 491 Anti-transglutaminase/anti-gliadin/anti-endomysial 492 Tead pipe" appearance of colon on abdominal imaging 493 Thousands of polyps on colonoscopy 499 Tending of bowel lumen on barium x-ray 490 Tending of bowel lumen on barium x-ray 491 Tending of bowel lumen on barium nerna x-ray 492 Tending of bowel lumen on barium nerna x-ray 493 Tending of bowel lumen on barium central x-ray 494 Tending of bowel lumen on barium central x-ray 495 Tending of bowel lumen on barium central x-ray 496 Tending of bowel lumen on barium nerna x-ray 496 Tending of bowel lumen on barium central x-ray 497 Tending of bowel lumen on barium central x-ray 498 Tending of bowel lumen on barium central x-ray 498 Tending of bowel lumen on barium central x-ray 498 Tending of bowel lumen on barium central x-ray 498 Tending of bowel lumen on barium central x-ray 499 Tending of bowel lumen on barium central x-ray 499 Tending of bowel lumen on barium x-ray 499 Tending of bowel lumen on barium x-ray 490 Tending of bowel lumen on barium x-ray 490 Tending of bowel lumen on barium x-ray 490 Tendi	LAB/DIAGNOSTIC FINDING	DIAGNOSIS/DISEASE	PAGE
Rib notching (inferior surface, on x-ray)  Heart nodules (granulomatous)  Antineutrophil cytoplasmic antibodies (ANCAs)  Hypertension, hypokalemia, metabolic alkalosis  Finlarged thyroid cells with ground-glass nuclei with central clearing  Mucin-filled cell with peripheral nucleus  Mucin-filled cell with peripheral nucleus  Anti-transglutaminase/anti-gliadin/anti-endomysial antibodies  Narrowing of bowel lumen on barium x-ray  Tead piper" appearance of colon on abdominal imaging  Thousands of polyps on colonoscopy  Pamilial adenomatous polyposis (autosomal dominant, mutation of APC gene)  "Nather elevation on barium enema x-ray  Eocretal cancer (usually left-sided)  Antimitochondrial antibodies (AMAs)  Antimitochondrial antibodies (AMAs)  Low serum ceruloplasmin  Migratory thromobollebitis (leading to migrating DVTs)  Rasophilic nuclear remnants in RBCs  Basophilic nuclear remnants in RBCs  Basophilic nuclear remnants in RBCs  Basophilic sitppling of RBCs  Howell-folly bodies (due to splenectomy or nonfunctional splece)  Hypersegmented neutrophils  Megaloblastic ancmia (B., deficiency; neurologic symptoms)  Antiplatelet antibodies  Hopathic remnants in Red. Sed. Sed. Sed. Sed. Sed. Sed. Sed. S	in the second of		294
Heart nodules (granulomatous)   Aschoff bodies (rheumatic fever)   312	"Boot-shaped" heart on x-ray	Tetralogy of Fallot (due to RVH)	298
Electrical alternans (alternating amplitude on ECC)  Antineutrophil cytoplasmic antibodics (ANCAs)  Antineutrophil cytoplasmic antibodics (ANCAs)  Antineutrophil cytoplasmic antibodics (ANCAs)  Antineutrophil cytoplasmic antibodics (ANCAs)  Wiscoscopic polyangiitis (MPO-ANCA/p-ANCA); granulomatosis with polyangiitis (Wegener; PR3-ANCA/p-ANCA)  Enlarged thyroid cells with ground-glass nuclei with central clearing  Mucin-filled cell with peripheral nucleus  "Signet ring" (gastric carcinoma)  Anti-transglutaminase/anti-gladin/anti-endomysial antibodics  Narrowing of bowel lumen on barium x-ray  "String sign" (Crohn discase)  "String sign" (Crohn discase)  "Apple core" lesion on barium nema x-ray  Colorectal cancer (usually left-sided)  Eosinophilic cytoplasmic inclusion in liver cell  Mallory body (alcoholic liver disease)  "Nutmeg" appearance of liver  Chronic passive congestion of liver due to right heart failure or Budd-Chiari syndrome  Antimitochondrial antibodies (AMAs)  Pibliary cholangitis (female, cholestasis, portal hypertension)  Migratory thrombophlebitis (leading to migrating DVTs and vasculitis)  Basophilic nuclear remnants in RBCs  Basophilic nuclear remnants in RBCs  Howell-Joly bodies (due to splenectomy or nonfunctional spleen)  "Hair on end" ("Crew-cut") appearance on x-ray  Heal poisoning, it alease (halpolisen) in purpora ane in the model of the homoglobin sometimes present)  "Hair on end" ("Crew-cut") appearance on x-ray  Heal poisoning or sideroblastic anemia  Homel-Joly bodies (due to splenectomy or nonfunctional spleen)  "Hair on end" ("Crew-cut") appearance on x-ray  Heal poisoning or sideroblastic anemia  Heal poisoning, thalassemia (fetal hemoglobin sometimes present)  Megaloblastic anemia (B <sub>10</sub> deficiency: neurologic symptoms)  Antiplatelet antibodies  High level of of-dimers  DVT, PE, DIC  428  Giant B cells with bilobed nuclei with prominent	Rib notching (inferior surface, on x-ray)	Coarctation of the aorta	299
Antineutrophil cytoplasmic antibodies (ANCAs)         Microscopic polyangiitis and cosinophilic granulomatosis with polyangiitis (MPO-ANCA/p-ANCA); granulomatosis with polyangiitis (Wegence PR3-ANCA/α-ANCA); primary selerosing cholangitis (MPO-ANCA/p-ANCA).         315           Hypertension, hypokalemia, metabolic alkalosis         1° hyperaldosteronism (Conn syndrome)         349           Enlarged thyroid cells with ground-glass nuclei with central clearing         "Orphan Annie" eyes nuclei (papillary carcinoma of the thyroid)         337           Mucin-filled cell with peripheral nucleus         "Signet ring" (gastric carcinoma)         379           Anti-transglutaminase/anti-gliadin/anti-endomysial antibodies         Celiae disease (diarrhea, weight loss)         381           Narrowing of bowel lumen on barium x-ray         "String sign" (Crohn disease)         582           "Lead pipe" appearance of colon on abdominal imaging         Ulcerative colitis (loss of haustra)         382           Thousands of polyps on colonoscopy         Familial adenomatous polyposis (autosomal dominant, mutation of APC gene)         388           "Apple core" lesion on barium enema x-ray         Colorectal cancer (usually left-sided)         388           Eoinophilic cytoplasmic inclusion in liver cell         Mallory body (alcoholic liver disease)         391           "Nutmeg" appearance of liver         Chronic passive congestion of liver due to right heart failure or Budd-Chiari syndrome         392           Antimito	Heart nodules (granulomatous)	Aschoff bodies (rheumatic fever)	312
with polyangitis (MPO-ANCA/p-ANCA); granulomatosis with polyangitis (Wegener; PR3-ANCA/c-ANCA); primary sclerosing cholangitis (MPO-ANCA/p-ANCA).  Hypertension, hypokalemia, metabolic alkalosis   1° hyperaldosteronism (Conn syndrome)   349  Enlarged thyroid cells with ground-glass nuclei with central clearing   "Orphan Annie" eyes nuclei (papillary carcinoma of the thyroid)   343  Mucin-filled cell with peripheral nucleus   "Signet ring" (gastric carcinoma)   379  Anti-transglutaminase/anti-gliadin/anti-endomysial antibodies   String sign" (Crohn disease)   382  "Lead pipe" appearance of colon on abdominal imaging   Ulcerative colitis (loss of haustra)   382  "Lead pipe" appearance of colon on abdominal imaging   Ulcerative colitis (loss of haustra)   382  "Thousands of polyps on colonoscopy   Familial adenomatous polyposis (autosomal dominant, mutation of APC gene)   388  Eosinophilic cytoplasmic inclusion in liver cell   Mallory body (alcoholic liver disease)   391  Triglyceride accumulation in liver cell vacuoles   Fatty liver disease (alcoholic or metabolic syndrome)   391  "Nutmeg" appearance of liver   Chronic passive congestion of liver due to right heart failure or Budd-Chiari syndrome   392  Antimitochondrial antibodics (AMAs)   1° biliary cholangitis (Ernale, cholestasis, portal hypertension)   395  Low serum ceruloplasmin   Vilson disease (hepatolenticular degeneration; Kayser-Fleischer rings due to copper accumulation)   395  Migratory thrombophlebitis (leading to migrating DVTs and vasculitis)   100   10	Electrical alternans (alternating amplitude on ECG)	Cardiac tamponade	310
Enlarged thyroid cells with ground-glass nuclei with central clearing"Opphan Annie" eyes nuclei (papillary carcinoma of the thyroid)343Mucin-filled cell with peripheral nucleus"Signet ring" (gastric carcinoma)379Anti-transglutaminase/anti-gliadin/anti-endomysial antibodiesCeliac disease (diarrhea, weight loss)381Narrowing of bowel lumen on barium x-ray"String sign" (Crohn disease)382"Lead pipe" appearance of colon on abdominal imagingUlcerative colitis (loss of haustra)382Thousands of polyps on colonoscopyFamilial adenomatous polyposis (autosomal dominant, mutation of APC gene)388"Apple core" lesion on barium enema x-rayColorectal cancer (usually left-sided)388Eosinophilic cytoplasmic inclusion in liver cellMallory body (alcoholic liver disease)391Triglyceride accumulation in liver cell vacuolesFatty liver disease (alcoholic or metabolic syndrome)391"Nutmeg" appearance of liverChronic passive congestion of liver due to right heart failure or Budd-Chiari syndrome392Antimitochondrial antibodies (AMAs)1' biliary cholangitis (female, cholestasis, portal hypertension)395Low serum ceruloplasminWilson disease (hepatolenticular degeneration; Kayser- Fleischer rings due to copper accumulation)398Migratory thrombophlebitis (leading to migrating DVTs and vasculitis)Trousseau syndrome (adenocarcinoma of pancreas or lung)398Basophilic stippling of RBCsLead poisoning or sideroblastic anemia416Hypochromic, microcytic anemiaLead poisoning or sideroblastic anemia4	Antineutrophil cytoplasmic antibodies (ANCAs)	with polyangiitis (MPO-ANCA/p-ANCA); granulomatosis with polyangiitis (Wegener; PR3-ANCA/c-ANCA); primary sclerosing cholangitis (MPO-	315
central clearingthyroid)Mucin-filled cell with peripheral nucleus"Signet ring" (gastric carcinoma)379Anti-ransglutaminasc/anti-gliadin/anti-endomysial antibodiesCeliac disease (diarrhea, weight loss)381Narrowing of bowel lumen on barium x-ray"String sign" (Crohn disease)382"Lead pipe" appearance of colon on abdominal imagingUlcerative colitis (loss of haustra)382Thousands of polyps on colonoscopyFamilial adenomatous polyposis (autosomal dominant, mutation of APC gene)387"Apple core" lesion on barium enema x-rayColorectal cancer (usually left-sided)388Eosinophilic cytoplasmic inclusion in liver cellMallory body (alcoholic liver disease)391Triglyceride accumulation in liver cell vacuolesFatty liver disease (alcoholic or metabolic syndrome)391"Nutmeg" appearance of liverChronic passive congestion of liver due to right heart failure or Budd-Chiari syndrome392Antimitochondrial antibodies (AMAs)1° biliary cholangitis (female, cholestasis, portal hypertension)395Low serum ceruloplasmin1° biliary cholangitis (female, cholestasis, portal hypertension)395Migratory thrombophlebitis (leading to migrating DVTs and vasculitis)Trousseau syndrome (adenocarcinoma of pancreas or lung)398Basophilic nuclear remnants in RBCsLead poisoning or sideroblastic anemia416Hypochromic, microcytic anemiaInon deficiency anemia, lead poisoning, thalassemia (fetal hemoglobin sometimes present)418"Hair on end" ("Crew-cut") appearance on x-rayβ-thalassemia, sickle cell disease (marrow expansion)	Hypertension, hypokalemia, metabolic alkalosis	1° hyperaldosteronism (Conn syndrome)	349
Anti-transglutaminase/anti-gliadin/anti-endomysial antibodiesCeliac disease (diarrhea, weight loss)381Narrowing of bowel lumen on barium x-ray"String sign" (Crohn disease)382"Lead pipe" appearance of colon on abdominal imagingUlcerative colitis (loss of haustra)382Thousands of polyps on colonoscopyFamilial adenomatous polyposis (autosomal dominant, mutation of APC gene)388"Apple core" lesion on barium enema x-rayColorectal cancer (usually left-sided)388Eosinophilic cytoplasmic inclusion in liver cellMallory body (alcoholic liver disease)391Triglyceride accumulation in liver cell vacuolesFatty liver disease (alcoholic or metabolic syndrome)391"Nutmeg" appearance of liverChronic passive congestion of liver due to right heart failure or Budd-Chiari syndrome392Antimitochondrial antibodies (AMAs)1° biliary cholangitis (female, cholestasis, portal hypertension)395Low serum ceruloplasminWilson disease (hepatolenticular degeneration; Kayser-Fleischer rings due to copper accumulation)398Migratory thrombophlebitis (leading to migrating DVTs and vasculitis)Trousseau syndrome (adenocarcinoma of pancreas or lung)398Basophilic nuclear remnants in RBCsLead poisoning or sideroblastic anemia416Hypochromic, microcytic anemiaIron deficiency anemia, lead poisoning, thalassemia (fetal hemoglobin sometimes present)418"Hair on end" ("Crew-cut") appearance on x-rayβ-thalassemia, sickle cell disease (marrow expansion)422Hypersegmented neutrophilsMegaloblastic anemia (B <sub>12</sub> deficiency: neurologic symptoms) <t< td=""><td></td><td></td><td>343</td></t<>			343
antibodiesString sign" (Crohn disease)382"Lead pipe" appearance of colon on abdominal imagingUlcerative colitis (loss of haustra)382Thousands of polyps on colonoscopyFamilial adenomatous polyposis (autosomal dominant, mutation of APC gene)387"Apple core" lesion on barium enema x-rayColorectal cancer (usually left-sided)388Eosinophilic cytoplasmic inclusion in liver cellMallory body (alcoholic liver disease)391Triglyceride accumulation in liver cell vacuolesFatty liver disease (alcoholic or metabolic syndrome)391"Nutmeg" appearance of liverChronic passive congestion of liver due to right heart failure or Buddi-Chiari syndrome392Antimitochondrial antibodies (AMAs)1° biliary cholangitis (female, cholestasis, portal hypertension)395Low serum ceruloplasminWilson disease (hepatolenticular degeneration; Kayser-Fleischer rings due to copper accumulation)398Migratory thrombophlebitis (leading to migrating DVTs and vasculitis)Trousseau syndrome (adenocarcinoma of pancreas or lung)398Basophilic nuclear remnants in RBCsHowell-Jolly bodies (due to splenectomy or nonfunctional spleen)416Basophilic stippling of RBCsLead poisoning or sideroblastic anemia416Hypochromic, microcytic anemiaIron deficiency anemia, lead poisoning, thalassemia (fetal hemoglobin sometimes present)418"Hair on end" ("Crew-cut") appearance on x-rayβ-thalassemia, sickle cell disease (marrow expansion)422Hypersegmented neutrophilsMegaloblastic anemia (B <sub>12</sub> deficiency: neurologic symptoms)420Antiplatelet antibo	Mucin-filled cell with peripheral nucleus	"Signet ring" (gastric carcinoma)	379
"Lead pipe" appearance of colon on abdominal imaging         Ulcerative colitis (loss of haustra)         382           Thousands of polyps on colonoscopy         Familial adenomatous polyposis (autosomal dominant, mutation of APC gene)         387           "Apple core" lesion on barium enema x-ray         Colorectal cancer (usually left-sided)         388           Eosinophilic cytoplasmic inclusion in liver cell         Mallory body (alcoholic liver disease)         391           Triglyceride accumulation in liver cell vacuoles         Fatty liver disease (alcoholic or metabolic syndrome)         391           "Nutmeg" appearance of liver         Chronic passive congestion of liver due to right heart failure or Budd-Chiari syndrome         392           Antimitochondrial antibodies (AMAs)         1° biliary cholangitis (female, cholestasis, portal hypertension)         395           Low scrum ceruloplasmin         Wilson disease (hepatolenticular degeneration; Kayser-Fleischer rings due to copper accumulation)         395           Migratory thrombophlebitis (leading to migrating DVTs and vasculitis)         Trousseau syndrome (adenocarcinoma of pancreas or lung)         398           Basophilic nuclear remnants in RBCs         Howell-Jolly bodies (due to splenectomy or nonfunctional spleen)         416           Hypochromic, microcytic anemia         Iron deficiency anemia, lead poisoning, thalassemia (fetal hemoglobin sometimes present)         419           "Hair on end" ("Crew-cut") appearance on x-ray <td></td> <td>Celiac disease (diarrhea, weight loss)</td> <td>381</td>		Celiac disease (diarrhea, weight loss)	381
Thousands of polyps on colonoscopyFamilial adenomatous polyposis (autosomal dominant, mutation of APC gene)387"Apple core" lesion on barium enema x-rayColorectal cancer (usually left-sided)388Eosinophilic cytoplasmic inclusion in liver cellMallory body (alcoholic liver disease)391Triglyceride accumulation in liver cell vacuolesFatty liver disease (alcoholic or metabolic syndrome)391"Nutmeg" appearance of liverChronic passive congestion of liver due to right heart failure or Budd-Chiari syndrome392Antimitochondrial antibodies (AMAs)1° biliary cholangitis (female, cholestasis, portal hypertension)395Low serum ceruloplasminWilson disease (hepatolenticular degeneration; Kayser-Fleischer rings due to copper accumulation)395Migratory thrombophlebitis (leading to migrating DVTs and vasculitis)Trousseau syndrome (adenocarcinoma of pancreas or lung)398Basophilic nuclear remnants in RBCsHowell-Jolly bodies (due to splenectomy or nonfunctional spleen)416Basophilic stippling of RBCsLead poisoning or sideroblastic anemia416Hypochromic, microcytic anemiaIron deficiency anemia, lead poisoning, thalassemia (fetal hemoglobin sometimes present)418"Hair on end" ("Crew-cut") appearance on x-rayβ-thalassemia, sickle cell disease (marrow expansion)422Hypersegmented neutrophilsMegaloblastic anemia (B <sub>12</sub> deficiency: neurologic symptoms; folate deficiency: no neurologic symptoms; folate deficiency: no neurologic symptoms; folate deficiency: no neurologic symptoms; folate deficiency: no neurologic symptoms; folate deficiency: no neurologic symptoms427High leve	Narrowing of bowel lumen on barium x-ray	"String sign" (Crohn disease)	382
"Apple core" lesion on barium enema x-rayColorectal cancer (usually left-sided)388Eosinophilic cytoplasmic inclusion in liver cellMallory body (alcoholic liver disease)391Triglyceride accumulation in liver cell vacuolesFatty liver disease (alcoholic or metabolic syndrome)391"Nutmeg" appearance of liverChronic passive congestion of liver due to right heart failure or Budd-Chiari syndrome392Antimitochondrial antibodies (AMAs)1° biliary cholangitis (female, cholestasis, portal hypertension)395Low serum ceruloplasminWilson disease (hepatolenticular degeneration; Kayser-Fleischer rings due to copper accumulation)395Migratory thrombophlebitis (leading to migrating DVTs and vasculitis)Trousseau syndrome (adenocarcinoma of pancreas or lung)398Basophilic nuclear remnants in RBCsHowell-Jolly bodies (due to splenectomy or nonfunctional spleen)416Basophilic stippling of RBCsLead poisoning or sideroblastic anemia416Hypochromic, microcytic anemiaIron deficiency anemia, lead poisoning, thalassemia (fetal hemoglobin sometimes present)418"Hair on end" ("Crew-cut") appearance on x-rayβ-thalassemia, sickle cell disease (marrow expansion)422Hypersegmented neutrophilsMegaloblastic anemia (B <sub>12</sub> deficiency: neurologic symptoms)420Antiplatelet antibodiesIdiopathic thrombocytopenic purpura427High level of p-dimersDVT, PE, DIC428Giant B cells with bilobed nuclei with prominentReed-Sternberg cells (Hodgkin lymphoma)429	"Lead pipe" appearance of colon on abdominal imaging	Ulcerative colitis (loss of haustra)	382
Eosinophilic cytoplasmic inclusion in liver cellMallory body (alcoholic liver disease)391Triglyceride accumulation in liver cell vacuolesFatty liver disease (alcoholic or metabolic syndrome)391"Nutmeg" appearance of liverChronic passive congestion of liver due to right heart failure or Budd-Chiari syndrome392Antimitochondrial antibodies (AMAs)1° biliary cholangitis (female, cholestasis, portal hypertension)395Low serum ceruloplasminWilson disease (hepatolenticular degeneration; Kayser-Fleischer rings due to copper accumulation)395Migratory thrombophlebitis (leading to migrating DVTs and vasculitis)Trousseau syndrome (adenocarcinoma of pancreas or lung)398Basophilic nuclear remnants in RBCsHowell-Jolly bodies (due to splenectomy or nonfunctional spleen)416Basophilic stippling of RBCsLead poisoning or sideroblastic anemia416Hypochromic, microcytic anemiaIron deficiency anemia, lead poisoning, thalassemia (fetal hemoglobin sometimes present)418"Hair on end" ("Crew-cut") appearance on x-rayβ-thalassemia, sickle cell disease (marrow expansion)422Hypersegmented neutrophilsMegaloblastic anemia (B12 deficiency: neurologic symptoms)420Antiplatelet antibodiesIdiopathic thrombocytopenic purpura427High level of p-dimersDVT, PE, DIC428Giant B cells with bilobed nuclei with prominentReed-Sternberg cells (Hodgkin lymphoma)429	Thousands of polyps on colonoscopy		387
Triglyceride accumulation in liver cell vacuolesFatty liver disease (alcoholic or metabolic syndrome)391"Nutmeg" appearance of liverChronic passive congestion of liver due to right heart failure or Budd-Chiari syndrome392Antimitochondrial antibodies (AMAs)1° biliary cholangitis (female, cholestasis, portal hypertension)395Low serum ceruloplasminWilson disease (hepatolenticular degeneration; Kayser-Fleischer rings due to copper accumulation)395Migratory thrombophlebitis (leading to migrating DVTs and vasculitis)Trousseau syndrome (adenocarcinoma of pancreas or lung)398Basophilic nuclear remnants in RBCsHowell-Jolly bodies (due to splenectomy or nonfunctional spleen)416Basophilic stippling of RBCsLead poisoning or sideroblastic anemia416Hypochromic, microcytic anemiaIron deficiency anemia, lead poisoning, thalassemia (fetal hemoglobin sometimes present)418"Hair on end" ("Crew-cut") appearance on x-rayβ-thalassemia, sickle cell disease (marrow expansion)422Hypersegmented neutrophilsMegaloblastic anemia (B <sub>12</sub> deficiency: neurologic symptoms)420Antiplatelet antibodiesIdiopathic thrombocytopenic purpura427High level of p-dimersDVT, PE, DIC428Giant B cells with bilobed nuclei with prominentReed-Sternberg cells (Hodgkin lymphoma)429	"Apple core" lesion on barium enema x-ray	Colorectal cancer (usually left-sided)	388
"Nutmeg" appearance of liver Chronic passive congestion of liver due to right heart failure or Budd-Chiari syndrome  Antimitochondrial antibodies (AMAs) lobilitary cholangitis (female, cholestasis, portal hypertension)  Low serum ceruloplasmin Wilson disease (hepatolenticular degeneration; Kayser-Fleischer rings due to copper accumulation)  Migratory thrombophlebitis (leading to migrating DVTs and vasculitis)  Basophilic nuclear remnants in RBCs Howell-Jolly bodies (due to splenectomy or nonfunctional spleen)  Basophilic stippling of RBCs Lead poisoning or sideroblastic anemia 416  Hypochromic, microcytic anemia Iron deficiency anemia, lead poisoning, thalassemia (fetal hemoglobin sometimes present)  "Hair on end" ("Crew-cut") appearance on x-ray β-thalassemia, sickle cell disease (marrow expansion) 422  Hypersegmented neutrophils Megaloblastic anemia (B <sub>12</sub> deficiency: no neurologic symptoms) 420  Antiplatelet antibodies Idiopathic thrombocytopenic purpura 427  High level of D-dimers DVT, PE, DIC 428  Giant B cells with bilobed nuclei with prominent Reed-Sternberg cells (Hodgkin lymphoma) 429	Eosinophilic cytoplasmic inclusion in liver cell	Mallory body (alcoholic liver disease)	391
Antimitochondrial antibodies (AMAs)  Antimitochondrial antibodies (AMAs)  Low serum ceruloplasmin  Migratory thrombophlebitis (leading to migrating DVTs and vasculitis)  Basophilic nuclear remnants in RBCs  Basophilic stippling of RBCs  Lead poisoning or sideroblastic anemia  Hypochromic, microcytic anemia  Homell-Jolly bodies (due to splenectomy or nonfunctional spleen)  Homell-Jolly bodies (anemia, lead poisoning, thalassemia (fetal hemoglobin sometimes present)  Hair on end" ("Crew-cut") appearance on x-ray  Hypersegmented neutrophils  Megaloblastic anemia (B <sub>12</sub> deficiency: neurologic symptoms)  Antiplatelet antibodies  Hodgkin lymphoma)  Faliliary cholangitis (female, cholestasis, portal hypertension)  Newlessen (hepatolenticular degeneration; Kayser-Fleischer rings due to copper accumulation)  Trousseau syndrome (adenocarcinoma of pancreas or lung)  Trousseau syndrome (adenocarcinoma of pancreas or lung)  Howell-Jolly bodies (due to splenectomy or nonfunctional spleen)   Triglyceride accumulation in liver cell vacuoles	Fatty liver disease (alcoholic or metabolic syndrome)	391	
Low serum ceruloplasminHypertension)Low serum ceruloplasminWilson disease (hepatolenticular degeneration; Kayser-Fleischer rings due to copper accumulation)395Migratory thrombophlebitis (leading to migrating DVTs and vasculitis)Trousseau syndrome (adenocarcinoma of pancreas or lung)398Basophilic nuclear remnants in RBCsHowell-Jolly bodies (due to splenectomy or nonfunctional spleen)416Basophilic stippling of RBCsLead poisoning or sideroblastic anemia416Hypochromic, microcytic anemiaIron deficiency anemia, lead poisoning, thalassemia (fetal hemoglobin sometimes present)418"Hair on end" ("Crew-cut") appearance on x-rayβ-thalassemia, sickle cell disease (marrow expansion)422Hypersegmented neutrophilsMegaloblastic anemia (B12 deficiency: neurologic symptoms)420Antiplatelet antibodiesIdiopathic thrombocytopenic purpura427High level of p-dimersDVT, PE, DIC428Giant B cells with bilobed nuclei with prominentReed-Sternberg cells (Hodgkin lymphoma)429	"Nutmeg" appearance of liver		392
Fleischer rings due to copper accumulation)  Migratory thrombophlebitis (leading to migrating DVTs and vasculitis)  Basophilic nuclear remnants in RBCs  Howell-Jolly bodies (due to splenectomy or nonfunctional spleen)  Basophilic stippling of RBCs  Lead poisoning or sideroblastic anemia  416  Hypochromic, microcytic anemia  Iron deficiency anemia, lead poisoning, thalassemia (fetal hemoglobin sometimes present)  "Hair on end" ("Crew-cut") appearance on x-ray  β-thalassemia, sickle cell disease (marrow expansion)  422  Hypersegmented neutrophils  Megaloblastic anemia (B <sub>12</sub> deficiency: neurologic symptoms; folate deficiency: no neurologic symptoms)  Antiplatelet antibodies  Idiopathic thrombocytopenic purpura  427  High level of D-dimers  DVT, PE, DIC  428  Giant B cells with bilobed nuclei with prominent  Reed-Sternberg cells (Hodgkin lymphoma)	Antimitochondrial antibodies (AMAs)		395
and vasculitis)  Basophilic nuclear remnants in RBCs  Howell-Jolly bodies (due to splenectomy or nonfunctional spleen)  Basophilic stippling of RBCs  Lead poisoning or sideroblastic anemia  Hypochromic, microcytic anemia  Iron deficiency anemia, lead poisoning, thalassemia (fetal hemoglobin sometimes present)  Hair on end" ("Crew-cut") appearance on x-ray  B-thalassemia, sickle cell disease (marrow expansion)  Hypersegmented neutrophils  Megaloblastic anemia (B <sub>12</sub> deficiency: neurologic symptoms)  Antiplatelet antibodies  Idiopathic thrombocytopenic purpura  High level of p-dimers  DVT, PE, DIC  Giant B cells with bilobed nuclei with prominent  Reed-Sternberg cells (Hodgkin lymphoma)  416	Low serum ceruloplasmin	\ 1	395
Basophilic stippling of RBCsLead poisoning or sideroblastic anemia416Hypochromic, microcytic anemiaIron deficiency anemia, lead poisoning, thalassemia (fetal hemoglobin sometimes present)418, hemoglobin sometimes present)"Hair on end" ("Crew-cut") appearance on x-rayβ-thalassemia, sickle cell disease (marrow expansion)422Hypersegmented neutrophilsMegaloblastic anemia (B₁₂ deficiency: neurologic symptoms)420Antiplatelet antibodiesIdiopathic thrombocytopenic purpura427High level of p-dimersDVT, PE, DIC428Giant B cells with bilobed nuclei with prominentReed-Sternberg cells (Hodgkin lymphoma)429		· · · · · · · · · · · · · · · · · · ·	398
Hypochromic, microcytic anemiaIron deficiency anemia, lead poisoning, thalassemia (fetal hemoglobin sometimes present)418, 419"Hair on end" ("Crew-cut") appearance on x-rayβ-thalassemia, sickle cell disease (marrow expansion)422Hypersegmented neutrophilsMegaloblastic anemia (B12 deficiency: neurologic symptoms; folate deficiency: no neurologic symptoms)420Antiplatelet antibodiesIdiopathic thrombocytopenic purpura427High level of p-dimersDVT, PE, DIC428Giant B cells with bilobed nuclei with prominentReed-Sternberg cells (Hodgkin lymphoma)429	Basophilic nuclear remnants in RBCs		416
hemoglobin sometimes present)  "Hair on end" ("Crew-cut") appearance on x-ray  β-thalassemia, sickle cell disease (marrow expansion)  422  Hypersegmented neutrophils  Megaloblastic anemia (B <sub>12</sub> deficiency: neurologic symptoms; folate deficiency: no neurologic symptoms)  Antiplatelet antibodies  Idiopathic thrombocytopenic purpura  427  High level of p-dimers  DVT, PE, DIC  428  Giant B cells with bilobed nuclei with prominent  Reed-Sternberg cells (Hodgkin lymphoma)  429	Basophilic stippling of RBCs	Lead poisoning or sideroblastic anemia	416
Hypersegmented neutrophils  Megaloblastic anemia (B <sub>12</sub> deficiency: neurologic symptoms; folate deficiency: no neurologic symptoms)  Antiplatelet antibodies  Idiopathic thrombocytopenic purpura  427  High level of p-dimers  DVT, PE, DIC  428  Giant B cells with bilobed nuclei with prominent  Reed-Sternberg cells (Hodgkin lymphoma)  429	Hypochromic, microcytic anemia		
symptoms; folate deficiency: no neurologic symptoms)  Antiplatelet antibodies  Idiopathic thrombocytopenic purpura  427  High level of D-dimers  DVT, PE, DIC  428  Giant B cells with bilobed nuclei with prominent  Reed-Sternberg cells (Hodgkin lymphoma)  429	"Hair on end" ("Crew-cut") appearance on x-ray	β-thalassemia, sickle cell disease (marrow expansion)	422
High level of p-dimers  DVT, PE, DIC  Giant B cells with bilobed nuclei with prominent  Reed-Sternberg cells (Hodgkin lymphoma)  429	Hypersegmented neutrophils	Megaloblastic anemia (B <sub>12</sub> deficiency: neurologic symptoms; folate deficiency: no neurologic symptoms)	420
Giant B cells with bilobed nuclei with prominent Reed-Sternberg cells (Hodgkin lymphoma) 429	Antiplatelet antibodies	Idiopathic thrombocytopenic purpura	427
	High level of p-dimers	DVT, PE, DIC	428
	•	Reed-Sternberg cells (Hodgkin lymphoma)	429

LAB/DIAGNOSTIC FINDING	DIAGNOSIS/DISEASE	PAGE
Sheets of medium-sized lymphoid cells with scattered pale, tingible body–laden macrophages ("starry sky" histology)	Burkitt lymphoma (t[8:14] c-myc activation, associated with EBV; "starry sky" made up of malignant cells)	430
Lytic ("punched-out") bone lesions on x-ray	Multiple myeloma	431
Monoclonal antibody spike	<ul> <li>Multiple myeloma (usually IgG or IgA)</li> <li>Monoclonal gammopathy of undetermined significance (MGUS consequence of aging)</li> <li>Waldenström (M protein = IgM) macroglobulinemia</li> <li>Primary amyloidosis</li> </ul>	431
Stacks of RBCs	Rouleaux formation (high ESR, multiple myeloma)	423
Azurophilic peroxidase $\oplus$ granular inclusions in granulocytes and myeloblasts	Auer rods (AML, especially the promyelocytic [M3] type)	432
WBCs that look "smudged"	CLL (almost always B cell)	432
"Tennis racket"-shaped cytoplasmic organelles (EM) in Langerhans cells	Birbeck granules (Langerhans cell histiocytosis)	434
"Brown" tumor of bone	Hyperparathyroidism or osteitis fibrosa cystica (deposited hemosiderin from hemorrhage gives brown color)	464
"Soap bubble" in femur or tibia on x-ray	Giant cell tumor of bone (generally benign)	464
Raised periosteum (creating a "Codman triangle")	Aggressive bone lesion (eg, osteosarcoma, Ewing sarcoma, osteomyelitis)	465
"Onion skin" periosteal reaction	Ewing sarcoma (malignant small blue cell tumor)	465
Anti-IgG antibodies	Rheumatoid arthritis (systemic inflammation, joint pannus, boutonniere and swan neck deformities)	466
Rhomboid crystals, ⊕ birefringent	Pseudogout (calcium pyrophosphate dihydrate crystals)	467
Needle-shaped, ⊖ birefringent crystals	Gout (monosodium urate crystals)	467
↑ uric acid levels	Gout, Lesch-Nyhan syndrome, tumor lysis syndrome, loop and thiazide diuretics	467
"Bamboo spine" on x-ray	Ankylosing spondylitis (chronic inflammatory arthritis: HLA-B27)	469
Antinuclear antibodies (ANAs: anti-Smith and anti-dsDNA)	SLE (type III hypersensitivity)	470
Anti-histone antibodies	Drug-induced SLE (eg, hydralazine, isoniazid, phenytoin, procainamide)	250
Anti-topoisomerase antibodies	Diffuse scleroderma	473
Keratin pearls on a skin biopsy	Squamous cell carcinoma	484
Bloody or yellow tap on lumbar puncture	Xanthochromia (due to subarachnoid hemorrhage)	513
Eosinophilic cytoplasmic inclusion in neuron	Lewy body (Parkinson disease and Lewy body dementia)	520
Extracellular amyloid deposition in gray matter of brain	Senile plaques (Alzheimer disease)	520
Depigmentation of neurons in substantia nigra	Parkinson disease (basal ganglia disorder: rigidity, resting tremor, bradykinesia)	520
Protein aggregates in neurons from hyperphosphorylation of tau protein	Neurofibrillary tangles (Alzheimer disease) and Pick bodies (Pick disease)	520
Silver-staining spherical aggregation of tau proteins in neurons	Pick bodies (Pick disease: progressive dementia, changes in personality)	520

FAS1\_2019\_17\_Rapid Rev.indd 697 11/7/19 6:09 PM

# RAPID REVIEW → CLASSIC LABS/FINDINGS

LAB/DIAGNOSTIC FINDING	DIAGNOSIS/DISEASE	PAGE
Pseudopalisading tumor cells on brain biopsy	Glioblastoma multiforme	526
Circular grouping of dark tumor cells surrounding pale neurofibrils	Homer-Wright rosettes (neuroblastoma, medulloblastoma)	528
"Waxy" casts with very low urine flow	Chronic end-stage renal disease	594
Nodular hyaline deposits in glomeruli	Kimmelstiel-Wilson nodules (diabetic nephropathy)	597
Podocyte fusion or "effacement" on electron microscopy	Minimal change disease (child with nephrotic syndrome)	597
"Spikes" on basement membrane, "dome-like" subepithelial deposits	Membranous nephropathy (nephrotic syndrome)	597
RBC casts in urine	Glomerulonephritis	594
"Tram-track" appearance of capillary loops of glomerular basement membranes on light microscopy	Membranoproliferative glomerulonephritis	596
Anti-glomerular basement membrane antibodies	Goodpasture syndrome (glomerulonephritis and hemoptysis)	596
Cellular crescents in Bowman capsule	Rapidly progressive (crescentic) glomerulonephritis	596
"Wire loop" glomerular capillary appearance on light microscopy	Diffuse proliferative glomerulonephritis (usually seen with lupus)	596
Linear appearance of IgG deposition on glomerular and alveolar basement membranes	Goodpasture syndrome	596
"Lumpy bumpy" appearance of glomeruli on immunofluorescence	Poststreptococcal glomerulonephritis (due to deposition of IgG, IgM, and C3)	596
Necrotizing vasculitis (lungs) and necrotizing glomerulonephritis	Granulomatosis with polyangiitis (Wegener; PR3-ANCA/ c-ANCA) and Goodpasture syndrome (anti–basement membrane antibodies)	596
Thyroid-like appearance of kidney	Chronic pyelonephritis (usually due to recurrent infections)	600
WBC casts in urine	Acute pyelonephritis	600
Renal epithelial casts in urine	Intrinsic renal failure (eg, ischemia or toxic injury)	601
hCG elevated	Choriocarcinoma, hydatidiform mole (occurs with and without embryo, and multiple pregnancy)	633
Dysplastic squamous cervical cells with "raisinoid" nuclei and hyperchromasia	Koilocytes (HPV: predisposes to cervical cancer)	645
Disarrayed granulosa cells arranged around collections of eosinophilic fluid	Call-Exner bodies (granulosa cell tumor of the ovary)	647
"Chocolate cyst" of ovary	Endometriosis (frequently involves both ovaries)	648
Mammary gland ("blue domed") cyst	Fibrocystic change of the breast	649
Glomerulus-like structure surrounding vessel in germ cells	Schiller-Duval bodies (yolk sac tumor)	647
Rectangular, crystal-like, cytoplasmic inclusions in Leydig cells	Reinke crystals (Leydig cell tumor)	653
Thrombi made of white/red layers	Lines of Zahn (arterial thrombus, layers of platelets/RBCs)	672
Hexagonal, double-pointed, needle-like crystals in bronchial secretions	Bronchial asthma (Charcot-Leyden crystals: eosinophilic granules)	674

FAS1\_2019\_17\_Rapid Rev.indd 698

DIAGNOSIS/DISEASE	PAGE
Curschmann spirals (bronchial asthma; can result in whorled mucous plugs)	674
Idiopathic pulmonary fibrosis	675
Cystic fibrosis (autosomal recessive mutation in <i>CFTR</i> gene → fat-soluble vitamin deficiency and mucous plugs)	675
Ferruginous bodies (asbestosis: † chance of lung cancer)	677
Pancoast tumor (can compress cervical sympathetic chain and cause Horner syndrome)	685
	Curschmann spirals (bronchial asthma; can result in whorled mucous plugs)  Idiopathic pulmonary fibrosis  Cystic fibrosis (autosomal recessive mutation in <i>CFTR</i> gene → fat-soluble vitamin deficiency and mucous plugs)  Ferruginous bodies (asbestosis: † chance of lung cancer)  Pancoast tumor (can compress cervical sympathetic chain

#### ► CLASSIC/RELEVANT TREATMENTS CONDITION COMMON TREATMENT(S) PAGE 72 Ethylene glycol/methanol intoxication Fomepizole (alcohol dehydrogenase inhibitor) IFN- $\alpha$ (HBV and HCV); ribavirin, simeprevir, sofosbuvir 121 Chronic hepatitis B or C (HCV) Penicillin prophylaxis; evaluation for colon cancer if 137 Streptococcus bovis linked to endocarditis 138 Clostridium botulinum Antitoxin 138 Clostridium tetani Antitoxin Haemophilus influenzae (B) Amoxicillin ± clavulanate (mucosal infections), 142 ceftriaxone (meningitis), rifampin (prophylaxis) Ceftriaxone (add doxycycline to cover likely concurrent 142 Neisseria gonorrhoeae C trachomatis) 142 Neisseria meningitidis Penicillin/ceftriaxone, rifampin (prophylaxis) Legionella pneumophila Macrolides (eg, azithromycin) 143 143 Pseudomonas aeruginosa Piperacillin/tazobactam, aminoglycosides, carbapenems Penicillin G 147 Treponema pallidum Doxycycline (+ ceftriaxone for gonorrhea coinfection), 148 Chlamydia trachomatis oral erythromycin to treat chlamydial conjunctivitis in infants 153 Candida albicans Topical azoles (vaginitis); nystatin, fluconazole, caspofungin (oral/esophageal); fluconazole, caspofungin, amphotericin B (systemic) Cryptococcus neoformans Induction with amphotericin B and flucytosine, 153 maintenance with fluconazole (in AIDS patients) 154 Sporothrix schenckii Itraconazole, oral potassium iodide Pneumocystis jirovecii TMP-SMX (prophylaxis and treatment in 154 immunosuppressed patients, CD4 < 200/mm<sup>3</sup>) 156 Toxoplasma gondii Sulfadiazine + pyrimethamine Malaria Chloroquine, mefloquine, atovaquone/proguanil (for 157 blood schizont), primaquine (for liver hypnozoite)

FAS1\_2019\_17\_Rapid Rev.indd 699 11/7/19 6:09 PM

# RAPID REVIEW ► CLASSIC/RELEVANT TREATMENTS

CONDITION	COMMON TREATMENT(S)	PAGE
Trichomonas vaginalis	Metronidazole (patient and partner)	158
Streptococcus pyogenes	Penicillin prophylaxis	187
Streptococcus pneumoniae	Penicillin/cephalosporin (systemic infection, pneumonia), vancomycin (meningitis)	187, 190
Staphylococcus aureus	MSSA: nafcillin, oxacillin, dicloxacillin (antistaphylococcal penicillins); MRSA: vancomycin, daptomycin, linezolid, ceftaroline	188, 190, 195
Enterococci	Vancomycin, aminopenicillins/cephalosporins	189, 190
Rickettsia rickettsii	Doxycycline, chloramphenicol	192
Clostridium difficile	Oral metronidazole; if refractory, oral vancomycin	190, 195
Mycobacterium tuberculosis	RIPE (rifampin, isoniazid, pyrazinamide, ethambutol)	196
UTI prophylaxis	TMP-SMX	198
Influenza	Oseltamivir, zanamivir	201
CMV	Ganciclovir, foscarnet, cidofovir	202
Patent ductus arteriosus	Close with indomethacin; keep open with PGE analogs	282
Stable angina	Sublingual nitroglycerin	304
Buerger disease	Smoking cessation	314
Kawasaki disease	IVIG, aspirin	314
Temporal arteritis	High-dose steroids	314
Granulomatosis with polyangiitis (Wegener)	Cyclophosphamide, corticosteroids	315
Hypercholesterolemia	Statin (first-line)	320
Hypertriglyceridemia	Fibrate	320
Arrhythmia in damaged cardiac tissue	Class IB antiarrhythmic (lidocaine, mexiletine)	322
Prolactinoma	Cabergoline/bromocriptine (dopamine agonists)	330
Diabetes insipidus	Desmopressin (central); hydrochlorothiazide, indomethacin, amiloride (nephrogenic)	338
SIADH	Fluid restriction, IV hypertonic saline, conivaptan/ tolvaptan, demeclocycline	338
Diabetic ketoacidosis	Fluids, insulin, K <sup>+</sup>	347
Diabetes mellitus type 1	Dietary intervention (low carbohydrate) + insulin replacement	347
Diabetes mellitus type 2	Dietary intervention, oral hypoglycemics, and insulin (if refractory)	347
Pheochromocytoma	$\alpha\text{-antagonists (eg, phenoxybenzamine)}$	350
Carcinoid syndrome	Octreotide	352
Crohn disease	Corticosteroids, infliximab, azathioprine	382
Ulcerative colitis	5-ASA preparations (eg, mesalamine), 6-mercaptopurine, infliximab, colectomy	382
Sickle cell disease	Hydroxyurea († fetal hemoglobin)	422

FAS1\_2019\_17\_Rapid Rev.indd 700 11/7/19 6:09 PM

CONDITION	COMMON TREATMENT(S)	PAGE
Chronic myelogenous leukemia	Imatinib	433
Acute promyelocytic leukemia (M3)	All-trans retinoic acid, arsenic trioxide	432
Drug of choice for anticoagulation in pregnancy or renal failure	Low-molecular-weight heparin	436
Heparin reversal	Protamine sulfate	436
Immediate anticoagulation	Heparin	436
Long-term anticoagulation	Warfarin, dabigatran, rivaroxaban and apixaban	436, 437
Warfarin reversal	Fresh frozen plasma (acute), vitamin K (non-acute)	436
Cyclophosphamide-induced hemorrhagic cystitis	Mesna	441
HER2/neu ⊕ breast cancer	Trastuzumab	443
Osteoporosis	Calcium/vitamin D supplementation (prophylaxis); bisphosphonates, PTH analogs, SERMs, calcitonin, denosumab (treatment)	462
Osteomalacia/rickets	Vitamin D supplementation	463
Chronic gout	Xanthine oxidase inhibitors (eg, allopurinol, febuxostat); pegloticase; probenecid	467
Acute gout attack	NSAIDs, colchicine, glucocorticoids	467
Neural tube defect prevention	Prenatal folic acid	491
Migraine	Abortive therapies (eg, sumatriptan, NSAIDs); prophylaxis (eg, propranolol, topiramate, CCBs, amitriptyline)	518
Multiple sclerosis	Disease-modifying therapies (eg, β-interferon, natalizumab); for acute flares, use IV steroids	523
Tonic-clonic seizures	Levetiracetam, phenytoin, valproate, carbamazepine	544
Absence seizures	Ethosuximide	544
Trigeminal neuralgia (tic douloureux)	Carbamazepine	544
Malignant hyperthermia	Dantrolene	551
Anorexia	Nutrition, psychotherapy, SSRIs	567
Bulimia nervosa	SSRIs	567
Alcoholism	Disulfiram, acamprosate, naltrexone, supportive care	571
ADHD	Methylphenidate, amphetamines, CBT, atomoxetine, guanfacine, clonidine	572
Alcohol withdrawal	Long-acting benzodiazepines	572
Bipolar disorder	Mood stabilizers (eg, lithium, valproic acid, carbamazepine), atypical antipsychotics	572
Depression	SSRIs (first-line)	572
Generalized anxiety disorder	SSRIs, SNRIs (first line); buspirone (second line)	572
Schizophrenia (positive symptoms)	Typical and atypical antipsychotics	573
Schizophrenia (negative symptoms)	Atypical antipsychotics	573

# 702 SECTION III RAPID REVIEW > KEY ASSOCIATIONS

CONDITION	COMMON TREATMENT(S)	PAGE
Hyperaldosteronism	Spironolactone	609
Benign prostatic hyperplasia	$\alpha_{_{\! 1}}$ -antagonists, $5\alpha$ -reductase inhibitors, PDE-5 inhibitors	654
Infertility	Leuprolide, GnRH (pulsatile), clomiphene	656
Breast cancer in postmenopausal woman	Aromatase inhibitor (anastrozole)	656
$ER \oplus breast cancer$	Tamoxifen	656
Prostate adenocarcinoma/uterine fibroids	Leuprolide, GnRH (continuous)	656
Medical abortion	Mifepristone	657
Prostate adenocarcinoma	Flutamide	658
Erectile dysfunction	Sildenafil, tadalafil, vardenafil	686
Pulmonary arterial hypertension (idiopathic)	Sildenafil, bosentan, epoprostenol	686

# ► KEY ASSOCIATIONS

	PAGE
Disease occurs in both males and females, inherited through females only	59
Down syndrome, fragile X syndrome	62, 63
Folate (pregnant women are at high risk; body stores only 3- to 4-month supply; prevents neural tube defects)	68
Gaucher disease	88
S pneumoniae	180
Group B streptococcus/E coli/Listeria monocytogenes (newborns), S pneumoniae/N meningitidis (kids/teens)	180
Diabetes mellitus type 1, SLE, Graves disease, Hashimoto thyroiditis (also associated with HLA-DR5), Addison disease	100
Diabetes mellitus type 1, rheumatoid arthritis, Addison disease	100
H pylori	146
Pneumocystis jirovecii pneumonia	154
Enterobius vermicularis	159
HSV-1	164
Hepatitis C	172
S aureus, B cereus	178
S aureus (most common overall)	180
Salmonella	180
Pseudomonas, Candida, S aureus	180
	through females only  Down syndrome, fragile X syndrome  Folate (pregnant women are at high risk; body stores only 3- to 4-month supply; prevents neural tube defects)  Gaucher disease  S pneumoniae  Group B streptococcus/E coli/Listeria monocytogenes (newborns), S pneumoniae/N meningitidis (kids/teens)  Diabetes mellitus type 1, SLE, Graves disease, Hashimoto thyroiditis (also associated with HLA-DR5), Addison disease  Diabetes mellitus type 1, rheumatoid arthritis, Addison disease  H pylori  Pneumocystis jirovecii pneumonia  Enterobius vermicularis  HSV-1  Hepatitis C  S aureus, B cereus  S aureus (most common overall)  Salmonella

DISEASE/FINDING	MOST COMMON/IMPORTANT ASSOCIATIONS	PAGE
UTI	E coli, Staphylococcus saprophyticus (young women)	181
Sexually transmitted disease	C trachomatis (usually coinfected with N gonorrhoeae)	184
Nosocomial pneumonia	S aureus, Pseudomonas, other enteric gram $\ominus$ rods	185
Pelvic inflammatory disease	C trachomatis, N gonorrhoeae	185
Infections in chronic granulomatous disease	S aureus, E coli, Aspergillus (catalase $\oplus$ )	186
Metastases to bone	Prostate, breast > kidney, thyroid, lung	223
Metastases to brain	Lung > breast > melanoma, colon, kidney	223
Metastases to liver	Colon >> stomach > pancreas	223
S3 heart sound	↑ ventricular filling pressure (eg, mitral regurgitation, HF), common in dilated ventricles	287
S4 heart sound	Stiff/hypertrophic ventricle (aortic stenosis, restrictive cardiomyopathy)	287
Constrictive pericarditis	TB (developing world); idiopathic, viral illness (developed world)	287
Holosystolic murmur	VSD, tricuspid regurgitation, mitral regurgitation	291
Ejection click	Aortic stenosis	291
Mitral valve stenosis	Rheumatic heart disease	291
Opening snap	Mitral stenosis	291
Heart murmur, congenital	Mitral valve prolapse	291
Chronic arrhythmia	Atrial fibrillation (associated with high risk of emboli)	295
Cyanosis (early; less common)	Tetralogy of Fallot, transposition of great vessels, truncus arteriosus, total anomalous pulmonary venous return, tricuspid atresia	298
Late cyanotic shunt (uncorrected left to right becomes right to left)	Eisenmenger syndrome (caused by ASD, VSD, PDA; results in pulmonary hypertension/polycythemia)	299
Congenital cardiac anomaly	VSD	299
Hypertension, 2°	Renal artery stenosis, chronic kidney disease (eg, polycystic kidney disease, diabetic nephropathy), hyperaldosteronism	300
Aortic aneurysm, thoracic	Marfan syndrome (idiopathic cystic medial degeneration)	302
Aortic aneurysm, abdominal	Atherosclerosis, smoking is major risk factor	302
Aortic aneurysm, ascending or arch	3° syphilis (syphilitic aortitis), vasa vasorum destruction	303
Sites of atherosclerosis	Abdominal aorta > coronary artery > popliteal artery > carotid artery	302
Aortic dissection	Hypertension	303
Right heart failure due to a pulmonary cause	Cor pulmonale	309
Heart valve in bacterial endocarditis	Mitral > aortic (rheumatic fever), tricuspid (IV drug abuse)	310
Endocarditis presentation associated with bacterium	<i>S aureus</i> (acute, IVDA, tricuspid valve), viridans streptococci (subacute, dental procedure), <i>S bovis</i> (colon cancer), culture negative ( <i>Coxiella</i> , <i>Bartonella</i> , HACEK)	310
Temporal arteritis	Risk of ipsilateral blindness due to occlusion of ophthalmic artery; polymyalgia rheumatica	314

# 704 SECTION III RAPID REVIEW > KEY ASSOCIATIONS

DISEASE/FINDING	MOST COMMON/IMPORTANT ASSOCIATIONS	PAGE
Recurrent inflammation/thrombosis of small/medium vessels in extremities	Buerger disease (strongly associated with tobacco)	314
Cardiac 1° tumor (kids)	Rhabdomyoma, often seen in tuberous sclerosis	316
Cardiac tumor (adults)	Metastasis, myxoma (90% in left atrium; "ball valve")	316
Congenital adrenal hyperplasia, hypotension	21-hydroxylase deficiency	335
Hypopituitarism	Pituitary adenoma (usually benign tumor)	339
Cretinism	Iodine deficit/congenital hypothyroidism	341
Thyroid cancer	Papillary carcinoma (childhood irradiation)	343
Hypoparathyroidism	Accidental excision during thyroidectomy	344
1° hyperparathyroidism	Adenomas, hyperplasia, carcinoma	345
2° hyperparathyroidism	Hypocalcemia of chronic kidney disease	345
Cushing syndrome	<ul> <li>Iatrogenic (from corticosteroid therapy)</li> <li>Adrenocortical adenoma (secretes excess cortisol)</li> <li>ACTH-secreting pituitary adenoma (Cushing disease)</li> <li>Paraneoplastic (due to ACTH secretion by tumors)</li> </ul>	348
1° hyperaldosteronism	Adrenal hyperplasia or adenoma	349
Tumor of the adrenal medulla (kids)	Neuroblastoma (malignant)	350
Tumor of the adrenal medulla (adults)	Pheochromocytoma (usually benign)	350
Refractory peptic ulcers and high gastrin levels	Zollinger-Ellison syndrome (gastrinoma of duodenum or pancreas), associated with MEN1	351, 352
Esophageal cancer	Squamous cell carcinoma (worldwide); adenocarcinoma (US)	378
Acute gastric ulcer associated with CNS injury	Cushing ulcer († intracranial pressure stimulates vagal gastric H+ secretion)	379
Acute gastric ulcer associated with severe burns	Curling ulcer (greatly reduced plasma volume results in sloughing of gastric mucosa)	379
Bilateral ovarian metastases from gastric carcinoma	Krukenberg tumor (mucin-secreting signet ring cells)	379
Chronic atrophic gastritis (autoimmune)	Predisposition to gastric carcinoma (can also cause pernicious anemia)	379
Gastric cancer	Adenocarcinoma	379
Alternating areas of transmural inflammation and normal colon	Skip lesions (Crohn disease)	382
Site of diverticula	Sigmoid colon	383
Diverticulum in pharynx	Zenker diverticulum (diagnosed by barium swallow)	384
Hepatocellular carcinoma	Cirrhotic liver (associated with hepatitis B and C, alcoholism, and hemochromatosis)	392
Liver disease	Alcoholic cirrhosis	391
l° liver cancer	Hepatocellular carcinoma (chronic hepatitis, cirrhosis, hemochromatosis, $\alpha_l$ -antitrypsin deficiency, Wilson disease)	392
Congenital conjugated hyperbilirubinemia (black liver)	Dubin-Johnson syndrome (inability of hepatocytes to secrete conjugated bilirubin into bile)	394

DISEASE/FINDING	MOST COMMON/IMPORTANT ASSOCIATIONS	PAGE
Hereditary harmless jaundice	Gilbert syndrome (benign congenital unconjugated hyperbilirubinemia)	394
Hemochromatosis	Multiple blood transfusions or hereditary <i>HFE</i> mutation (can result in heart failure, "bronze diabetes," and † risk of hepatocellular carcinoma)	395
Pancreatitis (acute)	Gallstones, alcohol	397
Pancreatitis (chronic)	Alcohol (adults), cystic fibrosis (kids)	397
Microcytic anemia	Iron deficiency	418
Autosplenectomy (fibrosis and shrinkage)	Sickle cell disease (hemoglobin S)	422
Bleeding disorder with GpIb deficiency	Bernard-Soulier syndrome (defect in platelet adhesion to von Willebrand factor)	427
Hereditary bleeding disorder	von Willebrand disease	428
DIC	Severe sepsis, obstetric complications, cancer, burns, trauma, major surgery, acute pancreatitis, APL	428
Malignancy associated with noninfectious fever	Hodgkin lymphoma	429
Type of Hodgkin lymphoma	Nodular sclerosis (vs mixed cellularity, lymphocytic predominance, lymphocytic depletion)	429
t(14;18)	Follicular lymphomas (BCL-2 activation, anti-apoptotic oncogene)	430
t(8;14)	Burkitt lymphoma (c- <i>myc</i> fusion, transcription factor oncogene)	430
Type of non-Hodgkin lymphoma	Diffuse large B-cell lymphoma	430
l° bone tumor (adults)	Multiple myeloma	431
Age ranges for patient with ALL/CLL/AML/CML	ALL: child, CLL: adult > 60, AML: adult ~ 65, CML: adult 45–85	432, 433
Malignancy (kids)	Leukemia, brain tumors	432, 526
Death in CML	Blast crisis	433
t(9;22)	Philadelphia chromosome, CML (BCR-ABL oncogene, tyrosine kinase activation), more rarely associated with ALL	434
Vertebral compression fracture	Osteoporosis (type I: postmenopausal woman; type II: elderly man or woman)	462
HLA-B27	Psoriatic arthritis, ankylosing spondylitis, IBD-associated arthritis, reactive arthritis (formerly Reiter syndrome)	469
Death in SLE	Lupus nephropathy	470
Tumor of infancy	Strawberry hemangioma (grows rapidly and regresses spontaneously by childhood)	478
Actinic (solar) keratosis	Precursor to squamous cell carcinoma	482
Cerebellar tonsillar herniation	Chiari I malformation	492
Atrophy of the mammillary bodies	Wernicke encephalopathy (thiamine deficiency causing ataxia, ophthalmoplegia, and confusion)	511

# 706 SECTION III RAPID REVIEW > KEY ASSOCIATIONS

DISEASE/FINDING	MOST COMMON/IMPORTANT ASSOCIATIONS	PAGE
Epidural hematoma	Rupture of middle meningeal artery (trauma; lentiform shaped)	513
Subdural hematoma	Rupture of bridging veins (crescent shaped)	513
Dementia	Alzheimer disease, multiple infarcts (vascular dementia)	520, 521
Demyelinating disease in young women	Multiple sclerosis	523
Brain tumor (adults)	Supratentorial: metastasis, astrocytoma (including glioblastoma multiforme), meningioma, schwannoma	526
Pituitary tumor	Prolactinoma, somatotropic adenoma	527
Brain tumor (kids)	Infratentorial: medulloblastoma (cerebellum) or supratentorial: craniopharyngioma	528
Mixed (UMN and LMN) motor neuron disease	Amyotrophic lateral sclerosis	530
Degeneration of dorsal column fibers	Tabes dorsalis (3° syphilis), subacute combined degeneration (dorsal columns, lateral corticospinal, spinocerebellar tracts affected)	530
Nephrotic syndrome (adults)	Membranous nephropathy	597
Nephrotic syndrome (kids)	Minimal change disease	597
Glomerulonephritis (adults)	Berger disease (IgA nephropathy)	596
Kidney stones	<ul> <li>Calcium = radiopaque</li> <li>Struvite (ammonium) = radiopaque (formed by urease         ⊕ organisms such as <i>Klebsiella</i>, <i>Proteus</i> species, and         <i>S saprophyticus</i>)</li> <li>Uric acid = radiolucent</li> <li>Cystine = faintly radiopaque</li> </ul>	598
Renal tumor	Renal cell carcinoma: associated with von Hippel-Lindau and cigarette smoking; paraneoplastic syndromes (EPO, renin, PTHrP, ACTH)	605
Obstruction of male urinary tract	ВРН	654
l° amenorrhea	Turner syndrome (45,XO or 45,XO/46,XX mosaic)	638
Neuron migration failure	Kallmann syndrome (hypogonadotropic hypogonadism and anosmia)	639
Clear cell adenocarcinoma of the vagina	DES exposure in utero	644
Ovarian tumor (benign, bilateral)	Serous cystadenoma	646
Ovarian tumor (malignant)	Serous cystadenocarcinoma	646
Tumor in women	Leiomyoma (estrogen dependent, not precancerous)	648
Gynecologic malignancy	Endometrial carcinoma (most common in US); cervical carcinoma (most common worldwide)	648
Breast mass	Fibrocystic change, carcinoma (in postmenopausal women)	649
Breast tumor (benign, young woman)	Fibroadenoma	649
Breast cancer	Invasive ductal carcinoma	650
Testicular tumor	Seminoma (malignant, radiosensitive), † placental ALP	652, 653

FAS1\_2019\_17\_Rapid Rev.indd 706 11/7/19 6:09 PM

**SECTION III** 

DISEASE/FINDING	MOST COMMON/IMPORTANT ASSOCIATIONS	PAGE
Pulmonary hypertension	Idiopathic, heritable, left heart disease (eg, HF), lung	679
	disease (eg, COPD), hypoxemic vasoconstriction (eg, OSA), thromboembolic (eg, PE)	
Hypercoagulability, endothelial damage, blood stasis	Virchow triad († risk of thrombosis)	671
SIADH	Small cell carcinoma of the lung	684

### ► EQUATION REVIEW TOPIC PAGE $V_d = \frac{\text{amount of drug in the body}}{\text{plasma drug concentration}}$ Volume of distribution 231 $t_{1\!/\!_2} = \frac{0.7 \times V_d}{CL}$ Half-life 231 $CL = \frac{\text{rate of elimination of drug}}{\text{plasma drug concentration}} = V_{\text{d}} \times K_{\text{e}} \text{ (elimination constant)}$ Drug clearance 231 $LD = \frac{C_p \times V_d}{F}$ Loading dose 231 $D = \frac{C_p \times CL \times \tau}{F}$ Maintenance dose 231 Sensitivity = TP / (TP + FN)Sensitivity 257 Specificity Specificity = TN / (TN + FP)257 PPV = TP / (TP + FP)Positive predictive value 257 NPV = TN / (FN + TN)Negative predictive value 257 $OR = \frac{a/c}{b/d} = \frac{ad}{bc}$ Odds ratio (for case-control studies) 258 Relative risk $RR = \frac{a/(a+b)}{c/(c+d)}$ 258 Attributable risk 258 RRR = 1 - RRRelative risk reduction 258 Absolute risk reduction 258 Number needed to treat NNT = 1/ARR258 Number needed to harm NNH = 1/AR258 $CO = \frac{\text{rate of O}_2 \text{ consumption}}{(\text{arterial O}_2 \text{ content} - \text{venous O}_2 \text{ content})}$ Cardiac output 285 285 $CO = stroke volume \times heart rate$

FAS1\_2019\_17\_Rapid Rev.indd 707 11/7/19 6:09 PM

# 708 SECTION III RAPID REVIEW ► EQUATION REVIEW

TOPIC	EQUATION	PAGE
Mean arterial pressure	$MAP = cardiac output \times total peripheral resistance$	285
	$MAP = \frac{2}{3}$ diastolic + $\frac{1}{3}$ systolic	285
Stroke volume	SV = EDV - ESV	285
Ejection fraction	$EF = \frac{SV}{EDV} = \frac{EDV - ESV}{EDV}$	285
Resistance	$Resistance = \frac{driving \ pressure \ (\Delta P)}{flow \ (Q)} = \frac{8\eta \ (viscosity) \times length}{\pi r^4}$	286
Capillary fluid exchange	$J_v = \text{net fluid flow} = K_f[(P_c - P_i) - \sigma(\pi_c - \pi_i)]$	297
Renal clearance	$C_{x} = (U_{x}V)/P_{x}$	582
Glomerular filtration rate	$C_{inulin} = GFR = U_{inulin} \times V/P_{inulin}$	582
	$=\mathrm{K_{f}}\left[(\mathrm{P_{GC}}-\mathrm{P_{BS}})-(\pi_{\mathrm{GC}}-\pi_{\mathrm{BS}})\right]$	
Effective renal plasma flow	$eRPF = U_{PAH} \times \frac{V}{P_{PAH}} = C_{PAH}$	582
Renal blood flow	$RBF = \frac{RPF}{1 - Hct}$	582
Filtration fraction	$FF = \frac{GFR}{RPF}$	583
Henderson-Hasselbalch equation (for extracellular pH)	$pH = 6.1 + log \frac{[HCO_3^-]}{0.03 Pco_2}$	592
Winters formula	$Pco_2 = 1.5 [HCO_3^-] + 8 \pm 2$	592
Anion gap	$Na^+ - (Cl^- + HCO_3^-)$	592
Physiologic dead space	$V_{D} = V_{T} \times \frac{Paco_{2} - Peco_{2}}{Paco_{2}}$	664
Pulmonary vascular resistance	$PVR = \frac{P_{\text{pulm artery}} - P_{\text{L atrium}}}{\text{cardiac output}}$	668
Alveolar gas equation	$PAO_2 = PIO_2 - \frac{Paco_2}{R}$	668

FAS1\_2019\_17\_Rapid Rev.indd 708 11/7/19 6:09 PM

► EASILY CONFUSED ME	DICATIONS
DRUG	CLINICAL USE/MECHANISM OF ACTION
Amiloride	K <sup>+</sup> -sparing diuretic
Amiodarone	Class III antiarrhythmic
Amlodipine	Dihydropyridine Ca <sup>2+</sup> channel blocker
Benztropine	Cholinergic antagonist
Bromocriptine	Dopamine agonist
Buspirone	Generalized anxiety disorder (5-HT <sub>1A</sub> -receptor agonist)
Bupropion	Depression, smoking cessation (NE-DA reuptake inhibitor)
Cimetidine	H <sub>2</sub> -receptor antagonist
Cetirizine	2nd-generation antihistamine
Chloramphenicol	Antibiotic (blocks 50S subunit)
Chlordiazepoxide	Long-acting benzodiazepine
Chlorpromazine	Typical antipsychotic
Chlorpropamide	1st-generation sulfonylurea
Chlorpheniramine	lst-generation antihistamine
Chlorthalidone	Thiazide diuretic
Clozapine	5-HT <sub>2A</sub> -agonist
Clomipramine	Tricyclic antidepressant
Clomiphene	Selective estrogen receptor modulator
Clonidine	$\alpha_2$ -agonist
Doxepin	Tricyclic antidepressant
Doxazosin	$\alpha_1$ -antagonist
Eplerenone	K <sup>+</sup> -sparing diuretic
Propafenone	Class IC antiarrhythmic
Fluoxetine	Selective serotonin reuptake inhibitor
Fluphenazine	Typical antipsychotic
Duloxetine	Serotonin-norepinephrine reuptake inhibitor
Guaifenesin	Expectorant (thins respiratory secretions)
Guanfacine	$\alpha_{\gamma}$ -agonist
Mifepristone	Progesterone receptor antagonist
Misoprostol	PGE <sub>1</sub> synthetic analog
Naloxone	Opioid receptor antagonist (treats toxicity)
Naltrexone	Opioid receptor antagonist (prevents relapse)
Nitroprusside	Hypertensive emergency († cGMP/NO)
Nitroglycerin	Antianginal († cGMP/NO)
Omeprazole	Proton pump inhibitor
Ketoconazole	Antifungal (inhibits fungal sterol synthesis)
KCtocollazoic	Antifungai (fillifotis fungai steroi synthesis)

710 SECTION III RAPID REVIEW > EASILY CONFUSED MEDICATIONS

DRUG	CLINICAL USE/MECHANISM OF ACTION
Aripiprazole	Atypical antipsychotic
Anastrozole	Aromatase inhibitor
Rifaximin	Hepatic encephalopathy (↓ ammoniagenic bacteria)
Rifampin	Antimicrobial (inhibits DNA-dependent RNA polymerase)
Sertraline	Selective serotonin reuptake inhibitor
Selegiline	MAO-B inhibitor
Trazodone	Insomnia (blocks 5-HT <sub>2</sub> , $\alpha_1$ -adrenergic, and H <sub>1</sub> receptors)
Tramadol	Chronic pain (weak opioid agonist)
Varenicline	Smoking cessation (nicotinic ACh receptor partial agonist)
Venlafaxine	Serotonin-norepinephrine reuptake inhibitor

FAS1\_2019\_17\_Rapid Rev.indd 710 11/7/19 6:09 PM

# SECTION IV

# **Top-Rated Review Resources**

"Some books are to be tasted, others to be swallowed, and some few to be chewed and digested."

-Sir Francis Bacon

"Always read something that will make you look good if you die in the middle of it."

-P.J. O'Rourke

"So many books, so little time."

—Frank Zappa

"If one cannot enjoy reading a book over and over again, there is no use in reading it at all."

-Oscar Wilde

▶ How to Use the Database 712 ▶ Question Banks and 714 ▶ Web and Mobile Apps 714 **▶** Comprehensive 715 ▶ Anatomy, Embryology, and Neuroscience ▶ Behavioral Science 716 **▶** Biochemistry 716 ▶ Cell Biology and 716 Histology ▶ Microbiology and **Immunology** 717 **▶** Pathology 717 **▶** Pharmacology 718 **▶** Physiology 718

711

## ► HOW TO USE THE DATABASE

This section is a database of top-rated basic science review books, sample examination books, software, websites, and apps that have been marketed to medical students studying for the USMLE Step 1. For each recommended resource, we list (where applicable) the Title, the First Author (or editor), the Current Publisher, the Copyright Year, the Number of Pages, the Approximate List Price, the Format of the resource, and the Number of Test Questions. Finally, each recommended resource receives a Rating. Within each section, resources are arranged first by Rating and then alphabetically by the first author within each Rating group.

For a complete list of resources, including summaries that describe their overall style and utility, go to www.firstaidteam.com/bonus.

A letter rating scale with six different grades reflects the detailed student evaluations for **Rated Resources**. Each rated resource receives a rating as follows:

A+	Excellent for boards review.
A A–	Very good for boards review; choose among the group.
B+ B	Good, but use only after exhausting better resources.
В-	Fair, but there are many better resources in the discipline; or low-yield subject material.

The Rating is meant to reflect the overall usefulness of the resource in helping medical students prepare for the USMLE Step 1. This is based on a number of factors, including:

- The cost
- The readability of the text or usability of the app
- The appropriateness and accuracy of the material
- The quality and number of sample questions
- The quality of written answers to sample questions
- The quality and appropriateness of the illustrations (eg, graphs, diagrams, photographs)
- The length of the text (longer is not necessarily better)
- The quality and number of other resources available in the same discipline
- The importance of the discipline for the USMLE Step 1

Please note that ratings do not reflect the quality of the resources for purposes other than reviewing for the USMLE Step 1. Many books with lower ratings are well written and informative but are not ideal for boards

**SECTION IV** 

preparation. We have not listed or commented on general textbooks available in the basic sciences.

Evaluations are based on the cumulative results of formal and informal surveys of thousands of medical students at many medical schools across the country. The ratings represent a consensus opinion, but there may have been a broad range of opinion or limited student feedback on any particular resource.

Please note that the data listed are subject to change in that:

- Publishers' prices change frequently.
- Bookstores often charge an additional markup.
- New editions come out frequently, and the quality of updating varies.
- The same book may be reissued through another publisher.

We actively encourage medical students and faculty to submit their opinions and ratings of these basic science review materials so that we may update our database. (See p. xvii, How to Contribute.) In addition, we ask that publishers and authors submit for evaluation review copies of basic science review books, including new editions and books not included in our database. We also solicit reviews of new books or suggestions for alternate modes of study that may be useful in preparing for the examination, such as flash cards, computer software, commercial review courses, apps, and websites.

#### **Disclaimer/Conflict of Interest Statement**

No material in this book, including the ratings, reflects the opinion or influence of the publisher. All errors and omissions will gladly be corrected if brought to the attention of the authors through our blog at www.firstaidteam.com. Please note that USMLE-Rx and the entire First Aid for the USMLE series are publications by certain authors of this book; the following ratings are based solely on recommendations from the student authors of this book as well as data from the student survey and feedback forms.

# ► TOP-RATED REVIEW RESOURCES

#### **Question Banks and Books**

		AUTHOR	PUBLISHER	TYPE	PRICE
<b>A</b> +	UWorld Qbank	UWorld	www.uworld.com	Test/2400 q	\$249-\$749
A	NBME Practice Exams	National Board of Medical Examiners	www.nbme.org/students/sas/ Comprehensive.html	Test/200 q	\$60
<b>A</b> -	AMBOSS	Amboss	www.amboss.com	Test/3500 q	\$9-\$365
<b>A</b> -	USMLE-Rx Qmax	USMLE-Rx	www.usmle-rx.com	Test/2300 q	\$89-\$339
B <sup>+</sup>	Kaplan Qbank	Kaplan	www.kaptest.com	Test/2100 q	\$99-\$349
В	BoardVitals		www.boardvitals.com	Test/1750 q	\$59–\$179
В	Kaplan USMLE Step 1 Qbook	Kaplan	Kaplan, 2017, 468 pages	Test/850 q	\$50
В	Pastest		www.pastest.com	Test/2100 q	\$79-\$249
В	TrueLearn Review		www.truelearn.com	Test/2200 q	\$159-\$399

### **Web and Mobile Apps**

		AUTHOR	PUBLISHER	ТҮРЕ	PRICE
A	Anki		www.ankisrs.net	Flash cards	Free
A	Boards and Beyond		www.boardsbeyond.com	Review/ Test/1300 q	\$19–\$249
A	Physeo		www.physeo.com	Review	\$30-\$150
A	SketchyMedical		www.sketchymedical.com	Review	\$99-\$369
<b>A</b> -	Cram Fighter		www.cramfighter.com	Study plan	\$29-\$159
<b>A</b> -	First Aid Step 1 Express		www.usmle-rx.com	Review/Test	\$69-\$299
B <sup>+</sup>	First Aid Step 1 Flash Facts		www.usmle-rx.com	Flash cards	\$29-\$149
B <sup>+</sup>	Medbullets		www.medbullets.com	Review/ Test/1000 q	Free
B <sup>+</sup>	Medical School Pathology		www.medicalschoolpathology.com	Review	Free
B <sup>+</sup>	OnlineMedEd		www.onlinemeded.org	Review	Free
B <sup>+</sup>	Osmosis		www.osmosis.org	Test	\$179-\$279
B <sup>+</sup>	USMLE Step 1 Mastery		builtbyhlt.com/medical/usmle-step- 1-mastery	Test/1400 q	\$2–\$10
B <sup>+</sup>	WebPath: The Internet Pathology Laboratory		webpath.med.utah.edu	Review/ Test/1300 q	Free
В	Blue Histology		www.lab.anhb.uwa.edu.au/mb140	Review/Test	Free
В	Digital Anatomist Project: Interactive Atlases	University of Washington	da.si.washington.edu/da.html	Review	Free
В	Dr. Najeeb Lectures		www.drnajeeblectures.com	Review	\$99

В	Firecracker	Firecracker Inc.	firecracker.lww.com	Review/ Test/2800 q	\$39-\$660		
В	KISSPrep		www.kissprep.com	Review	\$99-\$135		
В	Lecturio		www.lecturio.com	Review/ Test/2150 q	\$50-\$300		
В	Memorang	Memorang Inc.	www.memorangapp.com	Flash cards	\$19-\$239		
В	Picmonic		www.picmonic.com	Review	\$25-\$480		
B-	Radiopaedia.org		www.radiopaedia.org	Cases/Test	Free		
B-	The Pathology Guy	Friedlander	www.pathguy.com	Review	Free		
Comprehensive							
		AUTHOR	PUBLISHER	TYPE	PRICE		
A	First Aid for the Basic Sciences: General	Le	McGraw-Hill, 2017, 528 pages	Review	\$55		

		AUTHOR	PUBLISHER	TYPE	PRICE
A	First Aid for the Basic Sciences: General Principles	Le	McGraw-Hill, 2017, 528 pages	Review	\$55
A	First Aid Cases for the USMLE Step 1	Le	McGraw-Hill, 2018, 496 pages	Cases	\$50
<b>A</b> -	First Aid for the Basic Sciences: Organ Systems	Le	McGraw-Hill, 2017, 912 pages	Review	\$72
<b>A</b> -	Crush Step 1: The Ultimate USMLE Step 1 Review	O'Connell	Elsevier, 2017, 704 pages	Review	\$45
<b>A</b> -	Cracking the USMLE Step 1	Princeton Review	Princeton Review, 2013, 832 pages	Review	\$45
B <sup>+</sup>	USMLE Step 1 Secrets in Color	Brown	Elsevier, 2016, 800 pages, ISBN 9780323396790	Review	\$43
<b>B</b> +	Step-Up to USMLE Step 1 2015	Jenkins	Lippincott Williams & Wilkins, 2014, 528 pages	Review	\$50
B <sup>+</sup>	USMLE Step 1 Lecture Notes 2018	Kaplan	Kaplan Medical, 2018, ~2700 pages	Review	\$330
<b>B</b> +	USMLE Images for the Boards: A Comprehensive Image-Based Review	Tully	Elsevier, 2012, 296 pages	Review	\$42
В	USMLE Step 1 Made Ridiculously Simple	Carl	MedMaster, 2017, 416 pages,	Review/Test 1000 q	\$30
В	medEssentials for the USMLE Step 1	Manley	Kaplan, 2012, 588 pages	Review	\$55

### Anatomy, Embryology, and Neuroscience

		AUTHOR	PUBLISHER	TYPE	PRICE
<b>A</b> -	High-Yield Gross Anatomy	Dudek	Lippincott Williams & Wilkins, 2014, 320 pages	Review	\$43
<b>A</b> -	Clinical Anatomy Made Ridiculously Simple	Goldberg	MedMaster, 2016, 175 pages	Review	\$30
B <sup>+</sup>	High-Yield Embryology	Dudek	Lippincott Williams & Wilkins, 2013, 176 pages	Review	\$56
B <sup>+</sup>	High-Yield Neuroanatomy	Fix	Lippincott Williams & Wilkins, 2015, 208 pages	Review/ Test/50 q	\$40

### Anatomy, Embryology, and Neuroscience (continued)

		AUTHOR	PUBLISHER	TYPE	PRICE
B <sup>+</sup>	Anatomy—An Essential Textbook	Gilroy	Thieme, 2017, 528 pages	Text/ Test/400 q	\$48
B <sup>+</sup>	Netter's Anatomy Flash Cards	Hansen	Saunders, 2018, 688 flash cards	Flash cards	\$40
B <sup>+</sup>	Crash Course: Anatomy	Stenhouse	Elsevier, 2015, 288 pages	Review	\$45
В	BRS Embryology	Dudek	Lippincott Williams & Wilkins, 2014, 336 pages	Review/ Test/220 q	\$56
В	Anatomy Flash Cards: Anatomy on the Go	Gilroy	Thieme, 2013, 752 flash cards	Flash cards	\$60
В	Clinical Neuroanatomy Made Ridiculously Simple	Goldberg	MedMaster, 2014, 90 pages + CD- ROM	Review/Test/ Few q	\$26
В	Netter's Anatomy Coloring Book	Hansen	Elsevier, 2018, 392 pages	Review	\$20
В	Case Files: Anatomy	Toy	McGraw-Hill, 2014, 416 pages	Cases	\$35
B-	Case Files: Neuroscience	Toy	McGraw-Hill, 2014, 432 pages	Cases	\$35

#### **Behavioral Science**

			AUTHOR	PUBLISHER	TYPE	PRICE
4	A-	BRS Behavioral Science	Fadem	Lippincott Williams & Wilkins, 2016, 384 pages	Review/ Test/700 q	\$52
Ī	B⁺	High-Yield Biostatistics, Epidemiology, and Public Health	Glaser	Lippincott Williams & Wilkins, 2013, 168 pages	Review	\$43

# **Biochemistry**

		AUTHOR	PUBLISHER	TYPE	PRICE
<b>A</b> -	Pixorize		www.pixorize.com	Review	\$100-\$130
B <sup>+</sup>	Medical Biochemistry—An Illustrated Review	Panini	Thieme, 2013, 441 pages	Review/ Test/400 q	\$40
В	Lange Flash Cards Biochemistry and Genetics	Baron	McGraw-Hill, 2017, 196 flash cards	Flash cards	\$40
В	Lippincott Illustrated Reviews: Biochemistry	Ferrier	Lippincott Williams & Wilkins, 2017, 560 pages	Review/ Test/200 q	\$78
В	BRS Biochemistry, Molecular Biology, and Genetics	Lieberman	Lippincott Williams & Wilkins, 2013, 432 pages	Review/Test	\$54
В	Case Files: Biochemistry	Toy	McGraw-Hill, 2014, 480 pages	Cases	\$35
В	PreTest Biochemistry and Genetics	Wilson	McGraw-Hill, 2017, 592 pages	Test/500 q	\$38

### **Cell Biology and Histology**

		AUTHOR	PUBLISHER	TYPE	PRICE
B <sup>+</sup>	BRS Cell Biology and Histology	Gartner	Lippincott Williams & Wilkins, 2018, 448 pages	Review/ Test/320 q	\$54
B <sup>+</sup>	Crash Course: Cell Biology and Genetics	Stubbs	Elsevier, 2015, 216 pages	Review/Print + online	\$47
В	Wheater's Functional Histology	Young	Elsevier, 2013, 464 pages	Text	\$83

717

### **Microbiology and Immunology**

		AUTHOR	PUBLISHER	TYPE	PRICE
<b>A</b> -	Basic Immunology	Abbas	Elsevier, 2019, 336 pages	Review	\$70
<b>A</b> -	Clinical Microbiology Made Ridiculously Simple	Gladwin	MedMaster, 2019, 418 pages	Review	\$38
<b>A</b> -	Medical Microbiology and Immunology Flash Cards	Rosenthal	Elsevier, 2016, 192 flash cards	Flash cards	\$40
B <sup>+</sup>	Lippincott Illustrated Reviews: Immunology	Doan	Lippincott Williams & Wilkins, 2012, 384 pages	Reference/ Test/Few q	\$75
B <sup>+</sup>	Microcards: Microbiology Flash Cards	Harpavat	Lippincott Williams & Wilkins, 2015, 312 flash cards	Flash cards	\$53
B <sup>+</sup>	Review of Medical Microbiology and Immunology	Levinson	McGraw-Hill, 2018, 832 pages	Review/ Test/654 q	\$63
B <sup>+</sup>	How the Immune System Works	Sompayrac	Wiley-Blackwell, 2019, 168 pages	Review	\$50
В	Case Studies in Immunology: Clinical Companion	Geha	W. W. Norton & Company, 2016, 384 pages	Cases	\$62
В	Pretest: Microbiology	Kettering	McGraw-Hill, 2013, 480 pages	Test/500 q	\$38
В	Case Files: Microbiology	Toy	McGraw-Hill, 2014, 416 pages	Cases	\$36
В	Lange Microbiology and Infectious Diseases Flash Cards, 3e	Somers	McGraw-Hill Education, 2017, 358 pages	Flash cards	\$46
<b>B</b> -	Lippincott Illustrated Reviews: Microbiology	Cornelissen	Lippincott Williams & Wilkins, 2019, 448 pages	Review/Test/ Few q	\$73

### **Pathology**

ratii	lology				
		AUTHOR	PUBLISHER	TYPE	PRICE
<b>A</b> +	Pathoma: Fundamentals of Pathology	Sattar	Pathoma, 2019, 218 pages	Review/ Lecture	\$85-\$120
<b>A</b> -	Rapid Review: Pathology	Goljan	Elsevier, 2018, 864 pages	Review/ Test/500 q	\$65
<b>A</b> -	Robbins and Cotran Review of Pathology	Klatt	Elsevier, 2014, 504 pages	Test/1100 q	\$55
<b>A</b> -	Crash Course: Pathology	Xiu	Elsevier, 2019, 438 pages	Review	\$40
В	High-Yield Histopathology	Dudek	Lippincott Williams & Wilkins, 2017, 320 pages	Review	\$36
В	Pathophysiology of Disease: Introduction to Clinical Medicine	Hammer	McGraw-Hill, 2018, 832 pages	Text	\$90
В	Haematology at a Glance	Mehta	Blackwell Science, 2014, 136 pages	Review	\$49
В	Pocket Companion to Robbins and Cotran Pathologic Basis of Disease	Mitchell	Elsevier, 2016, 896 pages	Review	\$40
В	BRS Pathology	Schneider	Lippincott Williams & Wilkins, 2013, 480 pages	Review/ Test/450 q	\$54

# 718 SECTION IV

# TOP-RATED REVIEW RESOURCES >

### Pharmacology

		AUTHOR	PUBLISHER	TYPE	PRICE
B <sup>+</sup>	Crash Course: Pharmacology	Battista	Elsevier, 2019, 336 pages	Review	\$40
B <sup>+</sup>	Master the Boards USMLE Step 1 Pharmacology Flashcards	Fischer	Kaplan, 2015, 200 flash cards	Flash cards	\$55
B <sup>+</sup>	BRS Pharmacology	Rosenfeld	Lippincott Williams & Wilkins, 2019, 384 pages	Review/ Test/200 q	\$55
В	Lange Pharmacology Flash Cards	Baron	McGraw-Hill, 2017, 266 flash cards	Flash cards	\$39
В	Pharmacology Flash Cards	Brenner	Elsevier, 2017, 230 flash cards	Flash cards	\$45
В	Katzung & Trevor's Pharmacology: Examination and Board Review	Trevor	McGraw-Hill, 2018, 592 pages	Review/ Test/800 q	\$54
В	Lippincott Illustrated Reviews: Pharmacology	Whalen	Lippincott Williams & Wilkins, 2018, 576 pages	Review/ Test/380 q	\$75

# Physiology

		AUTHOR	PUBLISHER	TYPE	PRICE
<b>A</b> -	BRS Physiology	Costanzo	Lippincott Williams & Wilkins, 2018, 304 pages	Review/ Test/350 q	\$54
<b>A</b> -	Pathophysiology of Heart Disease	Lilly	Lippincott Williams & Williams, 2015, 480 pages	Review	\$57
<b>A</b> -	PreTest Physiology	Metting	McGraw-Hill, 2013, 528 pages	Test/500 q	\$38
<b>A</b> -	Color Atlas of Physiology	Silbernagl	Thieme, 2015, 472 pages	Review	\$50
B <sup>+</sup>	BRS Physiology Cases and Problems	Costanzo	Lippincott Williams & Wilkins, 2012, 368 pages	Cases	\$58
B <sup>+</sup>	Physiology	Costanzo	Saunders, 2017, 528 pages	Text	\$60
B <sup>+</sup>	Vander's Renal Physiology	Eaton	McGraw-Hill, 2018, 224 pages	Text	\$49
B <sup>+</sup>	Acid-Base, Fluids, and Electrolytes Made Ridiculously Simple	Preston	MedMaster, 2017, 166 pages	Review	\$24
B <sup>+</sup>	Pulmonary Pathophysiology: The Essentials	West	Lippincott Williams & Wilkins, 2017, 264 pages	Review/ Test/75 q	\$57
В	Rapid Review: Physiology	Brown	Elsevier, 2011, 384 pages	Test/350 q	\$39
В	Endocrine Physiology	Molina	McGraw-Hill, 2018, 320 pages	Review	\$59
B-	Netter's Physiology Flash Cards	Mulroney	Saunders, 2015, 450 flash cards	Flash cards	\$40

# SECTION IV

# **Abbreviations and Symbols**

ABBREVIATION	MEANING
1st MC*	1st metacarpal
A-a	alveolar-arterial [gradient]
AA	Alcoholics Anonymous, amyloid A
AAMC	Association of American Medical Colleges
AAo*	ascending aorta
Ab	antibody
ABPA	allergic bronchopulmonary aspergillosis
AC	adenylyl cyclase
ACA	anterior cerebral artery
Acetyl-CoA	acetyl coenzyme A
ACD	anemia of chronic disease
ACE	angiotensin-converting enzyme
ACh	acetylcholine
AChE	acetylcholinesterase
ACL	anterior cruciate ligament
ACom	anterior communicating [artery]
ACTH	adrenocorticotropic hormone
AD	Alzheimer disease, autosomal dominant
ADA	adenosine deaminase, Americans with Disabilities Act
ADH	antidiuretic hormone
ADHD	attention-deficit hyperactivity disorder
ADP	adenosine diphosphate
ADPKD	autosomal-dominant polycystic kidney disease
AFP	α-fetoprotein
Ag	antigen, silver
AICA	anterior inferior cerebellar artery
AIDS	acquired immunodeficiency syndrome
AIHA	autoimmune hemolytic anemia
AKI	acute kidney injury
AKT	protein kinase B
AL	amyloid light [chain]
ALA	aminolevulinate
ALI	acute lung injury
ALL	acute lymphoblastic (lymphocytic) leukemia
ALP	alkaline phosphatase
ALS	amyotrophic lateral sclerosis
ALT	alanine transaminase
AMA	American Medical Association, antimitochondrial antibody
AML	acute myelogenous (myeloid) leukemia
AMP	adenosine monophosphate
ANA	antinuclear antibody
ANCA	antineutrophil cytoplasmic antibody
ANOVA	analysis of variance

ABBREVIATION	MEANING
ANP	atrial natriuretic peptide
ANS	autonomic nervous system
Ant*	anterior
anti-CCP	anti-cyclic citrullinated peptide
Ao*	aorta
AOA	American Osteopathic Association
AP	action potential, A & P [ribosomal binding sites]
APC	antigen-presenting cell, activated protein C
Apo	apolipoprotein
APP	amyloid precursor protein
APRT	adenine phosphoribosyltransferase
aPTT	activated partial thromboplastin time
APUD	amine precursor uptake decarboxylase
AR	attributable risk, autosomal recessive, aortic regurgitation
ARB	angiotensin receptor blocker
ARDS	acute respiratory distress syndrome
Arg	arginine
ARPKD	autosomal-recessive polycystic kidney disease
ART	antiretroviral therapy
AS	aortic stenosis
ASA	anterior spinal artery
ASD	atrial septal defect
ASO	anti-streptolysin O
AST	aspartate transaminase
AT	angiotensin, antithrombin
ATN	acute tubular necrosis
ATP	adenosine triphosphate
ATPase	adenosine triphosphatase
ATTR	transthyretin-mediated amyloidosis
AUB	abnormal uterine bleeding
AV	atrioventricular
AZT	azidothymidine
BAL	British anti-Lewisite [dimercaprol]
BBB	blood-brain barrier
BCG	bacille Calmette-Guérin
$BH_4$	tetrahydrobiopterin
BM	basement membrane
BOOP	bronchiolitis obliterans organizing pneumonia
BP	bisphosphate, blood pressure
BPG	bisphosphoglycerate
BPH	benign prostatic hyperplasia
ВТ	bleeding time
BUN	blood urea nitrogen
Ca*	capillary
	* *

<sup>\*</sup>Image abbreviation only

# ABBREVIATIONS AND SYMBOLS

ABBREVIATION	MEANING
Ca <sup>2+</sup>	calcium ion
CAD	coronary artery disease
CAF	common application form
cAMP	cyclic adenosine monophosphate
CBG	corticosteroid-binding globulin
Cbm*	cerebellum
CBSE	Comprehensive Basic Science Examination
CBSSA	Comprehensive Basic Science Self-Assessment
CBT	computer-based test, cognitive behavioral therapy
CC*	corpus callosum
CCA*	common carotid artery
CCK	cholecystokinin
CCS	computer-based case simulation
CD	cluster of differentiation
CDK	cyclin-dependent kinase
cDNA	complementary deoxyribonucleic acid
CEA	carcinoembryonic antigen
CETP	cholesteryl-ester transfer protein
CF	cystic fibrosis
CFTR	cystic fibrosis transmembrane conductance regulator
CGD	chronic granulomatous disease
cGMP	cyclic guanosine monophosphate
CGRP	calcitonin gene-related peptide
$C_H l - C_H 3$	constant regions, heavy chain [antibody]
ChAT	choline acetyltransferase
CHD*	common hepatic duct
$\chi^2$	chi-squared
CI	confidence interval
CIN	candidate identification number, carcinoma in situ, cervical intraepithelial neoplasia
CIS	Communication and Interpersonal Skills
CK	clinical knowledge, creatine kinase
CKD	chronic kidney disease
CK-MB	creatine kinase, MB fraction
$C_{L}$	constant region, light chain [antibody]
CL	clearance
Cl-	chloride ion
CLL	chronic lymphocytic leukemia
CMC	carpometacarpal (joint)
CML	chronic myelogenous (myeloid) leukemia
CMV	cytomegalovirus
CN	cranial nerve
CN-	cyanide ion
CNS	central nervous system
CNV	copy number variation
CO	carbon monoxide, cardiac output
CO,	carbon dioxide
CoA	coenzyme A
COLIAI	collagen, type I, alpha 1
COL1A2	collagen, type I, alpha 2
COMT	catechol-O-methyltransferase
COP	coat protein
COPD	chronic obstructive pulmonary disease
CoQ	coenzyme Q

ABBREVIATION	MEANING
COX	cyclooxygenase
$C_p$	plasma concentration
CPAP	continuous positive airway pressure
CPR	cardiopulmonary resuscitation
Cr	creatinine
CRC	colorectal cancer
CREST	calcinosis, Raynaud phenomenon, esophageal dysfunction,
	sclerosis, and telangiectasias [syndrome]
CRH	corticotropin-releasing hormone
CRP	C-reactive protein
CS	clinical skills
C-section	cesarean section
CSF	cerebrospinal fluid
CT	computed tomography
CTP	cytidine triphosphate
CXR	chest x-ray
DA	dopamine
DAF	decay-accelerating factor
DAG	diacylglycerol
dATP	deoxyadenosine triphosphate
DCIS	ductal carcinoma in situ
DCT	distal convoluted tubule
ddI	didanosine
DES	diethylstilbestrol
DH	dehydrogenase
DHAP	dihydroxyacetone phosphate
DHEA	dehydroepiandrosterone
DHF	dihydrofolic acid
DHT	dihydrotestosterone
DI	diabetes insipidus
DIC	disseminated intravascular coagulation
DIP	distal interphalangeal [joint]
DKA	diabetic ketoacidosis
DLCO	diffusing capacity for carbon monoxide
DM	diabetes mellitus
DNA	deoxyribonucleic acid
DNR	do not resuscitate
dNTP	deoxynucleotide triphosphate
DO	doctor of osteopathy
DPGN	diffuse proliferative glomerulonephritis
DPM	doctor of podiatric medicine
DPP-4	dipeptidyl peptidase-4
DPPC	
	dipalmitoylphosphatidylcholine
DS	double stranded
dsDNA	double-stranded deoxyribonucleic acid
dsRNA	double-stranded ribonucleic acid
DRG	dorsal root ganglion
d4T	didehydrodeoxythymidine [stavudine]
dTMP	deoxythymidine monophosphate
DTR	deep tendon reflex
DTs	delirium tremens
dUDP	deoxyuridine diphosphate
dUMP	deoxyuridine monophosphate
DVT	deep venous thrombosis
E*	euthromatin, esophagus

<sup>\*</sup>Image abbreviation only

ABBREVIATION	MEANING
EBV	Epstein-Barr virus
ECA*	external carotid artery
ECF	extracellular fluid
ECFMG	Educational Commission for Foreign Medical Graduates
ECG	electrocardiogram
ECL	enterochromaffin-like [cell]
ECM	extracellular matrix
ECT	electroconvulsive therapy
$ED_{50}$	median effective dose
EDRF	endothelium-derived relaxing factor
EDTA	ethylenediamine tetra-acetic acid
EDV	end-diastolic volume
EEG	electroencephalogram
EF	ejection fraction
EGF	epidermal growth factor
EHEC	enterohemorrhagic E coli
EIEC	enteroinvasive E coli
ELISA	enzyme-linked immunosorbent assay
EM	electron micrograph/microscopy
EMB	eosin-methylene blue
EPEC	eneteropathogenic E coli
Ері	epinephrine
EPO	erythropoietin
EPS	extrapyramidal system
ER	endoplasmic reticulum, estrogen receptor
ERAS	Electronic Residency Application Service
ERCP	endoscopic retrograde cholangiopancreatography
ERP	effective refractory period
eRPF	effective renal plasma flow
ERT	estrogen replacement therapy
ERV	expiratory reserve volume
ESR	erythrocyte sedimentation rate
ESRD	end-stage renal disease
ESV	end-systolic volume
ETEC	enterotoxigenic <i>E coli</i>
EtOH	ethyl alcohol
EV	esophageal vein
F	bioavailability
FA	fatty acid
Fab	fragment, antigen-binding
FAD	flavin adenine dinucleotide
	reduced flavin adenine dinucleotide
FADH <sub>2</sub> FAP	
F1,6BP	familial adenomatous polyposis
	fructose-1,6-bisphosphate
F2,6BP FBPase	fructose-2,6-bisphosphate
FBPase-2	fructose bisphosphatase
	fructose bisphosphatase-2
Fc E <sub>0</sub> D	fragment, crystallizable
FcR	Fc receptor
5f-dUMP	5-fluorodeoxyuridine monophosphate
Fe <sup>2+</sup>	ferrous ion
Fe <sup>3+</sup>	ferric ion
Fem*	femur
FENa	excreted fraction of filtered sodium

ABBREVIATION	MEANING
FEV <sub>1</sub>	forced expiratory volume in 1 second
FF	filtration fraction
FFA	free fatty acid
FGF	fibroblast growth factor
FGFR	fibroblast growth factor receptor
FISH	fluorescence in situ hybridization
FIT	fecal immunochemical testing
FKBP	FK506 binding protein
fMet	formylmethionine
FMG	foreign medical graduate
FMN	flavin mononucleotide
FN	false negative
FP, FP*	false positive, foot process
FRC	functional residual capacity
FSH	follicle-stimulating hormone
FSMB	Federation of State Medical Boards
FTA-ABS	fluorescent treponemal antibody—absorbed
FTD*	frontotemporal dementia
5-FU	5-fluorouracil
FVC	forced vital capacity
GABA	γ-aminobutyric acid
GAG	glycosaminoglycan
Gal	galactose
GBM	glomerular basement membrane
GC	glomerular capillary
G-CSF	granulocyte colony-stimulating factor
GERD	gastroesophageal reflux disease
GFAP	glial fibrillary acid protein
GFR	glomerular filtration rate
GGT	γ-glutamyl transpeptidase
GH	growth hormone
GHB	γ-hydroxybutyrate
GHRH	growth hormone–releasing hormone
$G_{_{\rm I}}$	G protein, I polypeptide
GI	gastrointestinal
GIP	gastric inhibitory peptide
GIST	gastrointestinal stromal tumor
GLUT	glucose transporter
GM	granulocyte macrophage
GM-CSF	granulocyte-macrophage colony stimulating factor
GMP	guanosine monophosphate
GnRH	gonadotropin-releasing hormone
GP	glycoprotein
G6P	glucose-6-phosphate
G6PD	glucose-6-phosphate dehydrogenase
GPe	globus pallidus externa
GPi	globus pallidus interna
GPI	glycosyl phosphatidylinositol
GRP	gastrin-releasing peptide
G <sub>s</sub>	G protein, S polypeptide
GSH	reduced glutathione
~~~	
GSSG	oxidized glutathione
GSSG GTP	oxidized glutathione guanosine triphosphate

<sup>\*</sup>Image abbreviation only

# ABBREVIATIONS AND SYMBOLS

ADDDEVIATION	MEANING
ABBREVIATION	MEANING genitourinary
H*	heterochromatin
H+	
	hydrogen ion
$H_1, H_2$	histamine receptors
H <sub>2</sub> S	hydrogen sulfide
HAV	hepatitis A virus
HAVAb	hepatitis A antibody
Hb	hemoglobin
HBcAb/HBcAg	hepatitis B core antibody/antigen
HBeAb/HBeAg	hepatitis B early antibody/antigen
HBsAb/HBsAg	hepatitis B surface antibody/antigen
HbCO <sub>2</sub>	carbaminohemoglobin
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
hCG	human chorionic gonadotropin
HCO <sub>3</sub> -	bicarbonate
Het	hematocrit
HCTZ	hydrochlorothiazide
HCV	hepatitis C virus
HDL	high-density lipoprotein
HDN	hemolytic disease of the newborn
HDV	hepatitis D virus
H&E	hematoxylin and eosin
HEV	hepatitis E virus
HF	heart failure
Hfr	high-frequency recombination [cell]
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
HGPRT	hypoxanthine-guanine phosphoribosyltransferase
ННЬ	deoxygenated hemoglobin
HHS	hyperosmolar hyperglycemic state
HHV	human herpesvirus
5-HIAA	5-hydroxyindoleacetic acid
HIT	heparin-induced thrombocytopenia
HIV	human immunodeficiency virus
HL	hepatic lipase
HLA	human leukocyte antigen
HMG-CoA	hydroxymethylglutaryl-coenzyme A
HMP	hexose monophosphate
HMWK	high-molecular-weight kininogen
HNPCC	hereditary nonpolyposis colorectal cancer
hnRNA	heterogeneous nuclear ribonucleic acid
$H_2O_2$	hydrogen peroxide
HOCM	hypertrophic obstructive cardiomyopathy
HPA	hypothalamic-pituitary-adrenal [axis]
HPL	human placental lactogen
HPO	hypothalamic-pituitary-ovarian [axis]
HPV	human papillomavirus
HR	heart rate
HSP	Henoch-Schönlein purpura
HSV	herpes simplex virus
5-HT	5-hydroxytryptamine (serotonin)
HTLV	human T-cell leukemia virus
HTN	hypertension

ABBREVIATION	MEANING
HUS	hemolytic-uremic syndrome
HVA	homovanillic acid
IBD	inflammatory bowel disease
IBS	irritable bowel syndrome
IC	inspiratory capacity, immune complex
I <sub>Ca</sub>	calcium current [heart]
I <sub>Ca</sub>	funny current [heart]
ICA	internal carotid artery
ICAM	intercellular adhesion molecule
ICAWI	implantable cardioverter defibrillator
ICE	Integrated Clinical Encounter
ICE	intracellular fluid
ICF	
ID	intracranial pressure identification
	median infective dose
ID <sub>50</sub>	
IDL	intermediate-density lipoprotein
IF	immunofluorescence, initiation factor
IFN	interferon
lg	immunoglobulin
IGF	insulin-like growth factor
I <sub>K</sub>	potassium current [heart]
IL	interleukin
IM	intramuscular
IMA	inferior mesenteric artery
IMG	international medical graduate
IMP	inosine monophosphate
IMV	inferior mesenteric vein
$I_{Na}$	sodium current [heart]
INH	isoniazid
INO	internuclear ophthalmoplegia
INR	International Normalized Ratio
IO	inferior oblique [muscle]
IOP	intraocular pressure
$IP_3$	inositol triphosphate
IPV	inactivated polio vaccine
IR	current × resistance [Ohm's law], inferior rectus [muscle]
IRV	inspiratory reserve volume
ITP	idiopathic thrombocytopenic purpura
IUD	intrauterine device
IUGR	intrauterine growth restriction
IV	intravenous
IVC	inferior vena cava
IVDU	intravenous drug use
IVIG	intravenous immunoglobulin
JAK/STAT	Janus kinase/signal transducer and activator of transcription [pathway]
JGA	juxtaglomerular apparatus
JVD	jugular venous distention
JVP	jugular venous pulse
K <sup>+</sup>	potassium ion
KatG	catalase-peroxidase produced by M tuberculosis
K.	elimination constant
K <sub>r</sub>	filtration constant
KG	ketoglutarate
	O

<sup>\*</sup>Image abbreviation only

ABBREVIATION	MEANING
K <sub>m</sub>	Michaelis-Menten constant
КОН	potassium hydroxide
L	left, liver
LA	left atrial, left atrium
LAD	left anterior descending coronary artery
LAP	leukocyte alkaline phosphatase
Lat cond*	lateral condyle
Lb*	lamellar body
LCA	left coronary artery
LCAT	lecithin-cholesterol acyltransferase
LCC*	left common carotid artery
LCFA	long-chain fatty acid
LCL	lateral collateral ligament
LCME	Liaison Committee on Medical Education
LCMV	lymphocytic choriomeningitis virus
LCX	left circumflex coronary artery
LD	loading dose
LD <sub>50</sub>	median lethal dose
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LES	lower esophageal sphincter
LES	leukocyte function–associated antigen
LFT	liver function test
LH	
LLL*	luteinizing hormone
	left lower lobe (of lung)
LLQ	left lower quadrant
LMN	lateral meniscus, left main coronary artery, light microscop
LMN	lower motor neuron
LOS	lipooligosaccharide
LPA*	left pulmonary artery
LPL	lipoprotein lipase
LPS	lipopolysaccharide
LR	lateral rectus [muscle]
LT	labile toxin, leukotriene
LUL*	left upper lobe (of lung)
LV	left ventricle, left ventricular
$M_1$ - $M_5$	muscarinic (parasympathetic) ACh receptors
MAC	membrane attack complex, minimum alveolar concentration
MALT	mucosa-associated lymphoid tissue
MAO	monoamine oxidase
MAOI	monoamine oxidase inhibitor
MAP	mean arterial pressure, mitogen-activated protein
Max*	maxillary sinus
MC	midsystolic click
MCA	middle cerebral artery
MCAT	Medical College Admissions Test
MCHC	mean corpuscular hemoglobin concentration
MCL	medial collateral ligament
MCP	metacarpophalangeal [joint]
MCV	mean corpuscular volume
MD	maintenance dose
MDD	major depressive disorder
	, 1

ABBREVIATION	MEANING
MELAS	mitochondrial encephalopathy, lactic acidosis, and stroke-
syndrome	like episodes
MEN	multiple endocrine neoplasia
$Mg^{2+}$	magnesium ion
$MgSO_4$	magnesium sulfate
MGUS	monoclonal gammopathy of undetermined significance
MHC	major histocompatibility complex
MI	myocardial infarction
MIF	müllerian inhibiting factor
MIRL	membrane inhibitor of reactive lysis
MLCK	myosin light-chain kinase
MLF	medial longitudinal fasciculus
MMC	migrating motor complex
MMR	measles, mumps, rubella [vaccine]
6-MP	6-mercaptopurine
MPGN	membranoproliferative glomerulonephritis
MPO	myeloperoxidase
MPO-ANCA/	myeloperoxidase/perinuclear antineutrophil cytoplasmic
p-ANCA	antibody
MR	medial rectus [muscle], mitral regurgitation
MRI	magnetic resonance imaging
miRNA	microribonucleic acid
mRNA	messenger ribonucleic acid
MRSA	methicillin-resistant S aureus
MS	mitral stenosis, multiple sclerosis
MSH	melanocyte-stimulating hormone
mtDNA	mitochondrial DNA
mTOR	mammalian target of rapamycin
MTP	metatarsophalangeal [joint]
MTX	methotrexate
MVO <sub>2</sub>	myocardial oxygen consumption
MVP	mitral valve prolapse
N*	nucleus
Na <sup>+</sup>	sodium ion
NAT	nucleic acid testing
NAD	nicotinamide adenine dinucleotide
NAD+	oxidized nicotinamide adenine dinucleotide
NADH	reduced nicotinamide adenine dinucleotide
NADP+	oxidized nicotinamide adenine dinucleotide phosphate
NADPH	reduced nicotinamide adenine dinucleotide phosphate
NBME	National Board of Medical Examiners
NBOME	National Board of Osteopathic Medical Examiners
NBPME	National Board of Podiatric Medical Examiners
NE	norepinephrine
NF	neurofibromatosis
NFAT	nuclear factor of activated T-cell
NH <sub>3</sub>	ammonia
NH <sub>4</sub> <sup>+</sup>	ammonium
NK	natural killer [cells]
$N_{_{ m M}}$	muscarinic ACh receptor in neuromuscular junction
NMDA	N-methyl-d-aspartate
NMJ	neuromuscular junction
NMS	neuroleptic malignant syndrome
$N_{_{N}}$	nicotinic ACh receptor in autonomic ganglia

<sup>\*</sup>Image abbreviation only

# ABBREVIATIONS AND SYMBOLS

ABBREVIATION	MEANING
NRMP	National Residency Matching Program
NNRTI	non-nucleoside reverse transcriptase inhibitor
NO	nitric oxide
N <sub>2</sub> O	nitrous oxide
NPH	neutral protamine Hagedorn, normal pressure hydrocephalus
NPV	negative predictive value
NRTI	nucleoside reverse transcriptase inhibitor
NSAID	nonsteroidal anti-inflammatory drug
NSE	neuron-specific enolase
NSTEMI	non-ST-segment elevation myocardial infarction
Nu*	nucleolus
OAA	oxaloacetic acid
OCD	obsessive-compulsive disorder
OCP	oral contraceptive pill
ODC	oxygen-hemoglobin dissociation curve
HC	hydroxy
1,25-OH D <sub>3</sub>	calcitriol (active form of vitamin D)
25-OH D,	storage form of vitamin D
OPV	oral polio vaccine
OR	odds ratio
OS	opening snap
OSA	obstructive sleep apnea
OVLT	organum vasculosum of the lamina terminalis
P-body	processing body (cytoplasmic)
P-450	cytochrome P-450 family of enzymes
PA	posteroanterior, pulmonary artery
PABA	para-aminobenzoic acid
Paco <sub>2</sub>	arterial Pco <sub>2</sub>
Paco <sub>2</sub>	alveolar Pco <sub>2</sub>
PAH	para-aminohippuric acid
PAN	polyarteritis nodosa
Pao <sub>2</sub>	partial pressure of oxygen in arterial blood
PAO <sub>2</sub>	partial pressure of oxygen in alveolar blood
PAP	Papanicolaou [smear], prostatic acid phosphatase
PAPPA	pregnancy-associated plasma protein A
PAS	periodic acid–Schiff
Pat*	patella
PBP	penicillin-binding protein
PC	platelet count, pyruvate carboxylase
PCA	posterior cerebral artery
PCC	prothrombin complex concentrate
PCL	posterior cruciate ligament
Pco,	partial pressure of carbon dioxide
PCom	posterior communicating [artery]
PCOS	polycystic ovarian syndrome
PCP	phencyclidine hydrochloride, <i>Pneumocystis jirovecii</i> pneumonia
PCR	polymerase chain reaction
PCT	proximal convoluted tubule
PCV13	pneumococcal conjugate vaccine
PCWP	pulmonary capillary wedge pressure
PDA	patent ductus arteriosus, posterior descending artery
PDE	phosphodiesterase

ABBREVIATION	MEANING
PDGF	platelet-derived growth factor
PDH	pyruvate dehydrogenase
PE	pulmonary embolism
PECAM	platelet–endothelial cell adhesion molecule
PECO <sub>2</sub>	expired air Pco <sub>2</sub>
PEP	phosphoenolpyruvate
PF	platelet factor
PFK	phosphofructokinase
PFK-2	phosphofructokinase-2
PFT	pulmonary function test
PG	phosphoglycerate
$P_{i}$	plasma interstitial osmotic pressure, inorganic phosphate
PICA	posterior inferior cerebellar artery
PID	pelvic inflammatory disease
Pio <sub>2</sub>	Po <sub>2</sub> in inspired air
PIP	proximal interphalangeal [joint]
PIP <sub>2</sub>	phosphatidylinositol 4,5-bisphosphate
PIP <sub>3</sub>	phosphatidylinositol 3,4,5-bisphosphate
PKD	polycystic kidney disease
PKR	interferon-α-induced protein kinase
PKU	phenylketonuria
PLP	pyridoxal phosphate
PML	progressive multifocal leukoencephalopathy
PMN	polymorphonuclear [leukocyte]
P <sub>net</sub>	net filtration pressure
net PNET	primitive neuroectodermal tumor
PNS	peripheral nervous system
Po,	partial pressure of oxygen
PO <sub>2</sub> <sup>3-</sup>	phosphate
	popliteal artery
Pop*	
Pop a* Post*	popliteal artery
PPAR	posterior peroxisome proliferator-activated receptor
PPD	purified protein derivative
PPI	proton pump inhibitor
PPM	parts per million
PPSV23	pneumococcal polysaccharide vaccine
PPV	positive predictive value
PR3-ANCA/ c-ANCA	cytoplasmic antineutrophil cytoplasmic antibody
PrP	prion protein
	1 1
PRPP	phosphoribosylpyrophosphate
PSA	prostate-specific antigen
PSS	progressive systemic sclerosis
PT	prothrombin time
PTEN	phosphatase and tensin homolog
PTH	parathyroid hormone
PTHrP	parathyroid hormone-related protein
PTSD	post-traumatic stress disorder
PTT	partial thromboplastin time
PV	plasma volume, venous pressure
Pv*	pulmonary vein
PVC	polyvinyl chloride
PVR	pulmonary vascular resistance

<sup>\*</sup>Image abbreviation only

ABBREVIATION	MEANING		
R	correlation coefficient, right, R variable [group]		
R <sub>3</sub>	Registration, Ranking, & Results [system]		
RA			
	right atrium		
RAAS	renin-angiotensin-aldosterone system		
RANK-L	receptor activator of nuclear factor-κ B ligand		
RAS	reticular activating system		
RBF	renal blood flow		
RCA	right coronary artery		
REM	rapid eye movement		
RER	rough endoplasmic reticulum		
Rh	rhesus antigen		
RLL*	right lower lobe (of lungs)		
RLQ	right lower quadrant		
RML*	right middle lobe (of lung)		
RNA	ribonucleic acid		
RNP	ribonucleoprotein		
ROS	reactive oxygen species		
RPF	renal plasma flow		
RPGN	rapidly progressive glomerulonephritis		
RPR	rapid plasma reagin		
RR	relative risk, respiratory rate		
rRNA	ribosomal ribonucleic acid		
RS	Reed-Sternberg [cells]		
RSC*	right subclavian artery		
RSV			
RTA	respiratory syncytial virus renal tubular acidosis		
RUL*			
	right upper lobe (of lung)		
RUQ	right upper quadrant		
RV	residual volume, right ventricle, right ventricular		
RVH	right ventricular hypertrophy		
[S]	substrate concentration		
SA	sinoatrial		
SAA	serum amyloid-associated [protein]		
SAM	S-adenosylmethionine		
SARS	severe acute respiratory syndrome		
SCC	squamous cell carcinoma		
SCD	sudden cardiac death		
SCID	severe combined immunodeficiency disease		
SCJ	squamocolumnar junction		
SCM	sternocleidomastoid muscle		
SCN	suprachiasmatic nucleus		
SD	standard deviation		
SE	standard error [of the mean]		
SEP	Spoken English Proficiency		
SER	smooth endoplasmic reticulum		
SERM	selective estrogen receptor modulator		
SGLT	sodium-glucose transporter		
SHBG	sex hormone–binding globulin		
SIADH	syndrome of inappropriate [secretion of] antidiuretic hormone		
SIDS	sudden infant death syndrome		
SJS	Stevens-Johnson syndrome		
SLE	systemic lupus erythematosus		
SLL	small lymphocytic lymphoma		
SEE	знан туптриосунс туптрионы		

ABBREVIATION	MEANING		
SLT	Shiga-like toxin		
SMA	superior mesenteric artery		
SMX	sulfamethoxazole		
SNARE	soluble NSF attachment protein receptor		
SNc	substantia nigra pars compacta		
SNP	single nucleotide polymorphism		
SNr	substantia nigra pars reticulata		
SNRI	serotonin and norepinephrine receptor inhibitor		
snRNA	small nuclear RNA		
snRNP	small nuclear ribonucleoprotein		
SO	superior oblique [muscle]		
SOAP	Supplemental Offer and Acceptance Program		
Sp*	spleen		
spp SR	species		
SS	superior rectus [muscle] single stranded		
ssDNA	single-stranded deoxyribonucleic acid		
SSPE	-		
SSRI	subacute sclerosing panencephalitis selective serotonin reuptake inhibitor		
ssRNA	single-stranded ribonucleic acid		
St*	stomach		
ST	Shiga toxin		
StAR	steroidogenic acute regulatory protein		
STEMI	ST-segment elevation myocardial infarction		
STLWII	sexually transmitted infection		
STN	subthalamic nucleus		
SV			
SVC	splenic vein, stroke volume		
SVR	superior vena cava systemic vascular resistance		
SVT	supraventricular tachycardia		
T*	trachea		
t <sub>1/2</sub>	half-life		
T <sub>3</sub>	triiodothyronine		
T <sub>4</sub>	thyroxine		
TAPVR	total anomalous pulmonary venous return		
ТВ	tuberculosis		
TBG	thyroxine-binding globulin		
TBV	total blood volume		
3TC	dideoxythiacytidine [lamivudine]		
TCA	tricarboxylic acid [cycle], tricyclic antidepressant		
Tc cell	cytotoxic T cell		
TCR	T-cell receptor		
TDF	tenofovir disoproxil fumarate		
TdT	terminal deoxynucleotidyl transferase		
TE	tracheoesophageal		
TFT	thyroid function test		
TG	triglyceride		
TGF	transforming growth factor		
Th cell	helper T cell		
THF	tetrahydrofolic acid		
TI	therapeutic index		
TIA	transient ischemic attack		
Tib*	tibia		
TIBC	total iron-binding capacity		
TIPS	transjugular intrahepatic portosystemic shunt		
TI TIA Tib* TIBC	therapeutic index transient ischemic attack tibia total iron-binding capacity		

<sup>\*</sup>Image abbreviation only

# 726 SECTION IV ABBREVIATIONS AND SYMBOLS

ABBREVIATION	MEANING
TLC	total lung capacity
$T_{m}$	maximum rate of transport
TMP	trimethoprim
TN	true negative
TNF	tumor necrosis factor
TNM	tumor, node, metastases [staging]
TOP	topoisomerase
ToRCHeS	Toxoplasma gondii, rubella, CMV, HIV, HSV-2, syphilis
TP	true positive
tPA	tissue plasminogen activator
TPO	thyroid peroxidase, thrombopoietin
TPP	thiamine pyrophosphate
TPPA	Treponema pallidum particle agglutination assay
TPR	total peripheral resistance
TR	tricuspid regurgitation
TRAP	tartrate-resistant acid phosphatase
TRECs	T-cell receptor excision circles
TRH	thyrotropin-releasing hormone
tRNA	transfer ribonucleic acid
TSH	thyroid-stimulating hormone
TSI	triple sugar iron
TSS	toxic shock syndrome
TSST	toxic shock syndrome toxin
TTP	thrombotic thrombocytopenic purpura
TTR	transthyretin
TV	tidal volume
$TXA_2$	thromboxane A <sub>2</sub>
UDP	uridine diphosphate
UMN	upper motor neuron
UMP	uridine monophosphate
UPD	uniparental disomy
URI	upper respiratory infection
USMLE	United States Medical Licensing Examination
UTI	urinary tract infection
UTP	uridine triphosphate

*Ir	nage	ab	brevi	ation	onl	У
-----	------	----	-------	-------	-----	---

ABBREVIATION	MEANING
UV	ultraviolet
$V_1, V_2$	vasopressin receptors
VC	vital capacity
$V_d$	volume of distribution
VD	physiologic dead space
V(D)J	variable, (diversity), joining gene segments rearranged to form Ig genes
VDRL	Venereal Disease Research Laboratory
VEGF	vascular endothelial growth factor
$V_{_{ m H}}$	variable region, heavy chain [antibody]
VHL	von Hippel-Lindau [disease]
VIP	vasoactive intestinal peptide
VIPoma	vasoactive intestinal polypeptide-secreting tumor
VJ	light-chain hypervariable region [antibody]
$V_{_{\rm L}}$	variable region, light chain [antibody]
VLCFA	very-long-chain fatty acids
VLDL	very low density lipoprotein
VMA	vanillylmandelic acid
VMAT	vesicular monoamine transporter
$V_{max}$	maximum velocity
VPL	ventral posterior nucleus, lateral
VPM	ventral posterior nucleus, medial
VPN	vancomycin, polymyxin, nystatin [media]
Ý/Q	ventilation/perfusion [ratio]
VRE	vancomycin-resistant enterococcus
VSD	ventricular septal defect
$V_{T}$	tidal volume
VTE	venous thromboembolism
vWF	von Willebrand factor
VZV	varicella-zoster virus
VMAT	vesicular monoamine transporter
XR	X-linked recessive
XX/XY	normal complement of sex chromosomes for female/male
ZDV	zidovudine [formerly AZT]

### SECTION IV

# **Image Acknowledgments**

In this edition, in collaboration with MedIQ Learning, LLC, and a variety of other partners, we are pleased to include the following clinical images and diagrams for the benefit of integrative student learning.

Portions of this book identified with the symbol 🛭 are copyright © USMLE-Rx.com (MedIQ Learning, LLC).

Portions of this book identified with the symbol 🗓 are copyright © Dr. Richard Usatine and are provided under license through MedIQ Learning, LLC.

Portions of this book identified with the symbol ₹ are listed below by page number.

This symbol refers to material that is available in the public domain.

This symbol Reference to the Creative Commons Attribution license, full text at http://creativecommons.org/licenses/by/4.0/legalcode.

This symbol refers to the Creative Commons Attribution-Share Alike license, full text at: http://creativecommons.org/licenses/by-sa/4.0/legalcode.

#### **Biochemistry**

- **Chromatin structure.** Electron micrograph showing heterochromatin, euchromatin, and nucleolus. This image is a derivative work, adapted from the following source, available under Ra, Rickett JD, Stickle WB. The hypobranchial gland of the estuarine snail *Stramonita haemastoma canaliculata* (Gray) (Prosobranchia: Muricidae): a light and electron microscopical study. *Am Malac Bull.* 1995;11(2):177-190. Available at https://archive.org/details/americanm101119931994amer.
- 49 Cilia structure: Image A. Nine doublet + 2 singlet arrangement of microtubule. Courtesy of Louisa Howard and Michael Binder. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.
- **Cilia structure: Image B.** Cilia structure of basal body. This image is a derivative work, adapted from the following source, available under :: Riparbelli MG, Cabrera OA, Callaini G, et al. Unique properties of *Drosophila* spermatocyte primary cilia. *Biol Open.* 2013 Nov 15; 2(11): 1137–1147. DOI: 10.1242/bio.20135355.
- 49 Cilia structure: Image C. Dextrocardia. This image is a derivative work, adapted from the following source, available under O, Ayoka AO, Akomolafe RO, et al. The role of electrocardiogram in the diagnosis of dextrocardia with mirror image atrial arrangement and ventricular position in a young adult Nigerian in Ile-Ife: a case report. J Med Case Rep. 2015;9:222. DOI: 10.1186/s13256-015-0695-4.
- 51 Osteogenesis imperfecta: Image A. Skeletal deformities in upper extremity of child. This image is a derivative work, adapted from the following source, available under Vanakker OM, Hemelsoet D, De Paepe. Hereditary connective tissue diseases in young adult stroke: a comprehensive synthesis. Stroke Res Treat. 2011;712903. DOI: 10.4061/2011/712903. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.
- 51 Osteogenesis imperfecta: Image B. Blue sclera. This image is a derivative work, adapted from the following source, available under . Wheatley K, Heng EL, Sheppard M, et al. A case of spontaneous intestinal perforation in osteogenesis imperfects. *J Clin Med Res.* 2010;2(4):198–200. DOI: 10.4021/jocmr369w.
- **51 Ehlers-Danlos syndrome: Images A and B.** Hyperextensibility of skin and DIP joint. This image is a derivative work, adapted from the following source, available under Whitaker JK, Alexander, P,

- Chau DYS, et al. Severe conjunctivochalasis in association with classic type Ehlers-Danlos syndrome. *BMC Ophthalmol*. 2012;2:47. DOI: 10.1186/1471-2415-12-47.
- **Elastin: Image A.** Pes escavatum. This image is a derivative work, adapted from the following source, available under De Maio F, Fichera A, De Luna V, et al. Orthopaedic aspects of Marfan syndrome: the experience of a referral center for diagnosis of rare diseases. *Adv Orthop.* 2016; 2016: 8275391. DOI 10.1155/2016/8275391.
- Karyotyping. Paar C, Herber G, Voskova, et al. This image is a derivative work, adapted from the following source, available under Acase of acute myeloid leukemia (AML) with an unreported combination of chromosomal abnormalities: gain of isochromosome 5p, tetrasomy 8 and unbalanced translocation der(19)t(17;19) (q23;p13). Mol Cytogenet. 2013;6:40. DOI: 10.1186/1755-8166-6-40.
- **Fluorescence in situ hybridization.** This image is a derivative work, adapted from the following source, available under Paar C, Herber G, Voskova, et al. A case of acute myeloid leukemia (AML) with an unreported combination of chromosomal abnormalities: gain of isochromosome 5p, tetrasomy 8 and unbalanced translocation der(19)t(17;19)(q23;p13). *Mol Cytogenet*. 2013;6:40. DOI: 10.1186/1755-8166-6-40.
- 57 Genetic terms. Café-au-lait spots. This image is a derivative work, adapted from the following source, available under Dimittescu CE and Collins MT. Orphanet J Rare Dis. 2008;3:12. DOI: 10.1186/1750-1172-3-12.
- 61 Muscular dystrophies: Image A. Fibrofatty replacement of muscle.
  Courtesy of the Department of Health and Human Services and Dr. Edwin P. Ewing, Jr. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.
- **Williams syndrome.** This image is a derivative work, adapted from the following source, available under . Mazumdar J, Sarkar R, Badveli A, et al. Double chamber right ventricle in Williams syndrome: a rare cardiac anomaly reported. *Springerplus*. 2016; 5: 275. DOI: 10.1186/s40064-016-1897-v.
- **Vitamin A.** Bitot sponts on conjunctiva. This image is a derivative work, adapted from the following source, available under Baiyeroju A, Bowman R, Gilbert C, et al. Managing eye health in young children. *Comm Eye Health*. 2010;23(72):4-11. Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2873666.

FAS1 2019 20 ImageAck.indd 727 11/8/19 4:49 PM

- Vitamin B<sub>3</sub>. Pellagra. This image is a derivative work, adapted from the following source, available under with a Dijk HA, Fred H. Images of memorable cases: case 2. Connexions Web site. Dec 4, 2008. Available at: http://cnx.org/contents/3d3dcb2e-8e98-496f-91c2-fe94e93428a1@3@3/.
- 70 Vitamin D. X-ray of lower extremity in child with rickets. This image is a derivative work, adapted from the following source, available under . Dr. Michael L. Richardson. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under ...
- 71 Protein-energy malnutrition: Image A. Child with kwashiorkor.
  © Courtesy of the Department of Health and Human Services and Dr. Lyle Conrad.
- 71 Protein-energy malnutrition: Image B. Child with marasmus.

  Courtesy of the Department of Health and Human Services.
- 85 Cystinuria. Hexagonal cystine stones in urine. This image is a derivative work, adapted from the following source, available under Courtesy of Cayla Devine.
- **88** Lysosomal storage diseases: Image A. "Cherry-red" spot on macula in Tay-Sachs disease. This image is a derivative work, adapted from the following source, available under . Courtesy of Dr. Jonathan Trobe.
- 88 Lysosomal storage diseases: Image B. Angiokeratomas. This image is a derivative work, adapted from the following source, available under : Burlina AP, Sims KB, Politei JM, et al. Early diagnosis of peripheral nervous system involvement in Fabry disease and treatment of neuropathic pain: the report of an expert panel. BMC Neurol. 2011;11:61. DOI: 10.1186/1471-2377-11-61. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.
- 88 Lysosomal storage diseases: Image C. Gaucher cells in Gaucher disease. This image is a derivative work, adapted from the following source, available under Sokołowska B, Skomra D, Czartoryska B. et al. Gaucher disease diagnosed after bone marrow trephine biopsy—a report of two cases. Folia Histochem Cytobiol. 2011;49:352-356. DOI: 10.5603/FHC.2011.0048. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.
- 88 Lysosomal storage diseases: Image D. Foam cells in Niemann-Pick disease. This image is a derivative work, adapted from the following source, available under Prieto-Potin I, Roman-Blas JA, Martinez-Calatrava MJ, et al. Hypercholesterolemia boosts joint destruction in chronic arthritis. An experimental model aggravated by foam macrophage infiltration. Arthritis Res Ther. 2013;15:R81. DOI: 10.1186/ar4261.

#### **Immunology**

- 96 Lymph node: Images A and B. Lymph node histology. This image is a derivative work, adapted from the following source, available under P. Navid Golpur.
- 98 Spleen. Red and white pulp. This image is a derivative work, adapted from the following source, available under : Heinrichs S, Conover LF, Bueso-Ramos CE, et al. MYBL2 is a sub-haploinsufficient tumor suppressor gene in myeloid malignancy. eLife. 2013;2:e00825. DOI: 10.7554/eLife.00825. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.

- 78 Thymus: Image A. Hassall corpuscles. This image is a derivative work, adapted from the following source, available under :: Minato H, Kinoshita E, Nakada S, et al. Thymic lymphoid hyperplasia with multilocular thymic cysts diagnosed before the Sjögren syndrome diagnosis. Diagn Pathol. 2015;10:103. DOI: 10.1186/s13000-015-0332-v.
- 7 Thymus: Image B. "Sail sign" on x-ray of normal thymus in neonate. This image is a derivative work, adapted from the following source, available under : Di Serafino M, Esposito F, Severino R, et al. Think thymus, think well: the chest x-ray thymic signs. J Pediatr Moth Care. 2016;1(2):108-109. DOI: 10.19104/japm.2016.108.
- 107 Complement disorders. Paroxysmal nocturnal hemoglobinuria. This image is a derivative work, adapted from the following source, available under . Nakamura N, Sugawara T, Shirato K, et al. J Med Case Reports. 2011;5:550. doi: 10.1186/1752-1947-5-550
- 117 Immunodeficiencies: Image A. Spider angioma (telangiectasia). This image is a derivative work, adapted from the following source, available under Liapakis IE, Englander M, Sinani R, et al. Management of facial telangiectasias with hand cautery. World J Plast Surg. 2015 Jul;4(2):127-133.
- 117 Immunodeficiencies: Image B. Giant granules in granulocytes in Chédiak-Higashi syndrome. This image is a derivative work, adapted from the following source, available under □□□: Bharti S, Bhatia P, Bansal D, et al. The accelerated phase of Chediak-Higashi syndrome: the importance of hematological evaluation. Turk J Haematol. 2013;30:85-87. DOI: 10.4274/tjh.2012.0027. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.

#### Microbiology

- 125 Stains: Image A. Trypanosoma lewisi on Giemsa stain. Courtesy of the Department of Health and Human Services and Dr. Mae Melvin.
- 125 Stains: Image B. Periodic acid—Schiff stain reveals Tropheryma whipplei infection. This image is a derivative work, adapted from the following source, available under Courtesy of Dr. Ed Uthman.
- 125 Stains: Image C. Mycobacterium tuberculosis on Ziehl-Neelsen stain.
  Courtesy of the Department of Health and Human Services and Dr. George P. Kubica.
- 125 Stains: Image D. Cryptococcus neoformans on India ink stain.
  Courtesy of the Department of Health and Human Services.
- 125 Stains: Image E. Coccidioides immitis on silver stain. Courtesy of the Department of Health and Human Services and Dr. Edwin P. Ewing, Jr.
- 127 Encapsulated bacteria. Capsular swelling of Streptococcus pneumoniae using the Neufeld-Quellung test. Courtesy of the Department of Health and Human Services.
- Catalase-positive organisms. Oxygen bubbles released during catalase reaction. This image is a derivative work, adapted from the following source, available under sets: Stefano Nase. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under sets.
- 129 Spore-forming bacteria. This image is a derivative work, adapted from the following source, available under (I) Jones SW, Paredes CJ, Tracy B. The transcriptional program underlying the physiology of clostridial sporulation. Genome Biol. 2008;9:R114. DOI: 10.1186/gb-2008-9-7-r114.
- 135 α-hemolytic bacteria. α-hemolysis. This image is a derivative work, adapted from the following source, available under . Y. Tambe. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under ...

FAS1\_2019\_20\_ImageAck.indd 728 11/8/19 4:49 PM

- **β-hemolytic bacteria.** β-hemolysis. This image is a derivative work, adapted from the following source, available under : Wikimedia
- Staphylococcus aureus. Courtesy of the Department of Health and Human Services and Dr. Richard Facklam.
- Streptococcus pneumoniae. Courtesy of the Department of Health and Human Services and Dr. Mike Miller.
- 136 Streptococcus pyogenes: (group A streptococci). This image is a derivative work, adapted from the following source, available under See: Y. Tambe. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under ......
- **Bacillus anthracis.** Ulcer with black eschar. Courtesy of the Department of Health and Human Services and James H. Steele.
- **Clostridia: Image A.** Gas gangrene due to *Clostridium perfringens*. This image is a derivative work, adapted from the following source, available under Schröpfer E, Rauthe S, Meyer T. Diagnosis and misdiagnosis of necrotizing soft tissue infections: three case reports. Cases J. 2008;1:252. DOI: 10.1186/1757-1626-1-252.
- Clostridia: Image B. Pseudomembranous enterocolitis on colonoscopy. This image is a derivative work, adapted from the following source, available under see: Klinikum Dritter Orden für die Überlassung des Bildes zur Veröffentlichu. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under ....
- Corynebacterium diphtheriae. Pseudomembranous pharyngitis. This image is a derivative work, adapted from the following source, available under 2000: Wikimedia Commons. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under
- 139 Listeria monocytogenes. Actin rockets. This image is a derivative work, adapted from the following source, available under Schuppler M, Loessner MJ. The opportunistic pathogen Listeria monocytogenes: pathogenicity and interaction with the mucosal immune system. Int J Inflamm. 2010;2010:704321. DOI: 10.4061/2010/704321. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.
- Nocardia vs Actinomyces: Image A. Nocardia on acid-fast stain. This image is a derivative work, adapted from the following source, available under Esse: Venkataramana K. Human Nocardia infections: a review of pulmonary nocardiosis. Cereus. 2015;7(8):e304. DOI: 10.7759/cureus.304.
- Nocardia vs Actinomyces: Image B. Actinomyces israelii on Gram stain. See Courtesy of the Department of Health and Human
- Mycobacteria. Acid-fast stain. Courtesy of the Department of Health and Human Services and Dr. George P. Kubica
- **Tuberculosis.** Langhans giant cell in caseating granuloma. Courtesy of J. Hayman.
- **Leprosy: Image A.** "Glove and stocking" distribution. This image is a derivative work, adapted from the following source, available under Courtesy of Bruno Jehle.
- **Neisseria:** Image A. Intracellular N gonorrhoeae. Department of Health and Human Services and Dr. Mike Miller.
- **142** *Haemophilus influenzae*: Image A. Epiglottitis. This image is a derivative work, adapted from the following source, available under : Wikimedia Commons. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.
- Legionella pneumophila. Lung findings of unilateral and lobar infiltrate. This image is a derivative work, adapted from the following

- source, available under : Robbins NM, Kumar A, Blair BM. Legionella pneumophila infection presenting as headache, confusion and dysarthria in a human immunodeficiency virus-1 (HIV-1) positive patient: case report. BMC Infect Dis. 2012;12:225. DOI: 10.1186/1471-2334-12-225.
- *Pseudomonas aeruginosa*: Image A. Blue-green pigment on centrimide agar. This image is a derivative work, adapted from the following source, available under : Hansen. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under ....
- Pseudomonas aeruginosa: Image B. Ecthyma gangrenosum. This image is a derivative work, adapted from the following source, available under : Uludokumaci S, Balkan II, Mete B, et al. Ecthyma gangrenosum-like lesions in a febrile neutropenic patient with simultaneous Pseudomonas sepsis and disseminated fusariosis. Turk J Haematol. 2013 Sep;30(3):321-4. DOI: 10.4274/Tjh.2012.0030.
- 145 *Klebsiella*. © Courtesy of the Department of Health and Human
- Courtesy of the Department of Health and Human Services.
- Vibrio cholerae. This image is a derivative work, adapted from the following source, available under Phetsouvanh R, Nakatsu M, Arakawa E, et al. Fatal bacteremia due to immotile Vibrio cholerae serogroup O21 in Vientiane, Laos-a case report. Ann Clin Microbiol Antimicrob. 2008;7:10. DOI: 10.1186/1476-0711-7-10.
- Helicobacter pylori. Courtesy of the Department of Health and Human Services, Dr. Patricia Fields, and Dr. Collette Fitzgerald.
- **Spirochetes.** Appearance on darkfield microscopy. Courtesy of the Department of Health and Human Services.
- Lyme disease: Image A. Ixodes tick. Courtesy of the Department of Health and Human Services and Dr. Michael L. Levin.
- **Lyme disease: Image B.** Erythema migrans. Courtesy of the Department of Health and Human Services and James Gathany.
- **Syphilis: Image A.** Painless chancre in primary syphilis. Courtesy of the Department of Health and Human Services and M. Rein.
- **Syphilis: Image B.** Treponeme on darkfield microscopy. Courtesy of the Department of Health and Human Services and Renelle
- **Syphilis: Image D.** Rash on palms. This image is a derivative work, adapted from the following source, available under : Drahansky M, Dolezel M, Urbanek J, et al. Influence of skin diseases on fingerprint recognition. J Biomed Biotechnol. 2012;626148. DOI: 10.1155/2012/626148.
- Syphilis: Image E. Condyloma lata. Courtesy of the Department of Health and Human Services and Susan Lindsley.
- **Syphilis: Image F.** Gumma. This image is a derivative work, adapted from the following source, available under : Chakir K, Benchikhi H. Granulome centro-facial révélant une syphilis tertiaire. Pan Afr Med J. 2013;15:82. DOI: 10.11604/pamj.2013.15.82.3011.
- **Syphilis: Image G.** Congenital syphilis. Courtesy of the Department of Health and Human Services and Dr. Norman Cole.
- Syphilis: Image H. Hutchinson teeth. Courtesy of the Department of Health and Human Services and Susan Lindsley.
- Gardnerella vaginalis. Courtesy of the Department of Health and Human Services and M. Rein.
- Rickettsial diseases and vector-borne illnesses: Image A.  $\operatorname{Rash}$  of Rocky Mountain spotted fever. Courtesy of the Department of Health and Human Services.

FAS1\_2019\_20\_ImageAck.indd 729 11/8/19 4:49 PM

- Rickettsial diseases and vector-borne illnesses: Image B. Ehrlichia morulae. This image is a derivative work, adapted from the following source, available under see: Dantas-Torres F. Canine vector-borne diseases in Brazil. Parasit Vectors. 2008;1:25. DOI: 10.1186/1756-3305-1-25. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.
- 150 Rickettsial diseases and vector-borne illnesses: Image C. Anaplasma phagocytophilium in neutrophil. Courtesy of the Department of Health and Human Services and Dumler JS, Choi K, Garcia-Garcia JC, et al. Human granulocytic anaplasmosis. Emerg Infect Dis. 2005. DOI 10.3201/eid1112.050898.
- 150 Mycoplasma pneumoniae. This image is a derivative work, adapted from the following source, available under Rottem S, Kosower ND, Kornspan JD. Contamination of tissue cultures by Mycoplasma. In: Ceccherini-Nelli L, ed: Biomedical tissue culture. 2016. DOI: 10.5772/51518.
- 151 Systemic mycoses: Image A. Histoplasma. Courtesy of the Department of Health and Human Services and Dr. D.T. McClenan.
- 151 Systemic mycoses: Image B. Blastomyces dermatitidis undergoing broad-base budding. Courtesy of the Department of Health and Human Services and Dr. Libero Ajello.
- 151 Systemic mycoses: Image C. Coccidiomycosis with endospheres.
  Courtesy of the Department of Health and Human Services.
- **151 Systemic mycoses: Image D.** "Captain's wheel" shape of *Paracoccidioides.*. Courtesy of the Department of Health and Human Services and Dr. Lucille K. Georg.
- 152 Cutaneous mycoses: Image G. Tinea versicolor. This image is a derivative work, adapted from the following source, available under : Sarah (Rosenau) Korf. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under :
- **Opportunistic fungal infections: Image A.** Budding yeast of *Candida albicans*. This image is a derivative work, adapted from the following source, available under : T. Tambe. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under :
- 153 Opportunistic fungal infections: Image B. Germ tubes of Candida albicans.. This image is a derivative work, adapted from the following source, available under . T. Tambe. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under .
- **Opportunistic fungal infections: Image C.** Oral thrush.

  Courtesy of the Department of Health and Human Services and Dr. Sol Silverman, Jr.
- 153 Opportunistic fungal infections: Image E. Conidiophores of Aspergillus fumigatus. Courtesy of the Department of Health and Human Services.
- **Opportunistic fungal infections: Image F.** Aspergilloma in left lung. This image is a derivative work, adapted from the following source, available under . Souilamas R, Souilamas JI, Alkhamees K, et al. Extra corporal membrane oxygenation in general thoracic surgery: a new single veno-venous cannulation. *J Cardiothorac Surg.* 2011;6:52. DOI: 10.1186/1749-8090-6-52.
- **Opportunistic fungal infections: Image G.** *Cryptococcus neoformans.*Courtesy of the Department of Health and Human Services and Dr. Leanor Haley.
- **Opportunistic fungal infections: Image H.** *Cryptococcus neoformans* on mucicarmine stain. Courtesy of the Department of Health and Human Services and Dr. Leanor Haley.

- 153 Opportunistic fungal infections: Image I. Mucor. See Courtesy of the Department of Health and Human Services and Dr. Lucille K. Georg.
- 153 Opportunistic fungal infections: Image J. Mucormycosis. This image is a derivative work, adapted from the following source, available under . Jiang N, Zhao G, Yang S, et al. A retrospective analysis of eleven cases of invasive rhino-orbito-cerebral mucormycosis presented with orbital apex syndrome initially. BMC Ophthalmol. 2016; 16: 10. DOI: 10.1186/s12886-016-0189-1.
- 154 Pneumocystis jirovecii: Image A. Interstitial opacities in lung. This image is a derivative work, adapted from the following source, available under : Chuang C, Zhanhong X, Yinyin G, et al. Unsuspected Pneumocystis pneumonia in an HIV-seronegative patient with untreated lung cancer: circa case report. J Med Case Rep. 2007;1:15. DOI: 10.1186/1752-1947-1-115.
- Pneumocystis jirovecii: Image B. CT of lung. This image is a derivative work, adapted from the following source, available under all elements: Allen CM, Al-Jahdali HH, Irion KL, et al. Imaging lung manifestations of HIV/AIDS. Ann Thorac Med. 2010 Oct-Dec; 5(4): 201–216. DOI: 10.4103/1817-1737.69106.

- 155 Protozoa—Gl infections: Image A. Giardia lamblia trophozoite. This image is a derivative work, adapted from the following source, available under : Lipoldová M. Giardia and Vilém Dušan Lambl. PLoS Negl Trop Dis. 2014;8:e2686. DOI: 10.1371/journal. pntd.0002686.
- 155 Protozoa—Gl infections: Image B. Giardia lamblia cyst.
  Courtesy of the Department of Health and Human Services.
- 155 Protozoa—Gl infections: Image C. Entamoeba histolytica trophozoites. Courtesy of the Department of Health and Human Services.
- 155 Protozoa—Gl infections: Image D. Entamoeba histolytica cyst.
  Courtesy of the Department of Health and Human Services.
- **Protozoa—Gl infections: Image E.** *Cryptosporidium* oocysts. Courtesy of the Department of Health and Human Services.
- 156 Protozoa—CNS infections: Image A. Toxoplasma gondii. This image is a derivative work, adapted from the following source, available under . Agrawal A, Bhake A, Sangole VM, et al. Multiple-ring enhancing lesions in an immunocompetent adult. J Glob Infect Dis. 2010 Sep-Dec;2(3):313-4. DOI: 10.4103/0974-777X.68545.
- Protozoa—CNS infections: Image B. Toxoplasma gondii tachyzoite.
  Courtesy of the Department of Health and Human Services and Dr. L.L. Moore, Jr.
- Protozoa—CNS infections: Image C. Naegleria fowleri amoebas.
  Courtesy of the Department of Health and Human Services.
- Protozoa—CNS infections: Image D. Trypanosoma brucei gambiense.
  Courtesy of the Department of Health and Human Services and Dr. Mae Melvin.

FAS1\_2019\_20\_ImageAck.indd 730 11/8/19 4:49 PM

- Protozoa—hematologic infections: Image A. Plasmodium trophozoite ring form. Courtesy of the Department of Health and Human Services.
- Protozoa—hematologic infections: Image B. Plasmodium schizont containing merozoites. Courtesy of the Department of Health and Human Services and Steven Glenn.
- **Protozoa**—hematologic infections: Image C. *Babesia* with ring form and with "Maltese cross" form. Courtesy of the Department of Health and Human Services.
- 158 **Protozoa**—others: Image A. *Trypanosoma cruzi*. © Courtesy of the Department of Health and Human Services and Dr. Mae Melvin.
- Protozoa—others: Image B. Cutaneous leishmaniasis. This image is a derivative work, adapted from the following source, available under Sharara SL, Kanj SS. War and infectious diseases: challenges of the Syrian civil war. PLoS Pathog. 2014 Nov;10(11):e1004438. DOI: 10.1371/journal.ppat.1004438.
- **Protozoa**—others: Image C. *Leishmania* spp. Courtesy of the Department of Health and Human Services and Dr. Francis W. Chandler. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.
- **Protozoa**—others: Image D. *Trichomonas vaginalis*. Courtesy of the Department of Health and Human Services.
- Nematodes (roundworms): Image A. Enterobius vermicularis eggs. © Courtesy of the Department of Health and Human Services, BG Partin, and Dr. Moore.
- Nematodes (roundworms): Image B. Ascaris lumbricoides egg. Courtesy of the Department of Health and Human Services.
- **Nematodes (roundworms): Image C.** Ancylostoma spp rash This image is a derivative work, adapted from the following source, available under Es: Archer M. Late presentation of cutaneous larva migrans: a case report. Cases J. 2009; 2: 7553. doi:10.4076/1757-1626-
- Nematodes (roundworms): Image D. Trichinella spiralis cysts in muscle. This image is a derivative work, adapted from the following source, available under Franssen FFJ, Fonville M, Takumi K, et al. Vet Res. 2011; 42(1): 113. DOI: 10.1186/1297-9716-42-113.
- Nematodes (roundworms): Image E. Wuchereria bancrofti Elephantiasis. Courtesy of the Department of Health and Human Services.
- Cestodes (tapeworms): Image A. Taenia solium. Courtesy of the Department of Health and Human Services Robert J. Galindo. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under
- Cestodes (tapeworms): Image B. Neurocysticercosis. This image is a derivative work, adapted from the following source, available under \_\_\_\_: Coyle CM, Tanowitz HB. Diagnosis and treatment of neurocysticercosis. Interdiscip Perspect Infect Dis. 2009;2009:180742. DOI: 10.1155/2009/180742. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.
- Cestodes (tapeworms): Image C. Echinococcus granulosus. Courtesy of the Department of Health and Human Services.
- Cestodes (tapeworms): Image D. Hyatid cyst of Echinococcus granulosus. See Courtesy of the Department of Health and Human Services and Dr. I. Kagan
- Cestodes (tapeworms): Image E. Echinococcus granulosus cyst in liver. This image is a derivative work, adapted from the following source, available under . Ma Z, Yang W, Yao Y, et al. The adventitia resection in treatment of liver hydatid cyst: a case report

- of a 15-year-old boy. Case Rep Surg. 2014;2014:123149. DOI: 10.1155/2014/123149.
- **Trematodes (flukes): Image A.** Schistosoma mansoni egg with lateral spine. Courtesy of the Department of Health and Human Services.
- Trematodes (flukes): Image B. Schistosoma haematobium egg with terminal spine. Courtesy of the Department of Health and Human Services.
- 161 **Ectoparasites: Image A.** Scabies. This image is a derivative work, adapted from the following source, available under see: Siegfried EC, Hebert AA. Diagnosis of atopic dermatitis: mimics, overlaps, and complications. Clin Med. 2015 May; 4(5): 884-917. DOI: 10.3390/ jcm4050884.
- **Ectoparasites: Image B.** Nit of a louse. Courtesy of the Department of Health and Human Services and Joe Miller.
- 164 **DNA viruses: Image A.** Febrile pharyngitis. Balfour HH Jr, Dunmire SK, Hogquist KA. Clin Transl Immunology. 2015 Feb 27. DOI: 10.1038/cti.2015.1.
- **Herpesviruses: Image A.** Keratoconjunctivitis in HSV-1 infection. This image is a derivative work, adapted from the following source, available under Sang HK, Han YK, Wee WR, et al. Bilateral herpetic keratitis presenting with unilateral neurotrophic keratitis in pemphigus foliaceus: a case report. J Med Case Rep. 2011;5:328. DOI: 10.1186/1752-1947-5-328.
- **Herpesviruses: Image B.** Herpes labialis. Courtesy of the Department of Health and Human Services and Dr. Herrmann.
- **Herpesviruses: Image E.** Shingles (varicella-zoster virus infection). This image is a derivative work, adapted from the following source, available under .: Fisle. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under
- Herpesviruses: Image F. Hepatosplenomegaly due to EBV infection. This image is a derivative work, adapted from the following source, available under Gow NJ, Davidson RN, Ticehurst R, et al. Case report: no response to liposomal daunorubicin in a patient with drugresistant HIV-associated visceral leishmaniasis. PLoS Negl Trop Dis. 2015 Aug; 9(8):e0003983. DOI: 10.1371/journal.pntd.0003983.
- **Herpesviruses: Image G.** Atypical lymphocytes in Epstein-Barr virus infection. This image is a derivative work, adapted from the following source, available under \_\_\_\_\_: Coutesy of Dr. Ed Uthman. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.
- Herpesviruses: Image I. Roseola. Courtesy of Emiliano Burzagli.
- Herpesviruses: Image J. Kaposi sarcoma. Courtesy of the Department of Health and Human Services.
- **HSV identification.** Positive Tzanck smear in HSV-2 infection. This image is a derivative work, adapted from the following source, available under 222: Dr. Yale Rosen. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under @....
- Services and Erskine Palmer.
- Rubella virus. Rubella rash. Courtesy of the Department of Health and Human Services.
- $\begin{tabular}{ll} \textbf{Acute laryngotracheobronchitis.} & \textbf{Steeple sign.} & \textbf{Reproduced, with} \\ \end{tabular}$ 170 permission, from Dr. Frank Gaillard and www.radiopaedia.org.
- Measles (rubeola) virus: Image A. Koplik spots. © Courtesy of the Department of Health and Human Services. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.

FAS1\_2019\_20\_ImageAck.indd 731 11/8/19 4:49 PM

- 170 Measles (rubeola) virus: Image B. Rash of measles. Courtesy of the Department of Health and Human Services.
- 170 Mumps virus. Swollen neck and parotid glands. Courtesy of the Department of Health and Human Services.
- Rabies virus: Image A. Transmission electron micrograph.
   Courtesy of the Department of Health and Human Services Dr. Fred Murphy, and Sylvia Whitfield.
- 171 Rabies virus: Image B. Negri bodies. Courtesy of the Department of Health and Human Services and Dr. Daniel P. Perl.
- 171 Ebola virus. Courtesy of the Department of Health and Human Services and Cynthia Goldsmith.
- **180 Osteomyelitis.** X-ray (left) and MRI (right) views. This image is a derivative work, adapted from the following source, available under ⊞ Huang P-Y, Wu P-K, Chen C-F, et al. Osteomyelitis of the femur mimicking bone tumors: a review of 10 cases. World J Surg Oncol. 2013;11:283. DOI: 10.1186/1477-7819-11-283.
- 181 Common vaginal infections: Image B. Motile trichomonads.
  © Courtesy of Joe Miller.
- 181 Common vaginal infections: Image C. Candida vulvovaginitis.
  Courtesy of Mikael Häggström.
- **TORCH infections: Image A.** "Blueberry muffin" rash. This image is a derivative work, adapted from the following source, available under Benmiloud S, Elhaddou G, Belghiti ZA, et al. Blueberry muffin syndrome. *Pan Afr Med J.* 2012;13:23.
- **TORCH infections: Image B.** Cataract in infant with contenital rubella. Courtesy of the Department of Health and Human Services .
- **TORCH infections: Image C.** Periventricular calcifications in congenital cytomegalovirus infection. This image is a derivative work, adapted from the following source, available under Bonthius D, Perlman S. Congenital viral infections of the brain: lessons learned from lymphocytic choriomeningitis virus in the neonatal rat. *PLoS Pathog.* 2007;3:e149. DOI: 10.1371/journal.ppat.0030149. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.
- **Red rashes of childhood: Image C.** Child with scarlet fever. This image is a derivative work, adapted from the following source, available under \*\* www.badobadop.co.uk.
- 183 Red rashes of childhood: Image D. Chicken pox. See Courtesy of the Department of Health and Human Services.
- **Sexually transmitted infections: Image A.** Chancroid. Courtesy of the Department of Health and Human Services and Susan Lindsley.
- 184 Sexually transmitted infections: Image B. Donovanosis. Courtesy of the Department of Health and Human Services and Dr. Pinozzi.
- 185 Pelvic inflammatory disease: Image A. Purulent cervical discharge. This image is a derivative work, adapted from the following source, available under : SOS-AIDS Amsterdam The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under .
- **Pelvic inflammatory disease: Image B.** Adhesions in Fitz-Hugh–Curtis syndrome. Courtesy of Hic et nunc.
- 190 Vancomycin. Red man syndrome. This image is a derivative work, adapted from the following source, available under O'Meara P, Borici-Mazi R, Morton R, et al. DRESS with delayed onset acute interstitial nephritis and profound refractory eosinophilia secondary to vancomycin. Allergy Asthma Clin Immunol. 2011;7:16. DOI: 10.1186/1710-1492-7-16.

#### **Pathology**

- 209 Necrosis: Image A. Coagulative necrosis. Courtesy of the Department of Health and Human Services and Dr. Steven Rosenberg.
- 209 Necrosis: Image B. Liquefactive necrosis. See Courtesy of Daftblogger.
- 209 Necrosis: Image C. Caseous necrosis. This image is a derivative work, adapted from the following source, available under Rosen. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under
- 209 Necrosis: Image E. Fibrinoid necrosis. This image is a derivative work, adapted from the following source, available under come: Dr. Yale Rosen. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under
- 209 Necrosis: Image F. Acral gangrene. Courtesy of the Department of Health and Human Services and William Archibald.
- **210 Ischemia.** This image is a derivative work, adapted from the following source, available under Van Assche LM, Kim HW, Jensen CJ, et al. A new CMR protocol for non-destructive, high resolution, ex-vivo assessment of the area at risk simultaneous with infarction: validation with histopathology. *J Cardiovasc Magn Reson.* 2012; 14(Suppl 1): O7. DOI: 10.1186/1532-429X-14-S1-O7.
- 210 Types of infarcts: Image B. Pale infarct. Courtesy of the Department of Health and Human Services and the Armed Forces Institute of Pathology.
- **211 Types of calcification: Image A.** Dystrophic calcification. This image is a derivative work, adapted from the following source, available under .: Chun J-S, Hong R, Kim J-A. Osseous metaplasia with mature bone formation of the thyroid gland: three case reports. *Oncol Lett.* 2013;6:977-979. DOI: 10.3892/ol.2013.1475. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.
- 211 Lipofuscin. This image is a derivative work, adapted from the following source, available under : Dr. Michael Bonert. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under :
- **212 Amyloidosis: Image A.** Amyloid deposits on Congo red stain. This image is a derivative work, adapted from the following source, available under . Dr. Ed Uthman.
- 212 Amyloidosis: Image B. Apple green birefringence under polarized light. This image is a derivative work, adapted from the following source, available under Dr. Ed Uthman.
- **Acute inflammation: Image A.** Pericardium with severe inflammation, neutrophilic infiltration and fibrin with entrapped clusters of bacteria. This image is a derivative work, adapted from the following source, available under . Faida Ajili, et al. Coexistence of pyoderma gangrenosum and sweet's syndrome in a patient with ulcerative colitis. *Pan Afr Med J.* 2015 Jun 24. DOI: 10.11604/pamj.2015.21.151.6364.
- 217 Granulomatous diseases. Granuloma. Courtesy of Sanjay Mukhopadhyay.
- 218 Scar formation: Image A. Hypertrophic scar. This image is a derivative work, adapted from the following source, available under Sea: Baker R, Urso-Baiarda F, Linge C, et al. Cutaneous scarring: a clinical review. Dermatol Res Pract. 2009;2009:625376. DOI: 10.1155/2009/625376.

FAS1 2019 20 ImageAck.indd 732 11/8/19 4:49 PM

- **Scar formation: Image B.** Keloid scar. This image is a derivative work, adapted from the following source, available under . Dr. Andreas Settje. The image may have been modified by cropping, labeling, and/ or captions. MedIQ Learning, LLC makes this available under
- Neoplasia and neoplastic progression: Image A. Cervical tissue. This image is a derivative work, adapted from the following source, available under see: Courtesy of Dr. Ed Uthman. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.
- **223 Common metastases: Image A.** Brain metastases from breast cancer. This image is a derivative work, adapted from the following source, available under .: Imarchn. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under ......
- **Common metastases: Image B.** Brain metastasis. Courtesy of the Department of Health and Human Services and the Armed Forces Institute of Pathology.
- 223 **Common metastases: Image C.** Liver metastasis. This image is a derivative work, adapted from the following source, available under .: Dr. James Heilman The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under ......
- **Common metastases: Image D.** Liver metastasis. Courtesy of Havman.
- **Common metastases: Image E.** Bone metastasis. This image is a derivative work, adapted from the following source, available under 🖭: Dr. Paul Hellerhoff.
- **Common metastases: Image F.** Bone metastasis. This image is a derivative work, adapted from the following source, available under : Courtesy of M Emmanuel.
- Psammoma bodies. Courtesy of the Department of Health and Human Services and the Armed Forces Institute of Pathology.

#### Cardiovascular

- **Anatomy of the heart: Image A.** MRI showing normal cardiac anatomy. This image is a derivative work, adapted from the following source, available under : Zhang J, Chen L, Wang X, et al. Compounding local invariant features and global deformable geometry for medical image registration. PLoS One. 2014;9(8):e105815. DOI: 10.1371/journal.pone.0105815.
- Congenital heart diseases: Image A. Tetralogy of Fallot. This image is a derivative work, adapted from the following source, available under Rashid AKM: Heart diseases in Down syndrome. In: Dey S, ed: Down syndrome. DOI: 10.5772/46009. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.
- Congenital heart diseases: Image B. Ventricular septal defect. This image is a derivative work, adapted from the following source, available under Est Bardo DME, Brown P. Cardiac multidetector computed tomography: basic physics of image acquisition and clinical applications. Curr Cardiol Rev. 2008 Aug;4(3):231–243. DOI: 10.2174/157340308785160615.
- **Congenital heart diseases: Image C.** Atrial septal defect. This image is a derivative work, adapted from the following source, available under E: Teo KSL, Dundon BK, Molaee P, et al. Percutaneous closure of atrial septal defects leads to normalisation of atrial and ventricular volumes. J Cardiovasc Magn Reson. 2008;10(1):55. DOI: 10.1186/1532-429X-10-55.
- Congenital heart diseases: Image D. Patent ductus arteriosus. This image is a derivative work, adapted from the following source, available under Es: Henjes CR, Nolte I, Wesfaedt P. Multidetectorrow computed tomography of thoracic aortic anomalies in dogs

- and cats: patent ductus arteriosus and vascular rings. BMC Vet Res. 2011;7:57. DOI: 10.1186/1746-6148-7-57.
- **Congenital heart diseases: Image E.** Clubbing of fingers. Courtesy of Ann McGrath.
- **Congenital heart diseases: Image F.** MRI showing coarctation of the aorta. This image is a derivative work, adapted from the following source, available under Es: Vergales JE, Gangemi JJ, Rhueban KS, Lim DS. Coarctation of the aorta — the current state of surgical and transcatheter therapies. Curr Cardiol Rev. 2013 Aug; 9(3): 211–219. DOI: 10.2174/1573403X113099990032
- **Hypertension: Image A.** "String of beads" appearance in fibromuscular dysplasia. This image is a derivative work, adapted from the following source, available under : Plouin PF, Perdu J, LaBatide-Alanore A, et al. Fibromuscular dysplasia. Orphanet J Rare Dis. 2007;7:28. DOI: 10.1186/1750-1172-2-28. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.
- Hyperlipidemia signs: Image C. Tendinous xanthoma. This image is a derivative work, adapted from the following source, available under Raffa W, Hassam B. Xanthomes tendineux et tubéreux révélant une hypercholestérolémie familiale. Pan Afr Med J. 2013; 15: 49. DOI: 10.11604/pamj.2013.15.49.2636.
- **Arteriosclerosis: Image A.** Hyaline type. This image is a derivative work, adapted from the following source, available under Dr. Michael Bonert. The image may have been modified by cropping labeling, and/or captions. MedIQ Learning, LLC makes this available under 🛛 😳 .
- **Arteriosclerosis: Image B.** Hyperplastic type. This image is a derivative work, adapted from the following source, available under see: Paco Larosa. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under
- **Arteriosclerosis: Image C.** Monckeberg sclerosis (medial calcific sclerosis). This image is a derivative work, adapted from the following source, available under Es: Couri CE, da Silva GA, Martinez JA, et al. The image may have been modified by cropping, labeling, and/ or captions. All rights to this adaptation by MedIQ Learning, LLC are
- **Aortic dissection.** This image is a derivative work, adapted from the following source, available under Qi Y, Ma X, Li G, et al. Three-dimensional visualization and imaging of the entry tear and intimal flap of aortic dissection using CT virtual intravascular endoscopy. PLoS One. 2016; 11(10): e0164750. DOI: 10.1371/journal. pone.0164750.
- Myocardial infarction complications: Image A. Papillary muscle rupture. This image is a derivative work, adapted from the following source, available under Es: Routy B, Huynh T, Fraser R, et al. Vascular endothelial cell function in catastrophic antiphospholipid syndrome: a case report and review of the literature. Case Rep Hematol. 2013;2013:710365. DOI: 10.1155/2013/710365.
- Myocardial infarction complications: Image B. Drawing of pseudoaneurysm. This image is a derivative work, adapted from the following source, available under **EXE**: Patrick J. Lynch and Dr. C. Carl Jaffe.
- Myocardial infarction complications: Image C. Free wall rupture of left ventricle. This image is a derivative work, adapted from the following source, available under Zacarias ML, da Trindade H, Tsutsu J, et al. Left ventricular free wall impeding rupture in post-myocardial infarction period diagnosed by myocardial contrast echocardiography: case report. Cardiovasc Ultrasound. 2006;4:7. DOI: 10.1186/1476-7120-4-7.
- **Cardiomyopathies: Image A.** Dilated cardiomyopathy. This image is a derivative work, adapted from the following source, available under

FAS1 2019 20 ImageAck.indd 733 11/8/19 4:49 PM

- Scho JMIH, van Es R, Stathonikos N, et al. High resolution systematic digital histological quantification of cardiac fibrosis and adipose tissue in phospholamban p.Arg14del mutation associated cardiomyopathy. *PLoS One.* 2014;9:e94820. DOI: 10.1371/journal. pone.0094820.
- 308 Cardiomyopathies: Image B. Hypertrophic obstructive cardiomyopathy. This image is a derivative work, adapted from the following source, available under Benetti MA, Belo Nunes RA, Benvenuti LA. Case 2/2016 76-year-old male with hypertensive heart disease, renal tumor and shock. Arq Bras Cardiol. 2016 May; 106(5): 439–446. DOI: 10.5935/abc.20160067.
- **Heart failure.** Pedal edema. This image is a derivative work, adapted from the following source, available under Dr. James Heilman. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under Dr.
- 310 Cardiac tamponade: Image A. This image is a derivative work, adapted from the following source, available under □□□: Yousuf T, Kramer J, Kopiec A, et al. A rare case of cardiac tamponade induced by chronic rheumatoid arthritis. *J Clin Med Res.* 2015 Sep;7(9):720–723. DOI: 10.14740/jocmr2226w.
- **310 Cardiac tamponade: Image B.** This image is a derivative work, adapted from the following source, available under :: Maharaj SS, Chang SM. Cardiac tamponade as the initial presentation of systemic lupus erythematosus: a case report and review of the literature. *Pediatr Rheumatol Online J.* 2015; 13: 9. DOI: 10.1186/s12969-015-0005-0.
- **311 Bacterial endocarditis: Image A.** Courtesy of the Department of Health and Human Services and Dr. Edwin P. Ewing, Jr.
- 311 Bacterial endocarditis: Image C. Osler nodes. This image is a derivative work, adapted from the following source, available under and the second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second seco
- **311 Bacterial endocarditis: Image D.** Janeway lesions on sole. This image is a derivative work, adapted from the following source, available under .: Courtesy of DeNanneke.
- 312 Rheumatic fever. Aschoff body and Anitschkow cells. This image is a derivative work, adapted from the following source, available under . Dr. Ed Uthman. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.
- 313 Acute pericarditis. This image is a derivative work, adapted from the following source, available under Bogaert J, Francone M. Cardiovascular magnetic resonance in pericardial diseases. J Cardiovasc Magn Reson. 2009;11:14. DOI: 10.1186/1532-429X-11-14. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.
- 315 Vasculitides: Image A. Temporal arteritis histology. This image is a derivative work, adapted from the following source, available under ... Marvin. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under ...
- **Vasculitides: Image B.** Angiogram in patient with Takayasu arteritis.

  Courtesy of the Department of Health and Human Services and Justin Ly.
- 315 Vasculitides: Image C. Gangrene as a consequence of Buerger disease. This image is a derivative work, adapted from the following source, available under . Afsjarfard A, Mozaffar M, Malekpour F, et al. The wound healing effects of iloprost in patients with Buerger's disease: claudication and prevention of major amputations. Iran Red Crescent Med J. 2011;13:420-423.

- **Vasculitides: Image D.** Strawberry tongue in patient with Kawasaki disease. This image is a derivative work, adapted from the following source, available under ... Courtesy of Natr.
- 315 Vasculitides: Image E. Coronary artery aneurysm in Kawasaki disease. This image is a derivative work, adapted from the following source, available under Wikimedia Commons. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.
- 315 Vasculitides. Polyarteritis nodosa. Reproduced, with permission, from Dr. Frank Gaillard and www.radiopaedia.org.
- 315 Vasculitides: Image G. Churg-Strauss syndrome histology. This image is a derivative work, adapted from the following source, available under . Dr. Michael Bonert. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under .
- 315 Vasculitides: Image H. Granulomatosis with polyangiitis (formerly Wegener) and PR3-ANCA/c-ANCA. Courtesy of M.A. Little.
- 315 Vasculitides: Image I. Henoch-Schönlein purpura. See Courtesy of Okwikikim.
- **Vasculitides: Image J.** MPO-ANCA/p-ANCA in microscopic polyangiitis. Courtesy of and M.A. Little.

#### **Endocrine**

- **Thyroid development.** Thyroglossal duct cyst. This image is a derivative work, adapted from the following source, available under Adelchi C, Mara P, Melissa L, et al. Ectopic thyroid tissue in the head and neck: a case series. *BMC Res Notes*. 2014;7:790. DOI: 10.1186/1756-0500-7-790.
- 340 Hypothyroidism vs hyperthyroidism. Onycholysis. This image is a derivative work, adapted from the following source, available under Rajebi MR, Shahrokni A, Chaisson M. Uncommon osseous involvement in multisystemic sarcoidosis. *Ann Saudi Med.* 2009 Nov-Dec;29(6):485–486.
- **341 Hypothyroidism: Image B.** Before and after treatment of congenital hypothyroidism. Courtesy of the Department of Health and Human Services.
- **Thyroid adenoma: Image A.** This image is a derivative work, adapted from the following source, available under ☐☐☐☐ Terada T. Brain metastasis from thyroid adenomatous nodules or an encapsulated thyroid follicular tumor without capsular and vascular invasion: a case report. Cases J. 2009; 2: 7180. DOI: 10.4076/1757-1626-2-7180.
- **344 Hypoparathyroidism.** Shortened 4th and 5th digits. This image is a derivative work, adapted from the following source, available under Ferrario C, Gastaldi G, Portmann L, et al. Bariatric surgery in an obese patient with Albright hereditary osteodystrophy: a case report. *J Med Case Rep.* 2013; 7: 111. DOI: 10.1186/1752-1947-7-111.
- **345 Hyperparathyroidism.** Multiple lytic lesions. This image is a derivative work, adapted from the following source, available under : Khaoula BA, Kaouther BA, Ines C, et al. An unusual presentation of primary hyperparathyroidism: pathological fracture. *Case Rep Orthop.* 2011;2011:521578. DOI: 10.1155/2011/521578. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.
- **Adrenal insufficiency: Image A.** Mucosal hyperpigmentation in primary adrenal insufficiency. Courtesy of FlatOut. The image

FAS1\_2019\_20\_ImageAck.indd 734 11/8/19 4:49 PM

- may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.
- **Pheochromocytoma.** This image is a derivative work, adapted from the following source, available under Eldman.
- Multiple endocrine neoplasias. Mucosal neuroma. This image is a derivative work, adapted from the following source, available under Martucciello G, Lerone M, Bricco L, et al. Multiple endocrine neoplasias type 2B and RET proto-oncogene. Ital J Pediatr. 2012;38:9. DOI: 10.1186/1824-7288-38-9.
- Carcinoid syndrome. Courtesy of the Department of Health and Human Services and the Armed Forces Institute of Pathology.

#### Gastrointestinal

- **358** Ventral wall defects. Gastroschisis. This image is a derivative work, adapted from the following source, available under . Zvizdic Z. Gastroschisis with concomitant jejuno-ileal atresia complicated by jejunal perforation. J Neonatal Surg. 2016 Apr-Jun; 5(2): 25.
- **Ventral wall defects.** Omphalocele. This image is a derivative work, adapted from the following source, available under .: Khan YA, Qureshi MA, Akhtar J. Omphalomesenteric duct cyst in an omphalocele: a rare association. Pak J Med Sci. 2013 May-Jun; 29(3): 866-868
- Ventral wall defects. Drawings of gastroschisis (left) and omphalocele (right). Courtesy of the Department of Health and Human
- **Intestinal atresia.** This image is a derivative work, adapted from the following source, available under Saha M. Alimentary tract atresias associated with anorectal malformations: 10 years' experience. J Neonatal Surg. 2016 Oct-Dec; 5(4): 43. DOI: 10.21699/jns.v5i4.449.
- **Hypertrophic pyloric stenosis.** This image is a derivative work, adapted from the following source, available under Es: Hassan RAA, Choo YU, Noraida R, et al. Infantile hypertrophic pyloric stenosis in postoperative esophageal atresia with tracheoesophageal fistula. J Neonatal Surg. 2015 Jul-Sep;4(3):32.
- Pancreas and spleen embryology. Annular pancreas. This image is a derivative work, adapted from the following source, available under Mahdi B, Selim S, Hassen T, et al. A rare cause of proximal intestinal obstruction in adults—annular pancreas: a case report. Pan Afr Med J. 2011;10:56. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.
- **Retroperitoneal structures.** This image is a derivative work, adapted from the following source, available under :: Sammut J, Ahiaku E, Williams DT. Complete regression of renal tumour following ligation of an accessory renal artery during repair of an abdominal aortic aneurysm. Ann R Coll Surg Engl. 2012 Sep; 94(6): e198-e200. DOI: 10.1308/003588412X13373405384972.
- **Digestive tract anatomy.** Histology of stomach wall. This image is a derivative work, adapted from the following source, available under : Alexander Klepnev.
- **Digestive tract histology: Image A.** Courtesy of Dr. Michale
- **Digestive tract histology: Image B.** Courtesy of W. Ben Smith.
- 362 Digestive tract histology: Images C, D, E. This image is a derivative work, adapted from the following source, available under see: Wikimedia Commons.
- **Liver tissue architecture: Image A.** Portal triad. This image is a derivative work, adapted from the following source, available under Eiver development. In: Zorn AM. Stem book. Cambridge: Harvard Stem Cell Institute, 2008.

- **Liver tissue architecture: Image B.** Kupffer cells. This image is a derivative work, adapted from the following source, available under some Dr. Michael Bonert. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes
- Biliary structures. Gallstones. This image is a derivative work, adapted from the following source, available under :: J. Guntau. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under
- Hernias: Image A. Congenital diaphragmatic hernia. This image is a derivative work, adapted from the following source, available under Tovar J. Congenital diaphragmatic hernia. Orphanet J Rare Dis. 2012;7:1. DOI: 10.1186/1750-1172-7-1.
- Gastrointestinal secretory products. Histology of gastric pit. This image is a derivative work, adapted from the following source, available under sa: Dr. Michael Bonert. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under .....
- **Peyer patches.** This image is a derivative work, adapted from the following source, available under see: Plainpaper. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under
- Sialolithiasis. This image is a derivative work, adapted from the following source, available under Eastor-Ramos V, Cuervo-Diaz A, Aracil-Kessler L. Sialolithiasis. Proposal for a new minimally invasive procedure: piezoelectric surgery. J Clin Exp Dent. 2014 Jul;6(3):e295-e298. DOI: 10.4317/jced.51253.
- Salivary gland tumors. Pleomorphic adenoma histology. This image is a derivative work, adapted from the following source, available under :: Wikimedia Commons. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under
- **Achalasia.** This image is a derivative work, adapted from the following source, available under Estrowsh Farrokhi and Michael F. Vaezi. The image may have been modified by cropping, labeling, and/ or captions. All rights to this adaptation by MedIQ Learning, LLC are
- **Esophageal pathologies: Image A.** Pneumomediastinum in Boerhaave syndrome. This image is a derivative work, adapted from the following source, available under : Wikimedia Commons. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under
- **Esophageal pathologies: Image B.** Esophageal varices on endoscopy. This image is a derivative work, adapted from the following source, available under .: Costaguta A, Alvarez F. Etiology and management of hemorrhagic complications of portal hypertension in children. Int J Hepatol. 2012;2012:879163. DOI: 10.1155/2012/879163.
- **Esophageal pathologies: Image C.** Esophageal varices on CT. This image is a derivative work, adapted from the following source, available under : Dr. Paul Hellerhoff. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under 200
- **Esophageal pathologies: Image D.** Esophagitis. This image is a derivative work, adapted from the following source, available under Takahashi Y, Nagata N, Shimbo T. Long-term trends in esophageal candidiasis prevalence and associated risk factors with or without HIV infection: lessons from an endoscopic study of 80,219 patients. PLoS One. 2015; 10(7): e0133589. DOI: 10.1371/journal. pone.0133589.
- **Barrett esophagus: Image A.** Endoscopy. This image is a derivative work, adapted from the following source, available under Coda S, Thillainayagam AV. State of the art in advanced endoscopic

FAS1\_2019\_20\_ImageAck.indd 735 11/8/19 4:49 PM

- imaging for the detection and evaluation of dysplasia and early cancer of the gastrointestinal tract. *Clin Exp Gastroenterol.* 2014;7:133-150. DOI: 10.2147/CEG.S58157. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.
- 378 Barrett esophagus: Image B. Goblet cells. This image is a derivative work, adapted from the following source, available under community: Dr. Michael Bonert. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under community.
- 379 Ménétriere disease. This image is a derivative work, adapted from the following source, available under Dr. Paul Hellerhoff. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under Dr.
- **379 Gastric cancer Tan Y, Fu J, Li X.** This image is a derivative work, adapted from the following source, available under (<50%) signet-ring cell component associated with poor prognosis in colorectal cancer patients: a 26-year retrospective study in China. *PLoS One.* 2015; 10(3): e0121944. DOI: 10.1371/journal. pone.0121944.
- **380 Ulcer complications.** Free air under diaphragm in perforated ulcer. Reproduced, with permission, from Dr. Frank Gaillard and www. radiopaedia.org.
- **Malabsorption syndromes: Image A.** This image is a derivative work, adapted from the following source, available under :: Celiac disease. Sedda S, Caruso R, Marafini I, et al. Pyoderma gangrenosum in refractory celiac disease: a case report. *BMC Gastroenterol.* 2013; 13: 162. DOI: 10.1186/1471-230X-13-162.
- **381 Malabsorption syndromes: Image B.** *Tropheryma whippeli* on PAS stain. This image is a derivative work, adapted from the following source, available under **1992:** Tran HA. Reversible hypothyroidism and Whipple's disease. *BMC Endocr Disord.* 2006;6:3. DOI: 10.1186/1472-6823-6-3.
- 382 Inflammatory bowel diseases: Image A. "String sign" on barium swallow in Crohn disease. This image is a derivative work, adapted from the following source, available under : Al-Mofarreh MA, Al Mofleh IA, Al-Teimi IN, et al. Crohn's disease in a Saudi outpatient population: is it still rare? Saudi J Gastroenterol. 2009;15:111-116. DOI: 10.4103/1319-3767.45357. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.
- 382 Inflammatory bowel diseases: Images B (normal mucosa) and C (punched-out ulcers) in ulcerative colitis. This image is a derivative work, adapted from the following source, available under ☑ □:

  Ishikawa D, Ando T, Watanabe O, et al. Images of colonic real-time tissue sonoelastography correlate with those of colonoscopy and may predict response to therapy in patients with ulcerative colitis. BMC Gastroenterol. 2011;11:29. DOI: 10.1186/1471-230X-11-29.
- **Appendicitis.** Fecalith. This image is a derivative work, adapted from the following source, available under Dr. James Heilman. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under Dr.
- 383 Diverticula of the GI tract: Image B. Diverticulosis. This image is a derivative work, adapted from the following source, available under same: Sartelli M, Moore FA, Ansaloni L, et al. A proposal for a CT driven classification of left colon acute diverticulitis. World J Emerg Surg. 2015;10:3. DOI: 10.1186/1749-7922-10-3.
- **383 Diverticula of the GI tract: Image C.** This image is a derivative work, adapted from the following source, available under Hupfeld L, Burcharth J, Pommergaard HC, Rosenberg J. The best choice of treatment for acute colonic diverticulitis with purulent peritonitis is uncertain. Biomed Res Int. 2014; 2014: 380607. DOI: 10.1155/2014/380607.

- **Zenker diverticulum.** This image is a derivative work, adapted from the following source, available under : Courtesy of Bernd Brägelmann.
- **Maltotation.** This image is a derivative work, adapted from the following source, available under □□□: Mathews R, Thenabadu S, Jaiganesh T. Abdominal pain with a twist. *Int J Emerg Med.* 2011;4:21. DOI: 10.1186/1865-1380-4-21.
- **385** Intussusception: Image A. Interoperative image of intussusception. This image is a derivative work, adapted from the following source, available under (Vasiliadis K, Kogopoulos E, Katsamakas M, et al. Ileoileal intussusception induced by a gastrointestinal stromal tumor. World J Surg Oncol. 2008;6:133. DOI: 10.1186/1477-7819-6-133.
- Intussusception: Image B. Ultrasound showing target sign. This image is a derivative work, adapted from the following source, available under Abbo O, Pinnagoda K, Micol LA. Osteosarcoma metastasis causing ileo-ileal intussusception. World J Surg Oncol. 2013 Aug 12;11(1):188. DOI: 10.1186/1477-7819-11-188.
- **Volvulus.** Coffee bean sign. This image is a derivative work, adapted from the following source, available under Yigit M, Turkdogan KA. Coffee bean sign, whirl sign and bird's beak sign in the diagnosis of sigmoid volvulus. *Pan Afr Med J.* 1014;19:56. DOI: 10.11604/pamj.2014.19.56.5142.
- **Other intestinal disorders: Image A.** Necrosis due to occlusion of SMA. This image is a derivative work, adapted from the following source, available under See: Van De Winkel N, Cheragwandi A, Nieboer K, et al. Superior mesenteric arterial branch occlusion causing partial jejunal ischemia: a case report. *J Med Case Rep.* 2012;6:48. DOI: 10.1186/1752-1947-6-48.
- **Other intestinal disorders: Image B.** Loops of dilated bowel suggestive of small bowel obstruction. This image is a derivative work, adapted from the following source, available under Welte FJ, Crosso M. Left-sided appendicitis in a patient with congenital gastrointestinal malrotation: a case report. *J Med Case Rep.* 2007;1:92. DOI: 10.1186/1752-1947-1-92.
- **Other intestinal disorders: Image C.** Endoscopy showing dilated vessels. This image is a derivative work, adapted from the following source, available under Gunjan D, Sharma V, Rana SS, et al. Small bowel bleeding: a comprehensive review. *Gastroenterol Rep.* 2014 Nov;2(4):262-75. DOI: 10.1093/gastro/gou025.
- 386 Other intestinal disorders: Image D. Pneumatosis intestinalis.

  This image is a derivative work, adapted from the following source, available under □□□: Pelizzo G, Nakib G, Goruppi I, et al. Isolated colon ischemia with norovirus infection in preterm babies: a case series. *J Med Case Rep.* 2013;7:108. DOI: 10.1186/1752-1947-7-108.
- 887 Colonic polyps: Image A. This image is a derivative work, adapted from the following source, available under . M. Emannuel.
- 387 Colonic polyps: Image B. Adenomatous polyps. This image is a derivative work, adapted from the following source, available under Schussman N, Wexner SD. Colorectal polyps and polyposis syndromes. Gastroenterol Rep (Oxf). 2014 Feb;2(1):1-15. DOI: 10.1093/gastro/got041.
- **Colonic polyps: Image C.** This image is a derivative work, adapted from the following source, available under :: Rehani B, Chasen RM, Dowdy Y, et al. Advanced adenoma diagnosis with FDG PET in a visibly normal mucosa: a case report. *J Med Case Reports*. 2007; 1: 99. DOI: 10.1186/1752-1947-1-99.
- 388 Colorectal cancer: Image A. Polyp. This image is a derivative work, adapted from the following source, available under Takiyama A, Nozawa H, Ishihara S, et al. Secondary metastasis in the lymph node of the bowel invaded by colon cancer: a report of three cases. World J Surg Oncol. 2016; 14: 273. DOI: 10.1186/s12957-016-1026-y.
- **389** Cirrhosis and portal hypertension: Image A. Splenomegaly and liver nodularity in cirrhosis. This image is a derivative work, adapted from

FAS1\_2019\_20\_ImageAck.indd 736 11/8/19 4:50 PM

- the following source, available under : Inversitus. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under
- Cirrhosis and portal hypertension: Image B. This image is a derivative work, adapted from the following source, available under Blackburn PR, Hickey RD, Nace RA, et al. Silent tyrosinemia type I without elevated tyrosine or succinylacetone associated with liver cirrhosis and hepatocellular carcinoma. Hum Mutat. 2016 Oct; 37(10): 1097-1105.DOI: 10.1002/humu.23047.
- **391** Alcoholic liver disease: Image B. Mallory bodies. This image is a derivative work, adapted from the following source, available under . Dr. Michael Bonert. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under @ ....
- **Alcoholic liver disease: Image C.** Sclerosis in alcoholic cirrhosis. This image is a derivative work, adapted from the following source, available under see: Dr. Michael Bonert. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under .....
- Non-alcoholic fatty liver disease. This image is a derivative work, adapted from the following source, available under El-Karaksy HM, El-Koofy NM, Anwar GM, et al. Predictors of non-alcoholic fatty liver disease in obese and overweight Egyptian children: single center study. Saudi J Gastroenterol. 2011;17:40-46. DOI: 10.4103/1319-3767 74476
- 392 Hepatocellular carcinoma/hepatoma: Image A. Gross specimen. Reproduced, with permission, from Jean-Christophe Fournet and Humpath.
- Other liver tumors. Cavernous liver hemangioma. This image is a derivative work, adapted from the following source, available under 2001: Dr. Michael Bonert. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes
- 392  $\alpha_3$ -antitrypsin deficiency. Liver histology. This image is a derivative work, adapted from the following source, available under .: Dr. Jerad M. Gardner. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under ......
- **Jaundice.** Yellow sclera. Courtesy of the Department of Health and Human Services and Dr. Thomas F. Sellers.
- Wilson disease. This image is a derivative work, adapted from the following source, available under Es: Kodama H, Fujisawa C, Bhadhprasit W. Inherited copper transport disorders: biochemical mechanisms, diagnosis, and treatment. Curr Drug Metab. 2012 Mar; 13(3): 237-250. DOI: 10.2174/138920012799320455.
- **Hemochromatosis.** Hemosiderin deposits. This image is a derivative work, adapted from the following source, available under Mathew J, Leong MY, Morley N, et al. A liver fibrosis cocktail? Psoriasis, methotrexate and genetic hemochromatosis. BMC Dermatol. 2005;5:12. DOI: 10.1186/1471-5945-5-12.
- Cholelithiasis and related pathologies: Image A. Gross specimen of gallstones. This image is a derivative work, adapted from the following source, available under source, available under courtesy of M. Émmanuel.
- **Cholelithiasis and related pathologies: Image B.** Large gallstone. This image is a derivative work, adapted from the following source, available under Spangler R, Van Pham T, Khoujah D, et al. Abdominal emergencies in the geriatric patient. Int J Emerg Med. 2014; 7: 43. DOI: 10.1186/s12245-014-0043-2.
- 397 Cholelithiasis and related pathologies: Image C. Porcelain gallbladder. This image is a derivative work, adapted from the following source, available under Ered H, van Dijk H. Images of memorable cases: case 19. Connexions Web site. December 4, 2008. Available at: http://cnx.org/content/m14939/1.3/. The image may have

- been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.
- **Acute pancreatitis: Image A.** Acute exudative pancreatitis. This image is a derivative work, adapted from the following source, available under .: Dr. Paul Hellerhoff. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under
- Acute pancreatitis: Image B. Pancreatic pseudocyst. This image is a derivative work, adapted from the following source, available under : Thomas Zimmerman. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under .....
- **Chronic pancreatitis.** This image is a derivative work, adapted from the following source, available under 22: Dr. Paul Hellerhoff. The image may have been modified by cropping, labeling, and/or captions. MedIO Learning, LLC makes this available under
- Pancreatic adenocarcinoma: Image A. Histology. This image is a derivative work, adapted from the following source, available under : KGH. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under 🛛 👀 .
- Pancreatic adenocarcinoma: Image B. CT scan. Courtesy of MBq. The image may have been modified by cropping, labeling, and/ or captions. All rights to this adaptation by MedIQ Learning, LLC are

#### Hematology and Oncology

- **Neutrophils.** Courtesy of B. Lennert.
- **Erythrocytes.** © Courtesy of the Department of Health and Human Services and Drs. Noguchi, Rodgers, and Schechter.
- **Thrombocytes (platelets).** This image is a derivative work, adapted from the following source, available under 22: Dr. Ed Uthman. The image may have been modified by cropping, labeling, and/or captions. MedIO Learning, LLC makes this available under .....
- **Monocytes.** This image is a derivative work, adapted from the following source, available under see: Dr. Graham Beards. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under
- Macrophages. This image is a derivative work, adapted from the following source, available under : De Tommasi AS, Otranto D, Furlanello T, et al. Evaluation of blood and bone marrow in selected canine vector-borne diseases. Parasit Vectors. 2014;7:534. DOI: 10.1186/s13071-014-0534-2.
- **Eosinophils.** This image is a derivative work, adapted from the following source, available under : Dr. Ed Uthman.
- **Basophils.** This image is a derivative work, adapted from the following source, available under Esse. Dr. Erhabor Osaro. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under ....
- Mast cells. Courtesy of Wikimedia Commons. 408
- **Dendritic cells.** This image is a derivative work, adapted from the following source, available under Es: Cheng J-H, Lee S-Y, Lien Y-Y, et al. Immunomodulating activity of Nymphaea rubra roxb. extracts: activation of rat dendritic cells and improvement of the TH1 immune response. Int J Mol Sci. 2012;13:10722-10735. DOI: 10.3390/ ijms130910722.
- **Lymphocytes.** This image is a derivative work, adapted from the following source, available under : Fickleandfreckled.
- Plasma cells. © Courtesy of the Department of Health and Human Services and Dr. Francis W. Chandler. The image may have been

FAS1\_2019\_20\_ImageAck.indd 737 11/8/19 4:50 PM

- modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.
- 415 RBC morphology: Image J. Sickle cell. Courtesy of the Department of Health and Human Services and the Sickle Cell Foundation of Georgia, Jackie George, and Beverly Sinclair.
- 416 RBC inclusions: Image A. Ringed sideroblast. This image is a derivative work, adapted from the following source, available under : Paulo Henrique Orlandi Mourao. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under :
- 416 RBC inclusions: Image B. Howell-Jolly bodies. This image is a derivative work, adapted from the following source, available under .: Serio B, Pezzullo L, Giudice V, et al. OPSI threat in hematological patients. *Transl Med UniSa*. 2013 May-Aug;6:2-10.
- **416 RBC inclusions: Image C.** Bsaophilic stippling. This image is a derivative work, adapted from the following source, available under :: Dr. Erhabor Osaro.
- 416 RBC inclusions: Image D. Pappenheimer bodies. This image is a derivative work, adapted from the following source, available under . Paulo Henrique Orlandi Mourao. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under .
- 419 Microcytic, hypochromic anemias: Image A. This image is a derivative work, adapted from the following source, available under Bock F, Borucki K, Vorwerk P, et al. A two-and-a-half-year-old breastfed toddler presenting with anemia: a case report. BMC Res Notes. 2014; 7: 917. DOI: 10.1186/1756-0500-7-917.
- 419 Microcytic, hypochromic anemia: Image D. Lead lines in lead poisoning. Reproduced, with permission, from Dr. Frank Gaillard and www.radiopaedia.org.
- 419 Microcytic, hypochromic anemia: Image E. Sideroblastic anemia. This image is a derivative work, adapted from the following source, available under 22: Paulo Henrique Orlandi Moura. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under 22.
- **420** Macrocytic anemias. Megaloblastic anemia. This image is a derivative work, adapted from the following source, available under Courtesy of Dr. Ed Uthman.
- **422** Intrinsic hemolytic anemias. This image is a derivative work, adapted from the following source, available under .: El Ariss AB, Younes M, Matar J. Prevalence of sickle cell trait in the southern suburb of Beirut, Lebanon. Mediterr J Hematol Infect Dis. 2016; 8(1): e2016015. DOI: 10.4084/MJHID.2016.015.
- 425 Heme synthesis, porphyrias, and lead poisoning: Image A.
  Basophilic stippling in lead poisoning. This image is a derivative work, adapted from the following source, available under wan Dijk HA, Fred HL. Images of memorable cases: case 81. Connexions Web site. December 3, 2008. Available at http://cnx.org/contents/3196bf3e-lele-4c4d-alac-d4fc9ab65443@4@4.
- **425 Heme synthesis, porphyrias, and lead poisoning: Image B.** Porphyria cutanea tarda. This image is a derivative work, adapted from the following source, available under Bovenschen HJ, Vissers WHPM. Primary hemochromatosis presented by porphyria cutanea tarda: a case report. Cases J. 2009;2:7246. DOI: 10.4076/1757-1626-2-7246.
- 426 Coagulation disorders. This image is a derivative work, adapted from the following source, available under 3 2 Lakjiri S, Mernissi FZ. Tabetic arthropathy revealing neurosyphilis: a new observation. Pan Afr Med J. 2014; 18: 198. DOI: 10.11604/pamj.2014.18.198.4893.
- **429 Hodgkin lymphoma.** This image is a derivative work, adapted from the following source, available under . Knecht H, Righolt C, Mai S. Genomic instability: the driving force behind refractory/relapsing

- Hodgkin's lymphoma. Cancers (Basel). 2013 Jun; 5(2): 714–725. DOI: 10.3390/cancers5020714.
- 430 Non-Hodgkin lymphoma: Image B. This image is a derivative work, adapted from the following source, available under Bi CF, Tang Y, Zhang WY, et al. Sporadic Burkitt lymphomas of children and adolescents in Chinese: a clinicopathological study of 43 cases. Diagn Pathol. 2012;7:72. DOI:10.1186/1746-1596-7-72.
- **430 Non-Hodgkin lymphoma: Image C.** This image is a derivative work, adapted from the following source, available under Mansour A, Qandeel M, Abdel-Razeq H, et al. MR imaging features of intracranial primary CNS lymphoma in immune competent patients. *Cancer Imaging*. 2014;14(1):22. DOI: 10.1186/1470-7330-14-22.
- **Plasma cell dyscrasias: Image C.** This image is a derivative work, adapted from the following source, available under Mehrotra R, Singh M, Singh PA, et al. Should fine needle aspiration biopsy be the first pathological investigation in the diagnosis of a bone lesion? An algorithmic approach with review of literature. *Cytojournal*. 2007; 4: 9. DOI: 10.1186/1742-6413-4-9.
- 432 Myelodysplastic syndromes. This image is a derivative work, adapted from the following source, available under 2 2: Lukaszewska J, Allison RW, Stepkowska J. Congenital Pelger-Huët anomaly in a Danish/Swedish farmdog: case report. Acta Vet Scand. 2011; 53(1): 14. DOI: 10.1186/1751-0147-53-14.
- **Leukemias: Image A.** This image is a derivative work, adapted from the following source, available under . Chiaretti S, Zini G, Bassan R. Diagnosis and subclassification of acute lymphoblastic leukemia. *Mediterr J Hematol Infect Dis.* 2014; 6(1): e2014073. DOI: 10.4084/MJHID.2014.073.
- 433 Leukemias: Image C. Hairy cell leukemia. This image is a derivative work, adapted from the following source, available under ☑ ☑: Chan SM, George T, Cherry AM, et al. Complete remission of primary plasma cell leukemia with bortezomib, doxorubicin, and dexamethasone: a case report. Cases J. 2009;2:121. DOI: 10.1186/1757-1626-2-121.
- 433 Chronic myeloproliferative disorders: Image A. Erythromelalgia in polycythemia vera. This image is a derivative work, adapted from the following source, available under Experiment Fred H, van Dijk H. Images of memorable cases: case 151. Connexions Web site. December 4, 2008. Available at http://cnx.org/content/m14932/1.3/.
- **433 Chronic myeloproliferative disorders: Image C.** Myelofibrosis. This image is a derivative work, adapted from the following source, available under **Courtesy** of Dr. Ed Uthman.
- 434 Langerhans cell histiocytosis: Image A. Lytic bone lesion. This image is a derivative work, adapted from the following source, available under . Dehkordi NR, Rajabi P, Naimi A, et al. Langerhans cell histiocytosis following Hodgkin lymphoma: a case report from Iran. J Res Med Sci. 2010;15:58-61. PMCID PMC3082786.
- 434 Langerhans cell histiocytosis: Image B. Birbeck granules. This image is a derivative work, adapted from the following source, available under . The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under .
- 435 Hemophagocytic lymphohistiocytosis. This image is a derivative work, adapted from the following source, available under . Kashif M, Tariq H, Ijaz M. Disseminated histoplasmosis and secondary hemophagocytic syndrome in a non-HIV patient. Case Rep Crit Care. 2015; 2015: 295735. DOI: 10.1155/2015/295735.

FAS1\_2019\_20\_ImageAck.indd 738 11/8/19 4:50 PM

**Warfarin.** This image is a derivative work, adapted from the following source, available under see: Bakoyiannis C, Karaolanis G, Patelis N. Dabigatran in the treatment of warfarin-induced skin necrosis: A new hope. Case Rep Dermatol Med. 2016; 2016: 3121469. DOI: 10.1155/2016/3121469.

#### Musculoskeletal, Skin, and Connective Tissue

- Rotator cuff muscles. Glenohumeral instability. This image is a derivative work, adapted from the following source, available under Exercise Y, Sano H, Imamura I, et al. Changes with time in skin temperature of the shoulders in healthy controls and a patient with shoulder-hand syndrome. Ups J Med Sci 2010;115:260-265. DOI: 10.3109/03009734.2010.503354. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.
- **Brachial plexus lesions: Image A.** Cervical rib. This image is a derivative work, adapted from the following source, available under Dahlin LB, Backman C, Duppe H, et al. Compression of the lower trunk of the brachial plexus by a cervical rib in two adolescent girls: case reports and surgical treatment. J Brachial Plex Peripher Nerve Inj. 2009;4:14. DOI: 10.1186/1749-7221-4-14.
- Brachial plexus lesions: Image B. Winged scapula. This image is a derivative work, adapted from the following source, available under : Boukhris J, Boussouga M, Jaafar A, et al. Stabilisation dynamique d'un winging scapula (à propos d'un cas avec revue de la littérature). Pan Afr Med J. 2014; 19: 331. DOI: 10.11604/ pamj.2014.19.331.3429.
- **449** Wrist region: Image B. Anatomic snuff box. This image is a derivative work, adapted from the following source, available under Rhemrev SJ, Ootes D, Beeres FJP, et al. Current methods ofdiagnosis and treatment of scaphoid fractures. Int J Emerg Med. 2011;4:4. DOI: 10.1186/1865-1380-4-4.
- Motoneuron action potential to muscle contraction: Image A. This image is a derivative work, adapted from the following source, available under : Ottenheijm CAC, Heunks LMA, Dekhuijzen RPN. Diaphragm adaptations in patients with COPD. Respir Res. 2008; 9(1): 12. DOI: 10.1186/1465-9921-9-12.
- Wrist and hand injuries: Image A. Metacarpal neck fracture. This image is a derivative work, adapted from the following source, available under see: Bohr S, Pallua N. Early functional treatment and modern cast making for indications in hand surgery. Adv Orthop. 2016; 2016: 5726979. DOI: 10.1155/2016/5726979.
- Wrist and hand injuries: Image B. Thenar eminence atrophy in carpal tunnel syndrome. Courtesy of Dr. Harry Gouvas.
- Common hip and knee conditions: Image A. ACL tear. This image is a derivative work, adapted from the following source, available under Es: Chang MJ, Chang CB, Choi J-Y, et al. Can magnetic resonance imaging findings predict the degree of knee joint laxity in patients undergoing anterior cruciate ligament reconstruction? BMC Musculoskelet Disord. 2014;15:214. DOI: 10.1186/1471-2474-15-214. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.
- Common hip and knee conditions: Images B (prepatellar bursitis) and C (Baker cyst). This image is a derivative work, adapted from the following source, available under Euri Z, Hunhun JS, Choudur HN. Imaging of the bursae. J Clin Imaging Sci. 2011;1:22. DOI: 10.4103/2156-7514.80374. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.
- **462 Common pediatric fractures: Image A.** Greenstick fracture. This image is a derivative work, adapted from the following source, available under Randsborg PH, Sivertsen EA. Classification of distal radius fractures in children: good inter- and intraobserver

- reliability, which improves with clinical experience. BMC Musculoskelet Disord. 2013;13:6. DOI: 10.1186/1471-2474-13-6.
- **Common pediatric fractures: Image B.** Torus (buckle) fracture. This image is a derivative work, adapted from the following source, available under Es: Aksel Seyahi, et al. Tibial torus and toddler's fractures misdiagnosed as transient synovitis: a case series. J Med Case Reports. 2011; 5: 305. DOI: 10.1186/1752-1947-5-305.
- **Osteoporosis.** Vertebral compression fractures of spine. This image is a derivative work, adapted from the following source, available under : Imani F, Gharaei H, Rahimzadeh P, et al. Management of painful vertebral compression fracture with kyphoplasty in a sever cardio-respiratory compromised patient. Anesth Pain Med. 2012 summer;2(1):42-45. DOI: 10.5812/aapm.5030.
- Osteopetrosis. This image is a derivative work, adapted from the following source, available under Est. Kant P, Sharda N, Bhowate RR. Clinical and radiological findings of autosomal dominant osteopetrosis type II: a case report. Case Rep Dent. 2013;2013:707343. DOI: 10.1155/2013/707343.
- Osteomalacia/rickets: Image A, left. Clinical photo. This image is a derivative work, adapted from the following source, available under : Linglart A, Biosse-Duplan M, Briot K, et al. Therapeutic management of hypophosphatemic rickets from infancy to adulthood. Endocr Connect. 2014;3:R13-R30. DOI: 10.1530/EC-13-0103.
- **Osteomalacia/rickets: Image B.** Rachitic rosary on chest X-ray. This image is a derivative work, adapted from the following source, available under Essabar L, Meskini T, Ettair S, et al. Malignant infantile osteopetrosis: case report with review of literature. Pan Afr Med J. 2014;17:63. DOI: 10.11604/pamj.2014.17.63.3759.
- Osteitis deformans. Thickened calvarium. This image is a derivative work, adapted from the following source, available under \_\_\_\_: Dawes L. Paget's disease. [Radiology Picture of the Day Website]. Published June 21, 2007. Available at http://www.radpod.org/2007/06/21/pagets-
- Avascular necrosis of bone. Bilateral necrosis of femoral head. This image is a derivative work, adapted from the following source, available under : Ding H, Chen S-B, Lin S, et al. The effect of postoperative corticosteroid administration on free vascularized fibular grafting for treating osteonecrosis of the femoral head. Sci World J. 2013;708014. DOI: 10.1155/2013/708014. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.
- Primary bone tumors: Image A. Osteochondroma. This image is a derivative work, adapted from the following source, available under so: Lucien Monfils. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under @ ....
- **Primary bone tumors: Image B.** Osteoid osteoma. This image is a derivative work, adapted from the following source, available under Jankharia B, Burute N. Percutaneous radiofrequency ablation for osteoid osteoma: how we do it. Indian J Radiol Imaging. 2009 Feb; 19(1): 36-42. DOI: 10.4103/0971-3026.44523.
- **Primary bone tumors: Image C.** Giant cell tumor. Reproduced, with permission, from Dr. Frank Gaillard and www.radiopaedia.org.
- **Primary bone tumors: Image D.** This image is a derivative work, adapted from the following source, available under : Xu SF, Yu XC, Zu M, et al. Limb function and quality of life after various reconstruction methods according to tumor location following resection of osteosarcoma in distal femur. BMC Musculoskelet Disord. 2014; 15: 453. DOI: 10.1186/1471-2474-15-453
- **Primary bone tumors: Image E.** Starburst pattern in osteosarcoma. This image is a derivative work, adapted from the following source, available under Ding H, Yu G, Tu Q, et al. Computeraided resection and endoprosthesis design for the management of

FAS1\_2019\_20\_ImageAck.indd 739 11/8/19 4:50 PM

- malignant bone tumors around the knee: outcomes of 12 cases. BMC Musculoskelet Disord. 2013; 14: 331. DOI: 10.1186/1471-2474-14-331.
- 466 Osteoarthritis vs rheumatoid arthritis: Image A. Histology of rheumatoid nodule. This image is a derivative work, adapted from the following source, available under George: Gomez-Rivera F, El-Naggar AK, Guha-Thakurta N, et al. Rheumatoid arthritis mimicking metastatic squamous cell carcinoma. Head Neck Oncol. 2011;3:26. DOI: 10.1186/1758-3284-3-26.
- 467 Gout: Image B. Uric acid crystals under polarized light. This image is a derivative work, adapted from the following source, available under 222: Robert J. Galindo. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under 222
- **Gout: Image C.** Podagra. This image is a derivative work, adapted from the following source, available under : Roddy E. Revisiting the pathogenesis of podagra: why does gout target the foot? *J Foot Ankle Res.* 2011;4:13. DOI: 10.1186/1757-1146-4-13.
- 467 Calcium pyrophosphate deposition disease. Calcium phosphate crystals. This image is a derivative work, adapted from the following source, available under Dieppe P, Swan A. Identification of crystals in synovial fluid. Ann Rheum Dis. 1999 May;58(5):261–263.
- 468 Sjögren syndrome: Image B. Dry tongue. This image is a derivative work, adapted from the following source, available under Negrato CA, Tarzia O. Buccal alterations in diabetes mellitus. Diabetol Metab Syndr. 2010;2:3. DOI: 10.1186/1758-5996-2-3.
- **Septic arthritis.** Joint effusion. This image is a derivative work, adapted from the following source, available under . Dr. James Heilman. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under
- 469 Seronegative spondyloarthropathies: Image C, left. Bamboo spine. This image is a derivative work, adapted from the following source, available under : Stevenfruitsmaak. The image may have been modified by cropping, labeling, and/or captions. MedlQ Learning, LLC makes this available under :
- **Seronegative spondyloarthropathies: Image C, right.** Bamboo spine. Courtesy of Heather Hawker.
- **Polymyositis/dermatomyositis: Image A.** Groton papules of dermatomyositis. This image is a derivative work, adapted from the following source, available under Pan Afr Med J.2015; 21: 89. DOI: 10.11604/pamj.2015.21.89.6971.
- **472** Raynaud phenomenon. This image is a derivative work, adapted from the following source, available under : Jamclaassen. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under ...
- 474 Epithelial cell junctions: Image A. Intracellular membrane. This image is a derivative work, adapted from the following source, available under : Tang VW. Proteomic and bioinformatic analysis of epithelial tight junction reveals an unexpected cluster of synaptic molecules. Biol Direct. 2006; 1: 37. DOI: 10.1186/1745-6150-1-37.
- 474 Epithelial cell junctions: Image B. Large, electron-dense actin structures within adherens junction. This image is a derivative work, adapted from the following source, available under . Taylor RR, Jagger DJ, Saeed SR, et al. Characterizing human vestibular sensory epithelia for experimental studies: new hair bundles on old tissue and implications for therapeutic interventions in ageing. Neurobiol Aging. 2015 Jun;36(6):2068–2084. DOI: 10.1016/j. neurobiolaging.2015.02.013.
- **474 Epithelial cell junctions: Image C.** Desmosome. This image is a derivative work, adapted from the following source, available under

- \*\*Massa F, Devader C, Lacas-Gervais S, et al. Impairement of HT29 cancer cells cohesion by the soluble form of neurotensin receptor-3. *Genes Cancer*. 2014 Jul; 5(7-8):240–249. DOI: 10.18632/genesandcancer.22.
- **474 Epithelial cell junctions: Image D.** Gap junction. This image is a derivative work, adapted from the following source, available under See: Shu X, Lev-Ram V, Deerinck TJ. A Genetically encoded tag for correlated light and electron microscopy of intact cells, tissues, and organisms. *PLoS Biol.* 2011 Apr; 9(4): e1001041. DOI: 10.1371/journal.pbio.1001041.
- **474 Epithelial cell junctions: Image E.** Hemidesmosome. This image is a derivative work, adapted from the following source, available under . Nguyen NM, Pulkkinen L, Schlueter JA, et al. Lung development in laminin gamma2 deficiency: abnormal tracheal hemidesmosomes with normal branching morphogenesis and epithelial differentiation. *Respir Res.* 2006 Feb 16;7:28. DOI: 10.1186/1465-9921-7-28.
- **Seborrheic dermatitis.** This image is a derivative work, adapted from the following source, available under Roymishali.
- 477 Common skin disorders: Image O. Urticaria. This image is a derivative work, adapted from the following source, available under . Dr. James Heilman. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under .
- 478 Vascular tumors of skin: Image C. Glomus tumor under fingernail.

  This image is a derivative work, adapted from the following source, available under . Hazani R, Houle JM, Kasdan ML, et al. Glomus tumors of the hand. Eplasty. 2008;8:e48. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.
- **Skin infections: Image C.** Erysipelas. This image is a derivative work, adapted from the following source, available under Courtesy of Klaus D. Peter.
- **480 Autoimmune blistering skin disorders: Image D.** Bullous pemphigoid on immunofluorescence. This image is a derivative work, adapted from the following source, available under : Courtesy of M. Emmanuel.
- 484 Skin cancer: Image D. Basal cell palisading nuclei. This image is a derivative work, adapted from the following source, available under □□□: Yuri T. Jadotte, MD, et al. Superficial spreading basal cell carcinoma of the face: a surgical challenge. Eplasty. 2010; 10: e46. Published online 2010 Jun 21.

#### **Neurology and Special Senses**

- 491 Holoprosencephaly: Image A. This image is a derivative work, adapted from the following source, available under Alorainy IA, Barlas NB, Al-Boukai AA. Pictorial essay: infants of diabetic mothers. Indian J Radiol Imaging. 2010 Aug;20(3):174-81. DOI: 10.4103/0971-3026.69349.
- **Posterior fossa malformations: Image A.** Chiari I malformation. This image is a derivative work, adapted from the following source, available under Toldo I, De Carlo D, Mardari R, et al. Short lasting activity-related headaches with sudden onset in children: a case-based reasoning on classification and diagnosis. *J Headache Pain*. 2013;14(1):3. DOI: 10.1186/1129-2377-14-3.
- **492 Posterior fossa malformations: Image B.** Dandy-Walker malformation. This image is a derivative work, adapted from the following source, available under Krupa K, Bekiesinska-Figatowska M. Congenital and acquired abnormalities of the corpus callosum: a pictorial essay. Biomed Res Int. 2013;2013:265619. DOI: 10.1155/2013/265619.

FAS1\_2019\_20\_ImageAck.indd 740 11/8/19 4:50 PM

- Syringomyelia. Reproduced, with permission, from Dr. Frank Gaillard and www.radiopaedia.org.
- **Myelin.** Myelinated neuron. © Courtesy of the Electron Microscopy Facility at Trinity College.
- **Chromatolysis.** This image is a derivative work, adapted from the following source, available under 2001: Dr. Michael Bonnert. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under
- **Limbic system: Image A.** This image is a derivative work, adapted from the following source, available under : Schopf V, Fischmeister FP, Windischberger C, et al. Effects of individual glucose levels on the neuronal correlates of emotions. Front Hum Neurosci. 2013 May 21;7:212. DOI: 10.3389/fnhum.2013.00212.
- **Cerebellum.** This image is a derivative work, adapted from the following source, available under see: Jarius S, Wandinger KP, Horn S, et al. A new Purkinje cell antibody (anti-Ca) associated with subacute cerebellar ataxia: immunological characterization. J Neuroinflammation. 2010;7: 21. DOI: 10.1186/1742-2094-7-21.
- **Basal ganglia.** This image is a derivative work, adapted from the following source, available under Rudger P, Jaunmuktane Z, Adlard P, et al. Iatrogenic CJD due to pituitary-derived growth hormone with genetically determined incubation times of up to 40 years. Brain. 2015 Nov; 138(11): 3386-3399. DOI: 10.1093/brain/ awv235.
- **502** Cerebral arteries—cortical distribution. Cortical watershed areas. This image is a derivative work, adapted from the following source, available under Esabel C, Lecler A, Turc G, et al. Relationship between watershed infarcts and recent intra plaque haemorrhage in carotid atherosclerotic plaque. PLoS One. 2014;9(10):e108712. DOI: 10.1371/journal.pone.0108712.
- **Dural venous sinuses.** This image is a derivative work, adapted from the following source, available under :: Cikla U, Âagaard-Kienitz B, Turski PA, et al. Familial perimesencephalic subarachnoid hemorrhage: two case reports. J Med Case Rep. 2014;8. DOI: 10.1186/1752-1947-8-380. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.
- **Spinal cord and associated tracts: Image A.** Spinal cord cross-section. This image is a derivative work, adapted from the following source, available under : Regents of University of Michigan Medical School.
- 512 Neonatal interventricular hemorrhage. This image is a derivative work, adapted from the following source, available under Shooman D, Portess H, Sparrow O. A review of the current treatment methods for posthaemorrhagic hydrocephalus of infants. Cerebrospinal Fluid Res. 2009;6:1. DOI: 10.1186/1743-8454-6-1.
- 513 Intracranial hemorrhage: Images A and B. Axial CT of brain showing epidural blood. This image is a derivative work, adapted from the following source, available under : Dr. Paul Hellerhoff. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under
- Intracranial hemorrhage: Image C. Subdural hematoma. This image is a derivative work, adapted from the following source, available under . Dr. James Heilman. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under ......
- Intracranial hemorrhage: Image E. Subarachnoid hemorrhage. This image is a derivative work, adapted from the following source, available under : Hakan T, Turk CC, Celik H. Intra-operative real time intracranial subarachnoid haemorrhage during glial tumour resection: a case report. Cases J. 2008;1:306. DOI: 10.1186/1757-1626-1-306. The image may have been modified by cropping, labeling, and/

- or captions. All rights to this adaptation by MedIO Learning, LLC are reserved.
- 515 **Effects of strokes: Image A.** Large abnormality of the left MCA territory. This image is a derivative work, adapted from the following source, available under Es: Hakimelahi R, Yoo AJ, He J, et al. Rapid identification of a major diffusion/perfusion mismatch in distal internal carotid artery or middle cerebral artery ischemic stroke. BMC Neurol. 2012 Nov 5;12:132. DOI: 10.1186/1471-2377-12-132. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.
- **Effects of strokes: Image B.** MRI diffusion weighted image shows a hypersensitive lesion on posterior limb of internal capsular. This image is a derivative work, adapted from the following source, available under : Zhou L, Ni J, Yao M, et al. High-resolution MRI findings in patients with capsular warning syndrome. BMC Neurol. 2014;14:16. DOI: 10.1186/1471-2377-14-16.
- **Effects of strokes: Image C.** This image is a derivative work, adapted from the following source, available under : Nouh A, Remke J, Ruland S. Ischemic posterior circulation stroke: a review of anatomy, clinical presentations, diagnosis, and current management. Front Neurol. 2014 Apr 7;5:30. DOI: 10.3389/fneur.2014.00030.
- **Effects of strokes: Image D.** This image is a derivative work, adapted from the following source, available under : Mittal P, Kalia V, Dua S. Pictorial essay: Susceptibility-weighted imaging in cerebral ischemia. Indian J Radiol Imaging. 2010 Nov; 20(4): 250-253. DOI: 10.4103/0971-3026.73530.
- **Diffuse axonal injury.** Moenninghoff C, Kraff O, Maderwald S, et al. Diffuse axonal injury at ultra-high field MRI. PLoS One. 2015;10(3):e0122329. DOI: 10.1371/journal.pone.0122329.
- **Aneurysms.** This image is a derivative work, adapted from the following source, available under : Kayhan A, Koc O, Keskin S. The role of bone subtraction computed tomographic angiography in determining intracranial aneurysms in non-traumatic subarachnoid hemorrhage. Iran J Radiol. 2014 May; 11(2): e12670. DOI: 10.5812/ iranjradiol.12670.
- 521 Neurodegenerative disorders: Image A. Lewy body in substantia nigra. This image is a derivative work, adapted from the following source, available under :: Werner CJ, Heyny-von Haussen R, Mall G, et al. Parkinson's disease. Proteome Sci. 2008;6:8. DOI: 10.1186/1477-5956-6-8. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.
- Neurodegenerative disorders: Image B. Gross specimen of normal brain. This image is a derivative work, adapted from the following source, available under . Niedowicz DM, Nelson PT, Murphy MP. Alzheimer's disease: pathological mechanisms and recent insights. Curr Neuropharmacol. 2011 Dec;9(4):674-84. DOI: 10.2174/157015911798376181.
- Neurodegenerative disorders: Images C (brain atrophy in Alzheimer 521 disease) and F (atrophy in frontotemporal dementia). This image is a derivative work, adapted from the following source, available under : Niedowicz DM, Nelson PT, Murphy MP. Alzheimer's disease: pathological mechanisms and recent insights. Curr Neuropharmacol. 2011 Dec;9(4):674-84. DOI: 10.2174/157015911798376181.
- **Neurodegenerative disorders: Image G.** Frontotemporal dementia: Pick bodies in frontotemporal demendia (Pick disease). This image is a derivative work, adapted from the following source, available under with Neumann M. Molecular neuropathology of TDP-43 proteinopathies. *Int J Mol Sci.* 2009 Jan; 10(1): 232–246. DOI: 10.3390/ijms10010232.
- Neurodegenerative disorders: Image H. Spongiform changes in brain 521 in Creutzfeld-Jacob disease. This image is a derivative work, adapted from the following source, available under . DRdoubleB. The

FAS1 2019 20 ImageAck.indd 741 11/8/19 4:50 PM

- image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under
- **522 Hydrocephalus: Image B.** Communicating hydrocephalus. This image is a derivative work, adapted from the following source, available under ... Torres-Martin M, Pena-Granero C, Carceller F, et al. Homozygous deletion of *TNFRSF4*, *TP73*, *PPAP2B* and *DPYD* at 1p and *PDCD5* at 19q identified by multiplex ligation-dependent probe amplification (MLPA) analysis in pediatric anaplastic glioma with questionable oligodendroglial component. *Mol Cytogenet*. 2014;7:1. DOI: 10.1186/1755-8166-7-1.
- **522 Hydrocephalus: Image C.** Ex vacuo ventriculomegaly. This image is a derivative work, adapted from the following source, available under Ghetti B, Oblak AL, Boeve BF, et al. Frontotemporal dementia caused by microtubule-associated protein tau gene (*MAPT*) mutations: a chameleon for neuropathology and neuroimaging. Neurophathol Appl Neurobiol. 2015 Feb;41(1):24-46. DOI: 10.1111/nan.12213.
- **Multiple sclerosis.** Periventricular plaques. This image is a derivative work, adapted from the following source, available under open Dooley MC, Foroozan R. Optic neuritis. *J Ophthalmic Vis Res.* 2010 Jul;5(3):182–187.
- 524 Other demyelinating and dysmyelinating diseases: Image B.

  Progressive multifocal leukoencephalopathy. This image is a derivative work, adapted from the following source, available under Garrote H, de la Fuente A, Ona R, et al. Long-term survival in a patient with progressive multifocal leukoencephalopathy after therapy with rituximab, fludarabine and cyclophosphamide for chronic lymphocytic leukemia. Exp Hematol Oncol. 2015;4:8. DOI: 10.1186/s40164-015-0003-4.
- 524 Other demyelinated and dysmyelinating disorders: Image A. Central pontine myelinolysis. This image is a derivative work, adapted from the following source, available under :: Wikimedia Commons. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under
- **Neurocutaneous disorders: Image A.** Sturge-Weber syndrome and port wine stain. This image is a derivative work, adapted from the following source, available under :: Babaji P, Bansal A, Krishna G, et al. Sturge-Weber syndrome with osteohypertrophy of maxilla. *Case Rep Pediatr.* 2013. DOI: 10.1155/2013/964596.
- 525 Neurocutaneous disorders: Image B. Leptomeningeal angioma in Sturge-Weber syndrome. Reproduced, with permission, from Dr. Frank Gaillard and www.radiopaedia.org.
- 525 Neurocutaneous disorders: Image C. Tuberous sclerosis. This image is a derivative work, adapted from the following source, available under .: Fred H, van Dijk H. Images of memorable cases: case 143. Connexions Web site. December 4, 2008. Available at: http://cnx.org/content/m14923/1.3/.
- 525 Neurocutaneous disorders: Image D. Ash leaf spots in tuberous sclerosis. This image is a derivative work, adapted from the following source, available under : Tonekaboni SH, Tousi P, Ebrahimi A, et al. Clinical and para clinical manifestations of tuberous sclerosis: a cross sectional study on 81 pediatric patients. Iran J Child Neurol. 2012;6:25-31. PMCID PMC3943027.
- 525 Neurocutaneous disorders: Image E. Angiomyolipoma in tuberous sclerosis. This image is a derivative work, adapted from the following source, available under KGH. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under ...
- **Neurocutaneous disorders: Image F.** Café-au-lait spots in neurofibromatosis. This image is a derivative work, adapted from the following source, available under : Wikimedia Commons. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under :

- 525 Neurocutaneous disorders: Image G. Lisch nodules in neurofibromatosis. Courtesy of the Department of Health and Human Services.
- **Neurocutaneous disorders: Image H.** Cutaneous neurofibromas. This image is a derivative work, adapted from the following source, available under Kim BK, Choi YS, Gwoo S, et al. Neurofibromatosis type 1 associated with papillary thyroid carcinoma incidentally detected by thyroid ultrasonography: a case report. *J Med Case Rep.* 2012;6:179. DOI: 10.1186/1752-1947-6-179.
- 525 Neurocutaneous disorders: Image I. Cerebellar hemangioblastoma histology. This image is a derivative work, adapted from the following source, available under Dr. Michael Bonert. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under Dr.
- 525 Neurocutaneous disorders: Image J. Brainstem and spinal cord hemangioblastomas in von Hippel-Lindau disease. This image is a derivative work, adapted from the following source, available under Park DM, Zhuang Z, Chen L, et al. von Hippel-Lindau disease-associated hemangioblastomas are derived from embryologic multipotent cells. PLoS Med. 2007 Feb;4(2):e60. DOI: 10.1371/journal.pmed.0040060.
- 526 Adult primary brain tumors: Image A. This image is a derivative work, adapted from the following source, available under see: Rossmeisl JH, Clapp K, Pancotto TE. Canine butterfly glioblastomas: A neuroradiological review. Front Vet Sci. 2016; 3: 40. DOI: 10.3389/fvets.2016.00040.
- 526 Adult primary brain tumors: Image B. Glioblastoma multiforme histology. This image is a derivative work, adapted from the following source, available under Wikimedia Commons. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under
- **Adult primary brain tumors: Image C.** Oligodendroglioma in frontal lobes. This image is a derivative work, adapted from the following source, available under . Celzo FG, Venstermans C, De Belder F, et al. Brain stones revisited—between a rock and a hard place. *Insights Imaging*. 2013 Oct;4(5):625-35. DOI: 10.1007/s13244-013-0279-z.
- 526 Adult primary brain tumors: Image D. Oligodendroglioma, "fried egg" cells. This image is a derivative work, adapted from the following source, available under . Rephron. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under .
- 526 Adult primary brain tumors: Image E. Meningioma with dural tail. This image is a derivative work, adapted from the following source, available under . Smits A, Zetterling M, Lundin M, et al. Neurological impairment linked with cortico-subcortical infiltration of diffuse low-grade gliomas at initial diagnosis supports early brain plasticity. Front Neurol. 2015;6:137. DOI: 10.3389/fneur.2015.00137.
- 526 Adult primary brain tumors: Image F. Meningioma, psammoma bodies. This image is a derivative work, adapted from the following source, available under .: Nephron. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under ...
- **Adult primary brain tumors: Image G.** Cerebellar hemangioblastoma. This image is a derivative work, adapted from the following source, available under Park DM, Zhengping Z, Chen L, et al. von Hippel-Lindau disease-associated hemangioblastomas are derived from embryologic multipotent cells. *PLoS Med.* 2007 Feb;4(2):e60. DOI: 10.1371/journal.pmed.0040060.
- **Adult primary brain tumors: Image H.** Minimal parenchyma in hemangioblastoma. This image is a derivative work, adapted from the following source, available under Marvin 101. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under

FAS1\_2019\_20\_ImageAck.indd 742 11/8/19 4:50 PM

- Adult primary brain tumors: Image I. Field of vision in bitemporal hemianopia. This image is a derivative work, adapted from the following source, available under see: Wikimedia Commons. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under .....
- Adult primary brain tumors: Image J. Prolactinoma. This image is a derivative work, adapted from the following source, available under Wang CS, Yeh TC, Wu TC, et al. Pituitary macroadenoma coexistent with supraclinoid internal carotid artery cerebral aneurysm: a case report and review of the literature. Cases J. 2009;2:6459. DOI: 10.4076/1757-1626-2-6459.
- 527 Adult primary brain tumors: Image K. Schwannoma at cerebellopontine angle. Courtesy of MRT-Bild.
- Adult primary brain tumors: Image L. Schwann cell origin of schwannoma. This image is a derivative work, adapted from the following source, available under see: Nephron. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under
- 528 Childhood primary brain tumors: Image A. MRI of pilocytic astrocytoma. This image is a derivative work, adapted from the following source, available under : Hafez RFA. Stereotaxic gamma knife surgery in treatment of critically located pilocytic astrocytoma: preliminary result. World J Surg Oncol. 2007;5:39. doi 10.1186/1477-7819-5-39.
- Childhood primary brain tumors: Image C. CT of medulloblastoma. Courtesy of the Department of Health and Human Services and the Armed Forces Institute of Pathology.
- Childhood primary brain tumors: Image D. Medulloblastoma histology. This image is a derivative work, adapted from the following source, available under .: KGH. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under .....
- Childhood primary brain tumors: Image E. MRI of ependymoma. This image is a derivative work, adapted from the following source, available under .: Dr. Paul Hellerhoff. The image may have been modified by cropping, labeling, and/or captions. MedIO Learning, LLC makes this available under ......
- Childhood primary brain tumors: Image F. Ependymoma histology. This image is a derivative work, adapted from the following source, available under . Nephron. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under @ ....
- Childhood primary brain tumors: Image G. CT of craniopharyngioma. This image is a derivative work, adapted from the following source, available under Garnet MR, Puget S, Grill J, et al. Craniopharyngioma. Orphanet J Rare Dis. 2007;2:18. DOI: 10.1186/1750-1172-2-18.
- Childhood primary brain tumors: Image H. Craniopharyngioma histology. This image is a derivative work, adapted from the following source, available under Es: Nephron. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under .....
- Friedreich ataxia: Image A. Clinical kyphoscoliosis. This image is a derivative work, adapted from the following source, available under :: Axelrod FB, Gold-von Simson. Hereditary sensory and autonomic neuropathies: types II, III, and IV. Orphanet J Rare Dis. 2007;2:39. DOI: 10.1186/1750-1172-2-39.
- **531** Friedreich ataxia: Image B. Radiograph showing kyphoscoliosis. This image is a derivative work, adapted from the following source, available under Essensia Bounakis N, Karampalis C, Tsirikos AI. Surgical treatment of scoliosis in Rubinstein-Taybi syndrome type 2: a case report. J Med Case Rep. 2015; 9: 10. doi 10.1186/1752-1947-9-10.

- **Facial nerve lesions.** Facial nerve palsy. This image is a derivative work, adapted from the following source, available under Socolovsky M, Paez MD, Di Masi G, et al. Bell's palsy and partial hypoglossal to facial nerve transfer: Case presentation and literature review. Surg Neurol Int. 2012;3:46. DOI: 10.4103/2152-7806.95391.
- **Cholesteatoma.** This image is a derivative work, adapted from the following source, available under : Welleschik. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under ....
- **Normal eye anatomy.** This image is a derivative work, adapted from the following source, available under see: Jan Kaláb. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under
- Conjunctivitis. This image is a derivative work, adapted from the following source, available under Baiyeroju A, Bowman R, Gilbert Č, et al. Managing eye health in young children. Community Eye Health. 2010;23:4-11.
- Cataract. Juvenile cataract. This image is a derivative work, adapted from the following source, available under : Roshan M, Vijaya PH, Lavanya GR, et al. A novel human CRYGD mutation in a juvenile autosomal dominant cataract. Mol Vis. 2010;16:887-896. PMCID PMC2875257.
- Glaucoma: Image C. Closed/narrow angle glaucoma. This image is a derivative work, adapted from the following source, available under Low S, Davidson AE, Holder GE, et al. Autosomal dominant Best disease with an unusual electrooculographic light rise and risk of angle-closure glaucoma: a clinical and molecular genetic study. Mol Vis. 2011;17:2272-2282. PMCID PMC3171497. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.
- **Glaucoma: Image D.** Acute angle closure glaucoma. This image is a derivative work, adapted from the following source, available under . Courtesy of Dr. Jonathan Trobe.
- **Uveitis: Image A.** This image is a derivative work, adapted from the following source, available under : Weber AC, Levison AL, Srivastava, et al. A case of Listeria monocytogenes endophthalmitis with recurrent inflammation and novel management. J Ophthalmic Inflamm Infect. 2015;5(1):28. DOI: 10.1186/s12348-015-0058-8.
- Age-related macular degeneration. Courtesy of the 536 Department of Health and Human Services.
- **Diabetic retinopathy.** This image is a derivative work, adapted from 537 the following source, available under Sundling V, Gulbrandsen P, Straand J. Sensitivity and specificity of Norwegian optometrists' evaluation of diabetic retinopathy in single-field retinal images - a cross-sectional experimental study. BMC Health Services Res. 2013;13:17. DOI: 10.1186/1472-6963-13-17.
- **Hypertensive retinopathy.** This image is a derivative work, adapted from the following source, available under : Diallo JW, Méda N, Tougouma SJB, et al. Intérêts de l'examen du fond d'œil en pratique de ville: bilan de 438 cas. Pan Afr Med J. 2015;20:363. DOI: 10.11604/ pamj.2015.20.363.6629.
- Retinal vein occlusion. This image is a derivative work, adapted from the following source, available under Essen Alasil T, Rauser ME. Intravitreal bevacizumab in the treatment of neovascular glaucoma secondary to central retinal vein occlusion: a case report. Cases J. 2009;2:176. DOI: 10.1186/1757-1626-2-176. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.
- 537 Retinal detachment. Courtesy of EyeRounds.
- **Retinitis pigmentosa.** Courtesy of EyeRounds. 538
- **Leukocoria.** This image is a derivative work, adapted from the following source, available under East I, Lumbroso-Le Rouic L,

FAS1\_2019\_20\_ImageAck.indd 743 11/8/19 4:50 PM

- Gauthier-Villars M, et al. Retinoblastoma. *Orphanet J Rare Dis.* 2006 Aug 25;1:31. DOI: 10.1186/1750-1172-1-31.
- Ocular motility. Testing ocular muscles. This image is a derivative work, adapted from the following source, available under Au.yousef. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under
- 541 CN III, IV, VI palsies: Image A. Cranial nerve III damage. This image is a derivative work, adapted from the following source, available under :: Hakim W, Sherman R, Rezk T, et al. An acute case of herpes zoster ophthalmicus with ophthalmoplegia. Case Rep Ophthalmol Med. 1012; 2012:953910. DOI: 10.1155/2012/953910.
- **CN III, IV, VI palsies: Image B.** Cranial nerve IV damage. This image is a derivative work, adapted from the following source, available under . Mendez JA, Arias CR, Sanchez D, et al. Painful ophthalmoplegia of the left eye in a 19-year-old female, with an emphasis in Tolosa-Hunt syndrome: a case report. *Cases J.* 2009; 2: 8271. DOI: 10.4076/1757-1626-2-8271.

#### **Psychiatry**

**563** Trichotillomania. Courtesy of Robodoc.

#### Renal

- 578 Potter sequence (syndrome). Courtesy of the Department of Health and Human Services and the Armed Forces Institute of Pathology.
- 580 Kidney anatomy and glomerular structure. This image is a derivative work, adapted from the following source, available under Ramidi GA, Kurukumbi MK, Sealy PL. Collapsing glomerulopathy in sickle cell disease: a case report. J Med Case Reports. 2011; 5: 71. DOI: 10.1186/1752-1947-5-71.
- **Course of ureters.** This image is a derivative work, adapted from the following source, available under : Wikimedia Commons. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under ...
- **581 Glomerular filtration barrier.** This image is a derivative work, adapted from the following source, available under Feng J, Wei H, Sun Y, et al. Regulation of podocalyxin expression in the kidney of streptozotocin-induced diabetic rats with Chinese herbs (Yishen capsule). BMC Complement Altern Med. 2013;13:76. DOI: 10.1186/1472-6882-13-76.
- **Casts in urine: Image D.** Fatty casts. This image is a derivative work, adapted from the following source, available under **Source**: Li S, Wang ZJ, Chang TT. Temperature oscillation modulated self-assembly of periodic concentric layered magnesium carbonate microparticles. *PLoS One.* 2014;9(2):e88648. DOI:10.1371/journal.pone.0088648
- **Nephritic syndrome: Image A.** Histology of acute poststreptococcal glomerulonephritis. This image is a derivative work, adapted from the following source, available under Dr. Michael Bonert. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under

- Nephritic syndrome: Image B. This image is a derivative work, adapted from the following source, available under 
  Immunofluorescence of acute poststreptococcal glomerulonephritis. Oda T, Yoshizawa N, Yamakami K, et al. The role of nephritis-associated plasmin receptor (naplr) in glomerulonephritis associated with streptococcal infection. Biomed Biotechnol. 2012;2012:417675. DOI 10.1155/2012/417675.
- 596 Nephritic syndrome: Image C. Histology of rapidly progressive glomerulonephritis. Courtesy of the Department of Health and Human Services and Uniformed Services University of the Health Sciences.
- 596 Nephritic syndrome: Image D. This image is a derivative work, adapted from the following source, available under Exercise Kiremitci S, Ensari A. Classifying lupus nephritis: an ongoing story. Scientific World Journal. 2014; 2014: 580620. DOI: 10.1155/2014/580620.
- 597 Nephrotic syndrome: Image A. This image is a derivative work, adapted from the following source, available under .: Teoh DCY, El-Modir A. Managing a locally advanced malignant thymoma complicated by nephrotic syndrome: a case report. *J Med Case Reports.* 2008; 2: 89. DOI: 10.1186/1752-1947-2-89.
- 597 Nephrotic syndrome: Image B. Histology of focal segmental glomerulosclerosis. This image is a derivative work, adapted from the following source, available under . The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under .
- 597 Nephrotic syndrome: Image D. Diabetic glomerulosclerosis with Kimmelstiel-Wilson lesions. This image is a derivative work, adapted from the following source, available under . Doc Mari. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under .
- 598 Kidney stones: Image A. Nair S, George J, Kumar S, et al. Acute oxalate nephropathy following ingestion of Averrhoa bilimbi juice. Case Rep Nephrol. 2014; 2014: DOI: 10.1155/2014/240936.
- **598 Kidney stones: Image B.** This image is a derivative work, adapted from the following source, available under . Joel Mills. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under .
- **Hydronephrosis.** Ultrasound. This image is a derivative work, adapted from the following source, available under Wikimedia Commons. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under
- **Pyelonephritis: Image A.** This image is a derivative work, adapted from the following source, available under . Dr. Michael Bonert. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under .....
- 600 Pyelonephritis: Image B. CT scan. Courtesy of the Department of Health and Human Services and the Armed Forces Institute of Pathology.
- 602 Renal papillary necrosis. Courtesy of the Department of Health and Human Services and William D. Craig, Dr. Brent J. Wagner, and Mark D. Travis.
- **Renal cyst disorders: Image C.** Ultrasound of simple cyst. This image is a derivative work, adapted from the following source, available under . Nevit Dilmen. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under .
- **Renal cell carcinoma: Image A.** Histoilogy. This image is a derivative work, adapted from the following source, available under ...

FAS1\_2019\_20\_ImageAck.indd 744 11/8/19 4:50 PM

- Dr. Yale Rosen. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under 🙉 🕫
- Renal cell carcinoma: Image C. CT scan. This image is a derivative work, adapted from the following source, available under Behnes CL, Schlegel C, Shoukier M, et al. Hereditary papillary renal cell carcinoma primarily diagnosed in a cervical lymph node: a case report of a 30-year-old woman with multiple metastases. BMC Urol. 2013;13:3. DOI: 10.1186/1471-2490-13-3.
- Renal cell carcinoma: Image B. Gross specimen. Courtesy of Dr. Ed Uthman.
- **Renal oncocytoma: Image A.** Gross specimen. This image is a derivative work, adapted from the following source, available under Courtesy of M. Emmanuel.
- **Renal oncocytoma: Image B.** Histology. This image is a derivative work, adapted from the following source, available under see: Dr. Michael Bonert. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under 💇 💇 .
- **Nephroblastoma.** This image is a derivative work, adapted from the following source, available under Es: Refaie H, Sarhan M, Hafez A. Role of CT in assessment of unresectable Wilms tumor response after preoperative chemotherapy in pediatrics. Sci World J. 2008;8:661-669. doi 10.1100/tsw.2008.96.
- **Urothelial carcinoma of the bladder: Image A.** This image is a derivative work, adapted from the following source, available under Geavlete B, Stanescu F, Moldoveanu C, et al. NBI cystoscopy and bipolar electrosurgery in NMIBC management—an overview of daily practice. J Med Life. 2013;6:140-145. PMCID PMC3725437.

#### Reproductive

- **615 Fetal alcohol syndrome.** This image is a derivative work, adapted from the following source, available under see: Courtesy of Teresa Kellerman. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under
- **618 Umbilical cord: Image A.** Cross-section of normal umbilical cord. This image is a derivative work, adapted from the following source, available under .: Dr. Ed Uthman. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under ......
- **Meckel diverticulum: Image B.** This image is a derivative work, adapted from the following source, available under : Mathur P, Gupta R, Simlot A, et al. Congenital pouch colon with double Meckel's diverticulae. J Neonatal Surg. 2013 Oct-Dec; 2(4): 48.
- Uterine (Müllerian) duct anomalies: Images A-D. This image is a derivative work, adapted from the following source, available under Ahmadi F, Zafarani F, Haghighi H, et al. Application of 3D ultrasonography in detection of uterine abnormalities. Int J Fertil Steril. 2011; 4:144-147. PMCID PMC4023499.
- Female reproductive epithelial histology. Transformation zone. This image is a derivative work, adapted from the following source, available under :: Courtesy of Dr. Ed Uthman. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.
- **Seminiferous tubules.** This image is a derivative work, adapted from the following source, available under source: Dr. Anlt Rao. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under
- **Pregnancy complications.** This image is a derivative work, adapted from the following source, available under : Li W, Wang C, Lin

- T, et al. Misdiagnosis of bilateral tubal pregnancy: a case report. I Med Case Rep. 2014;8:342. DOI: 10.1186/1752-1947-8-342.
- **Hydatidiform mole: Image A.** Cluster of cluster of grapes appearance in complete hydatidiform mole. This image is a derivative work, adapted from the following source, available under . Dr. Ed
- 642 Choriocarcinoma: Image B. "Cannonball" metastases. This image is a derivative work, adapted from the following source, available under Ese Lekanidi K, Vlachou PA, Morgan B, et al. Spontaneous regression of metastatic renal cell carcinoma: case report. J Med Case Rep. 2007;1:89. DOI: 10.1186/1752-1947-1-89.
- Vulvar pathology: Image A. Bartholin cyst. 
  Courtesy of the Department of Health and Human Services and Susan Lindsley.
- Vulvar pathology: Image B. Lichen sclerosis. This image is a derivative work, adapted from the following source, available under Lambert J. Pruritus in female patients. Biomed Res Int. 2014;2014:541867. DOI: 10.1155/2014/541867.
- **Vulvar pathology: Image C.** Vulvar carcinoma. This image is a derivative work, adapted from the following source, available under Ramli I, Hassam B. Carcinome épidermoïde vulvaire: pourquoi surveiller un lichen scléro-atrophique. Pan Afr Med J. 2015;21:48. DOI: 10.11604/pamj.2015.21.48.6018.
- Vulvar pathology: Image D. Extramallary Paget disease. This image is a derivative work, adapted from the following source, available under Wang X, Yang W, Yang J. Extramammary Paget's disease with the appearance of a nodule: a case report. BMC Cancer. 2010;10:405. DOI: 10.1186/1471-2407-10-405.
- Polycystic ovarian syndrome. This image is a derivative work, adapted from the following source, available under : Kopera D, Wehr E, Obermayer-Pietsch B. Endocrinology of hirsutism. Int J Trichology. 2010;2(1):30-35. doi:10.4103/0974-7753.66910
- **Dysgerminoma: Image B.** This image is a derivative work, adapted from the following source, available under : Montesinos L, Acien P, Martinez-Beltran M, et al. Ovarian dysgerminoma and synchronic contralateral tubal pregnancy followed by normal intra-uterine gestation: a case report. J Med Rep. 2012;6:399. DOI: 10.1186/1752-1947-6-399.
- Ovarian neoplasms: Image D. Mature cystic teratoma. This image is a derivative work, adapted from the following source, available under .: Dr. Michael Bonert. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under
- Ovarian neoplasms: Image E. Yolk sac tumor. This image is a derivative work, adapted from the following source, available under see: Jensflorian. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under @ 👓
- **Ovarian neoplasms: Image F.** Call-Exner bodies. This image is a derivative work, adapted from the following source, available under Estrogen-producing Katoh T, Yasuda M, Hasegawa K, et al. Estrogen-producing endometrioid adenocarcinoma resembling sex cord-stromal tumor of the ovary: a review of four postmenopausal cases. Diagn Pathol. 2012;7:164. DOI: 10.1186/1746-1596-7-164.
- **Uterine conditions: Image A.** Endometrial tissue found outside the uterus. This image is a derivative work, adapted from the following source, available under Estings JM, Fazleabas AT. A baboon model for endometriosis: implications for fertility. Reprod Biol Endocrinol. 2006;4(suppl 1):S7. DOI: 10.1186/1477-7827-4-S1-S7.
- Uterine conditions: Image B. Endometritis with inflammation of the endometrium. This image is a derivative work, adapted from the following source, available under : Montesinos L, Acien P, Martinez-Beltran M, et al. Ovarian dysgerminoma and synchronic contralateral tubal pregnancy followed by normal intra-uterine

FAS1 2019 20 ImageAck.indd 745 11/8/19 4:50 PM

- gestation: a case report. J Med Rep. 2012;6:399. DOI: 10.1186/1752-1947-6-399.
- 648 Uterine conditions: Image C. Endometrial carcinoma. This image is a derivative work, adapted from the following source, available under !! Izadi-Mood N, Yarmohammadi M, Ahmadi SA, et al. Reproducibility determination of WHO classification of endometrial hyperplasia/well differentiated adenocarcinoma and comparison with computerized morphometric data in curettage specimens in Iran. Diagn Pathol. 2009;4:10. DOI:10.1186/1746-1596-4-10.
- **Uterine conditions: Image D.** Leiomyoma (fibroid), gross specimen. This image is a derivative work, adapted from the following source, available under Courtesy of Hic et nunc.
- **Uterine conditions: Image E.** Leiomyoma (fibroid) histology. This image is a derivative work, adapted from the following source, available under : Londero AP, Perego P, Mangioni C, et al. Locally relapsed and metastatic uterine leiomyoma: a case report. *J Med Case Rep.* 2008;2:308. DOI: 10.1186/1752-1947-2-308. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.
- 649 Benign breast disease: Image A. Fibroadenomas. This image is a derivative work, adapted from the following source, available under Gokhale S. Ultrasound characterization of breast masses. Indian J Radiol Imaging. 2009 Aug;19(3):242-7. DOI: 10.4103/0971-3026.54878.
- **Benign breast disease: Images B (phyllodes tumor on ultrasound) and C (phyllodes cyst).** This image is a derivative work, adapted from the following source, available under :: Muttarak MD, Lerttumnongtum P, Somwangjaroen A, et al. Phyllodes tumour of the breast. *Biomed Imaging Interv J.* 2006 Apr-Jun;2(2):e33. DOI: 10.2349/biij.2.2.e33.
- 650 Breast cancer: Image A. Mammography of breast cancer. This image is a derivative work, adapted from the following source, available under : Molino C, Mocerino C, Braucci A, et al. Pancreatic solitary and synchronous metastasis from breast cancer: a case report and systematic review of controversies in diagnosis and treatment. World J Surg Oncol. 2014;12:2. DOI:10.1186/1477-7819-12-2
- 650 Breast cancer: Image C. Comedocarcinoma. This image is a derivative work, adapted from the following source, available under Costarelli L, Campagna D, Mauri M, et al. Intraductal proliferative lesions of the breast—terminology and biology matter: premalignant lesions or preinvasive cancer? Int J Surg Oncol. 2012;501904. DOI: 10.1155/2012/501904. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.
- 650 Breast cancer: Image D. Paget disease of breast. This image is a derivative work, adapted from the following source, available under See: Muttarak M, Siriya B, Kongmebhol P, et al. Paget's disease of the breast: clinical, imaging and pathologic findings: a review of 16 patients. Biomed Imaging Interv J. 2011;7:e16. DOI: 10.2349/biij.7.2.e16.
- 650 Breast cancer: Image E. Invasive lobular carcinoma. This image is a derivative work, adapted from the following source, available under Franceschini G, Manno A, Mule A, et al. Gastro-intestinal symptoms as clinical manifestation of peritoneal and retroperitoneal spread of an invasive lobular breast cancer: report of a case and review of the literature. BMC Cancer. 2006;6:193. DOI: 10.1186/1471-2407-6-193.
- 650 **Breast cancer: Image E.** Peau d'orange of inflammatory breast cancer. This image is a derivative work, adapted from the following source, available under :: Levine PH, Zolfaghari L, Young H, et al. What Is inflammatory breast cancer? Revisiting the case definition. *Cancers* (Basel). 2010 Mar;2(1):143–152. DOI: 10.3390/cancers2010143.
- **Penile pathology: Image A.** Peyronie disease. This image is a derivative work, adapted from the following source, available

- under Eran VQ, Kim DH, Lesser TF, et al. Review of the surgical approaches for Peyronie's disease: corporeal plication and plaque incision with grafting. Adv Urol. 2008; 2008: 263450. DOI: 10.1155/2008/263450.
- Penile pathology: Image B. Squamous cell carcinoma. This image is a derivative work, adapted from the following source, available under a treated with topical 5-fluorouracil. An Bras Dermatol. 2016 Sep-Oct; 91(5 Suppl 1): 42–44. DOI: 10.1590/abd1806-4841.20164595.
- 651 Cryptorchidism. This image is a derivative work, adapted from the following source, available under Pandey A, Gangopadhyay AN, Kumar V. High anorectal malformation in a five-month-old boy: a case report. J Med Case Reports. 2010; 4: 296. DOI: 10.1186/1752-1947-4-296
- Varicocele. This image is a derivative work, adapted from the following source, available under Mak CW, Tzeng WS. Sonography of the scrotum. DOI: 10.5772/27586.
- 652 Scrotal masses: Image A. Congenital hydrocele. This image is a derivative work, adapted from the following source, available under Elements: Leonardi S, Barone P, Gravina G, et al. Severe Kawasaki disease in a 3-month-old patient: a case report. BMC Res Notes. 2013;6:500. DOI: 10.1186/1756-0500-6-500.

#### Respiratory

- 661 Alveolar cell types: Image A. Electron micrograph of type II pneumocyte. This image is a derivative work, adapted from the following source, available under Electron Fehrenbach H, Tews S, Fehrenbach A, et al. Improved lung preservation relates to an increase in tubular myelin-associated surfactant protein A. Respir Res. 2005 Jun 21;6:60. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.
- Alveolar cell types: Image B. Micrograph of type II pneumocyte. This image is a derivative work, adapted from the following source, available under .: Courtesy of Dr. Thomas Caceci.
- 661 Neonatal respiratory distress syndrome: Image A. This image is a derivative work, adapted from the following source, available under : Alorainy IA, Balas NB, Al-Boukai AA. Pictorial essay: infants of diabetic mothers. *Indian J Radiol Imaging*. 2010;20:174-181. DOI: 10.4103/0971-3026.69349.
- 663 Lung anatomy: Image A. X-ray of normal lung. This image is a derivative work, adapted from the following source, available under : Namkoong H, Fujiwara H, Ishii M, et al. Immune reconstitution inflammatory syndrome due to Mycobacterium avium complex successfully followed up using 18 F-fluorodeoxyglucose positron emission tomography-computed tomography in a patient with human immunodeficiency virus infection: A case report. BMC Med Imaging. 2015;15:24. DOI 10.1186/s12880-015-0063-2.
- 667 Cyanide vs carbon monoxide poisoning. This image is a derivative work, adapted from the following source, available under Subhaschandra S, Jatishwor W, Suraj Th. Isolated symmetrical bilateral basal ganglia T2 hyperintensity in carbon monoxide poisoning. Ann Indian Acad Neurol. 2008 Oct-Dec; 11(4): 251–253. DOI: 10.4103/0972-2327.44563.
- **Rhinosinusitis.** This image is a derivative work, adapted from the following source, available under Extremely P, Zagolski O, Sktadzien

FAS1\_2019\_20\_ImageAck.indd 746 11/8/19 4:50 PM

- J. Fatty tissue within the maxillary sinus: a rare finding. Head Face Med. 2006;2:28. DOI: 10.1186/1746-160X-2-28.
- **Deep venous thrombosis.** This image is a derivative work, adapted from the following source, available under see: Dr. James Heilman. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under
- **672 Pulmonary emboli: Image B.** CT scan. This image is a derivative work, adapted from the following source, available under 22: Dr. Carl Chartrand-Lefebvre. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under @ ? .
- **Mediastinal pathology.** This image is a derivative work, adapted from the following source, available under : Aga Z, Avelino J, Darling GE. An unusual case of spontaneous esophageal rupture after swallowing a boneless chicken nugget. Case Rep Emerg Med. 2016; 2016: 5971656. DOI: 10.1155/2016/5971656.
- Obstructive lung diseases: Image A. Lung tissue with enlarged alveoli in emphysema. This image is a derivative work, adapted from the following source, available under 200: Dr. Michael Bonnert.
- Obstructive lung diseases: Image B. CT of centriacinar emphysema. Courtesy of the Department of Health and Human Services and Dr. Edwin P. Ewing, Jr.
- **Obstructive lung diseases: Image C.** Emphysema histology. This image is a derivative work, adapted from the following source, available under see: Dr. Michael Bonert. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under @....
- **675 Obstructive lung diseases: Image D.** Barrel-shaped chest in emphysema. This image is a derivative work, adapted from the following source, available under . Dr. James Heilman. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under
- **Obstructive lung diseases: Image E.** Mucus plugs in asthma. This image is a derivative work, adapted from the following source, available under see: Courtesy of Dr. Yale Rosen. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under
- Obstructive lung disease: Image F. Curschmann spirals. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under @ ... Dr. James Heilman.
- **Obstructive lung diseases: Image G.** Charcot-Leyden crystals on bronchalverolar lavage. This image is a derivative work, adapted from the following source, available under : Gholamnejad M, Rezaie N. Unusual presentation of chronic eosinophilic pneumonia with "reversed halo sign": a case report. Iran J Radiol. 2014 May;11(2):e7891. DOI: 10.5812/iranjradiol.7891.
- **Obstructive lung disease: Image H.** Bronchiectasis in cystic fibrosis. This image is a derivative work, adapted from the following source, available under see: Dr. Yale Rosen. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under @...
- **Restrictive lung diseases: Image A.** Pulmonary fibrosis. This image is a derivative work, adapted from the following source, available under Walsh SLF, Wells AU, Sverzellati N, et al. Relationship between fibroblastic foci profusion and high resolution CT morphology in fibrotic lung disease. BMC Med. 2015;13:241. DOI: 10.1186/s12916-015-0479-0.
- Sarcoidosis: Images A. Kajal B, Harvey J, Alowami S. Melkerrson-Rosenthal Syndrome, a rare case report of chronic evelid swelling. Diagn Pathol. 2013; 8: 188. DOI: 10.1186/1746-1596-8-188.

- Sarcoidosis: Images B (X-ray of the chest) and C (CT of the chest). X-ray of the chest) and C CT of the chest. This image is a derivative work, adapted from the following source, available under Euroborg J, Ward M, Gill A, et al. Utility of cardiac magnetic resonance in assessing right-sided heart failure in sarcoidosis. BMC Med Imaging. 2013;13:2. DOI: 10.1186/1471-2342-13-2.
- Inhalational injury and sequelae: Images A (18 hours after inhalation injury) and B (11 days after injury). This image is a derivative work, adapted from the following source, available under Bai C, Huang H, Yao X, et al. Application of flexible bronchoscopy in inhalation lung injury. Diagn Pathol. 2013;8:174. DOI: 10.1186/1746-1596-8-174.
- **Pneumoconioses: Image A.** Pleural plaques in asbestosis. This image is a derivative work, adapted from the following source, available under see: Dr. Yale Rosen. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under
- **Pneumoconioses: Image B.** CT scan of asbestosis. This image is a derivative work, adapted from the following source, available under Miles SE, Sandrini A, Johnson AR, et al. Clinical consequences of asbestos-related diffuse pleural thickening: a review. *J Occup Med Toxicol*. 2008;3:20. DOI: 10.1186/1745-6673-3-20.
- **Pneumoconioses: Image C.** Ferruginous bodies in asbestosis. This image is a derivative work, adapted from the following source, available under see: Dr, Michael Bonert. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under .....
- Pneumoconioses: Image D. Berylliosis: non-caseous granuloma. Ann Saudi Med. 2009 Nov-Dec; 29(6): 485-486. DOI: 10.4103/0256-4947.57175.
- **Mesothelioma.** This image is a derivative work, adapted from the following source, available under :: Weiner SJ, Neragi-Miandoab S. Pathogenesis of malignant pleural mesothelioma and the role of environmental and genetic factors. J Carcinog. 2008;7:3. DOI: 10.1186/1477-3163-7-3.
- Acute respiratory distress syndrome: Image A. This image is a derivative work, adapted from the following source, available under Pires-Neto RĈ, Del Carlo Bernardi F, de Araujo PA. The expression of water and ion channels in diffuse alveolar damage is not dependent on DAD etiology. PLoS One. 2016; 11(11): e0166184. DOI: 10.1371/journal.pone.0166184.
- 678 Acute respiratory distress syndrome: Image B. Bilateral lung opacities. This image is a derivative work, adapted from the following source, available under Emanaka H, Takahara B, Yamaguchi H, et al. Chest computed tomography of a patient revealing severe hypoxia due to amniotic fluid embolism: a case report. J Med Case Reports. 2010;4:55. DOI: 10.1186/1752-1947-4-55.
- **Atelectasis.** This image is a derivative work, adapted from the following source, available under Es: Khan AN, Al-Jahdali H, Al-Ghanem S, et al. Reading chest radiographs in the critically ill (Part II): Radiography of lung pathologies common in the ICU patient. Ann Thorac Med. 2009;4(3):149–157. DOI:10.4103/1817-1737.53349
- Pleural effusions: Images A and B. This image is a derivative work, adapted from the following source, available under Toshikazu A, Takeoka H, Nishioka K, et al. Successful management of refractory pleural effusion due to systemic immunoglobulin light chain amyloidosis by vincristine adriamycin dexamethasone chemotherapy: a case report. Med Case Rep. 2010;4:322. DOI: 10.1186/1752-1947-4-
- **Pneumothorax: Image A.** This image is a derivative work, adapted 682 from the following source, available under \_\_\_\_: Miura K, Kondo R, Kurai M, et al. Birt-Hogg-Dubé syndrome detected incidentally by asymptomatic bilateral pneumothorax in health screening: a

FAS1\_2019\_20\_ImageAck.indd 747 11/8/19 4:50 PM

# 748 SECTION IV

#### **IMAGE ACKNOWLEDGMENTS**

- case of a young Japanese woman. Surg Case Rep. 2015 Dec; 1: 17. DOI: 10.1186/s40792-015-0014-8.
- 682 Pneumothorax: Image B. This image is a derivative work, adapted from the following source, available under :: Rosat A, Díaz C. Reexpansion pulmonary edema after drainage of tension pneumothorax. Pan Afr Med J. 2015; 22: 143.DOI: 10.11604/pamj.2015.22.143.8097.
- **Pneumonia: Image A.** This image is a derivative work, adapted from the following source, available under Yoon BW, Song YG, Lee SH. Severe community-acquired adenovirus pneumonia treated with oral ribavirin: a case report. *BMC Res Notes*. 2017; 10: 47. DOI: 10.1186/s13104-016-2370-2.
- 683 Pneumonia: Image B. Lobar pneumonia, gross specimen. This image is a derivative work, adapted from the following source, available under . Dr. Yale Rosen. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under .
- **Pneumonia: Image C.** Acute inflammatory infiltrates in bronchopneumonia. This image is a derivative work, adapted from the following source, available under .: Dr. Yale Rosen. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under ...
- **Pneumonia: Image D.** Bronchopneumonia, gross specimen. This image is a derivative work, adapted from the following source, available under . Dr. Yale Rosen. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under .
- **Pneumonia: Image E.** This image is a derivative work, adapted from the following source, available under Allen CM, AL-Jahdali HH, Irion KL, et al. Imaging lung manifestations of HIV/AIDS.

  Ann Thorac Med. 2010 Oct-Dec; 5(4): 201–216. DOI: 10.4103/1817-1737.69106.

- 684 Lung cancer: Image B. Adenocarcinoma histology. See Courtesy of the Department of Health and Human Services and the Armed Forces Institute of Pathology.
- **Lung cancer: Image C.** Squamous cell carcinoma. This image is a derivative work, adapted from the following source, available under . Dr. James Heilman. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under .
- 685 Lung abscess: Image A. Gross specimen. This image is a derivative work, adapted from the following source, available under Dr. Yale Rosen. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under ...
- **685** Lung abscess: Image B. X-ray. This image is a derivative work, adapted from the following source, available under . Courtesy of Dr. Yale Rosen.
- 685 Pancoast tumor. This image is a derivative work, adapted from the following source, available under Manenti G, Raguso M, D'Onofrio S, et al. Pancoast tumor: the role of magnetic resonance imaging. Case Rep Radiol. 2013; 2013:479120. DOI: 10.1155/2013/479120.
- Superior vena cava syndrome: Images A (blanching of skin with pressure) and B (CT of chest). This image is a derivative work, adapted from the following source, available under Shaikh I, Berg K, Kman N. Thrombogenic catheter-associated superior vena cava syndrome. Case Rep Emerg Med. 2013; 2013: 793054. DOI 10.1155/2013/793054.

FAS1\_2019\_20\_ImageAck.indd 748 11/8/19 4:50 PM

## Index

A A-a gradient by age, 668	Abruptio placentae, 640 cocaine use, 614 preeclampsia, 643	for osteoarthritis, 466 toxicity effects, 485 toxicity treatment for, 248	Acid phosphatase in neutrophils, 406 Acid reflux H <sub>2</sub> blockers for, 399
with oxygen deprivation, 669 restrictive lung disease, 675	Abscesses, 479 acute inflammation and, 214	Acetazolamide, 252, 552, <b>608</b> pseudotumor cerebri, 521	proton pump inhibitors for, 399 Acid suppression therapy, <b>398</b>
Abacavir, 203 Abciximab	brain, 156, 177, 180 calcification with, 211	Acetoacetate metabolism, 90 Acetone breath, 347	Acinetobacter baumannii highly resistant bacteria, 198
Glycoprotein IIb/IIIa inhibitors, 438	cold staphylococcal, 116 frontal lobe, 153	Acetylation chromatin, 34	nosocomial infections, <b>142</b> Acinetobacter spp
therapeutic antibodies, 122 thrombogenesis and, 411	Klebsiella spp, 145 liver, 155, 179	drug metabolism, 232 histones, 34	nosocomial infections, 185 Acne, 475, 477
Abdominal aorta	lung, 685	posttranslation, 45	danazol, 658
atherosclerosis in, 302	necrosis with, 209	Acetylcholine (ACh)	tetracyclines for, 192
bifurcation of, 663	Staphylococcus aureus, 135 Toxoplasma gondii, 177	anticholinesterase effect on, 240 change with disease, 495	Acquired hydrocele (scrotal), 652
branches, 363 Abdominal aortic aneurysm, 302	treatment of lung, 192	Clostridium botulinum inhibition	Acrodermatitis enteropathica, 71 Acromegaly, <b>339</b>
Abdominal pain	in unvaccinated children, 186	of release, 138	carpal tunnel syndrome, 459
bacterial peritonitis, 390	Absence seizures	opioid analgesics, 551	GH, 329
Budd-Chiari syndrome, 392	characteristics of, 517	pacemaker action potential and,	octreotide for, 400
diabetic ketoacidosis and, 347	drug therapy for, 544 Absolute risk reduction (ARR), 258	292 Acetylcholine (ACh) receptor	somatostatin analogs for, 328
ectopic pregnancy, 641 Henoch-Schönlein purpura, 315	AB toxin, 132	agonists, 551	Actin cytoskeleton, 48
hypercalcemia, 591	Abuse	Acetylcholine receptors, 228, 236	muscular dystrophies, 61
hyperparathyroidism, 345	child, 269, <b>556</b>	Acetylcholinesterase (AChE)	Acting out, 554
intussusception, 385 irritable bowel syndrome, 383	intimate partner violence, 269 Acalculia, 511	in amniotic fluid, 491 malathion and, 200	Actinic keratosis, 482
Meckel diverticulum, 618	Acalculous cholecystitis, 396	neural tube defects and, 491	squamous cell carcinoma, 484 Actinomyces israelii
pancreas divisum, 360	Acanthocytes, 414	Acetylcholinesterase (AChE)	culture requirements of, 127
pancreatic cancer, 398	Acantholysis, 475, 480	inhibitors	oral infections, 186
polyarteritis nodosa, 314 porphyria, 425	Acanthosis, 475 psoriasis, 477	naming convention for, 253 for neuromuscular junction	pigment production, 128
postprandial, 363	Acanthosis nigricans, 228, 482	disease, 472	Actinomyces spp
RLQ pain, 384	stomach cancer, 379	toxicity treatment for, 248	effects and treatment of, 139 penicillin G/V for, 187
RUQ pain, 396	Acarbose, 353	Acetyl-CoA carboxylase	Action/willpower stage, substance
Abdominal wall anatomy, 369	Accessory nerve (CN XI), 506 arm abduction, 446	fatty acid synthesis, 73 vitamin B <sub>7</sub> and, 68	addiction, 568
inguinal hernias, <b>369</b>	lesion of, 532	Achalasia, <b>376</b>	Activated carrier molecules and
ventral defects, 358	Accessory pancreatic duct, 360, 368	esophageal cancer and, 378	form, <b>75</b> Active errors, 274
Abducens nerve (CN VI), 506	Accommodation, eye, 506, 535	LES tone in, 371	Active enois, 274 Active immunity, 110
ocular motility, 540 palsy, 541	Accuracy (validity), 259 Acebutolol, 245, 319	Achilles reflex, 510 Achilles tendon xanthomas, 301	Acute chest syndrome, 422
Abduction	ACE inhibitors, <b>610</b>	Achlorhydria	Acute cholestatic hepatitis
arm, 446	acute coronary syndromes, 307	stomach cancer, 379	drug reactions and, 249
hand, 450	C1 esterase inhibitor deficiency,	VIPomas, 371	macrolides, 193 Acute coronary syndrome
hip, 451, 453 passive, abnormal, 454	107 dilated cardiomyopathy, 308	Achondroplasia, <b>462</b> chromosome disorder, 64	ADP receptor inhibitors for, 437
Abductor digiti minimi muscle, 450	dry cough, 251	endochondral ossification in, 458	heparin for, 436
Abductor pollicis brevis muscle, 450	heart failure, 309	inheritance, 60	nitrates for, 318
Abetalipoproteinemia, <b>94</b> , 414	hypertension, 316	Acid-base physiology, <b>592</b>	treatments for, <b>307</b> Acute cystitis, 594, <b>600</b>
Abnormal uterine bleeding (AUB) non-structural causes (COEIN),	naming convention for, 253 preload/afterload effects, 284	Acid-fast oocysts, 177 Acid-fast organisms, 125, 155	Acute disseminated (postinfectious)
633	teratogenicity, 614	Acidic amino acids, 81	encephalomyelitis, 524
structural causes (PALM), 633	Acetaldehyde, 72	Acid maltase, 86	Acute dystonia, 569
ABO blood classification, 405	Acetaldehyde dehydrogenase, 72	Acidosis, <b>592</b>	treatment of, 241
hemolytic disease of the newborn, 405	Acetaminophen, <b>485</b> vs aspirin for pediatric patients,	acidemia diuretic effect on, 609 cardiac contractility in, 284	Acute gastritis, 379 Acute hemolytic transfusion
Abortion	485	hyperkalemia with, 590	reactions, 114
ethical situations, 268	free radical injury and, 210	metabolic, 85, 349	Acute hemorrhagic cystitis, 164
methotrexate for, 440	hepatic necrosis from, 249	renal tubular, 592	Acute inflammation, <b>214</b>

FAS1\_2019\_21\_Index\_749-806.indd 749 11/21/19 12:27 PM

INDEX

Acute inflammatory demyelinating
polyradiculopathy, <b>524</b>
Acute intermittent porphyria, 425
Acute interstitial nephritis, 601
Acute kidney injury, 601
Acute laryngotracheobronchitis,
170
Acute lymphoblastic leukemia (ALL),
432
methotrexate for, 440
oncogenes and, 224
Acute mesenteric ischemia, 386
Acute myelogenous leukemia (AML),
432
chromosomal translocations, 434
cytarabine for, 440
myelodysplastic syndromes, 432
Acute pancreatitis, <b>397</b>
hyperparathyroidism, 345
necrosis and, 209
Acute pericarditis, 313
Acute-phase proteins, 108, 213
Acute-phase reactants, 213
IL-6, 108
Acute poststreptococcal
glomerulonephritis, 596
Acute promyelocytic leukemia
vitamin A for, 66
Acute pulmonary edema
opioid analgesics, 551
Acute pyelonephritis, 600
WBC casts in, 594
Acute respiratory distress syndrome
(ARDS), <b>678</b>
eclampsia and, 643
Acute stress disorder, 564
Acute transplant rejection, 119
Acute tubular necrosis, 602
Acyclovir, 201
Adalimumab, 122, 487
for Crohn disease, 382
Adaptive immunity, 99
Addiction, stages of change in
radiction, stages of change in
overcoming, 568
Addison disease, 349
HLA subtype association, 100
Additive effect
Additive effect of drugs, 235
Additive effect of drugs, 235 Adduction
Additive effect of drugs, 235 Adduction arm (rotator cuff), 446
Additive effect of drugs, 235 Adduction arm (rotator cuff), 446 hand, 450
Additive effect of drugs, 235 Adduction arm (rotator cuff), 446 hand, 450 hip, 451
Additive effect of drugs, 235 Adduction arm (rotator cuff), 446 hand, 450 hip, 451 passive, abnormal, 454
Additive effect of drugs, 235 Adduction arm (rotator cuff), 446 hand, 450 hip, 451 passive, abnormal, 454
Additive effect of drugs, 235 Adduction arm (rotator cuff), 446 hand, 450 hip, 451 passive, abnormal, 454 thigh, 452
Additive effect of drugs, 235 Adduction arm (rotator cuff), 446 hand, 450 hip, 451 passive, abnormal, 454 thigh, 452 Adductor brevis, 452
Additive effect of drugs, 235 Adduction arm (rotator cuff), 446 hand, 450 hip, 451 passive, abnormal, 454 thigh, 452 Adductor brevis, 452 Adductor longus, 451, 452
Additive effect of drugs, 235 Adduction arm (rotator cuff), 446 hand, 450 hip, 451 passive, abnormal, 454 thigh, 452 Adductor brevis, 452
Additive effect of drugs, 235 Adduction arm (rotator cuff), 446 hand, 450 hip, 451 passive, abnormal, 454 thigh, 452 Adductor brevis, 452 Adductor longus, 451, 452
Additive effect of drugs, 235 Adduction arm (rotator cuff), 446 hand, 450 hip, 451 passive, abnormal, 454 thigh, 452 Adductor brevis, 452 Adductor longus, 451, 452 Adductor magnus, 452 Adductor magnus, 452 Adenine
Additive effect of drugs, 235 Adduction arm (rotator cuff), 446 hand, 450 hip, 451 passive, abnormal, 454 thigh, 452 Adductor brevis, 452 Adductor longus, 451, 452 Adductor magnus, 452 Adductor magnus, 452 Adenine Shiga/Shiga-like toxins and, 132
Additive effect of drugs, 235 Adduction arm (rotator cuff), 446 hand, 450 hip, 451 passive, abnormal, 454 thigh, 452 Adductor brevis, 452 Adductor longus, 451, 452 Adductor magnus, 452 Adductor magnus, 452 Adenine Shiga/Shiga-like toxins and, 132 Adenocarcinomas
Additive effect of drugs, 235 Adduction arm (rotator cuff), 446 hand, 450 hip, 451 passive, abnormal, 454 thigh, 452 Adductor brevis, 452 Adductor longus, 451, 452 Adductor magnus, 452 Adenine Shiga/Shiga-like toxins and, 132 Adenocarcinomas carcinogens causing, 225
Additive effect of drugs, 235 Adduction arm (rotator cuff), 446 hand, 450 hip, 451 passive, abnormal, 454 thigh, 452 Adductor brevis, 452 Adductor longus, 451, 452 Adductor magnus, 452 Adenine Shiga/Shiga-like toxins and, 132 Adenocarcinomas carcinogens causing, 225 esophagus, 378
Additive effect of drugs, 235 Adduction arm (rotator cuff), 446 hand, 450 hip, 451 passive, abnormal, 454 thigh, 452 Adductor brevis, 452 Adductor longus, 451, 452 Adductor magnus, 452 Adenine Shiga/Shiga-like toxins and, 132 Adenocarcinomas carcinogens causing, 225 esophagus, 378 gastric, 216, 226
Additive effect of drugs, 235 Adduction arm (rotator cuff), 446 hand, 450 hip, 451 passive, abnormal, 454 thigh, 452 Adductor brevis, 452 Adductor longus, 451, 452 Adductor magnus, 452 Addenine Shiga/Shiga-like toxins and, 132 Adenocarcinomas carcinogens causing, 225 esophagus, 378 gastric, 216, 226 lung, 224, 684
Additive effect of drugs, 235 Adduction arm (rotator cuff), 446 hand, 450 hip, 451 passive, abnormal, 454 thigh, 452 Adductor brevis, 452 Adductor longus, 451, 452 Adductor magnus, 452 Adenine Shiga/Shiga-like toxins and, 132 Adenocarcinomas carcinogens causing, 225 esophagus, 378 gastric, 216, 226
Additive effect of drugs, 235 Adduction arm (rotator cuff), 446 hand, 450 hip, 451 passive, abnormal, 454 thigh, 452 Adductor brevis, 452 Adductor longus, 451, 452 Adductor magnus, 452 Addenine Shiga/Shiga-like toxins and, 132 Adenocarcinomas carcinogens causing, 225 esophagus, 378 gastric, 216, 226 lung, 224, 684 nomenclature for, 220
Additive effect of drugs, 235 Adduction arm (rotator cuff), 446 hand, 450 hip, 451 passive, abnormal, 454 thigh, 452 Adductor brevis, 452 Adductor longus, 451, 452 Adductor magnus, 452 Addenine Shiga/Shiga-like toxins and, 132 Adenocarcinomas carcinogens causing, 225 esophagus, 378 gastric, 216, 226 lung, 224, 684 nomenclature for, 220 nonbacterial thrombotic
Additive effect of drugs, 235 Adduction arm (rotator cuff), 446 hand, 450 hip, 451 passive, abnormal, 454 thigh, 452 Adductor brevis, 452 Adductor longus, 451, 452 Adductor magnus, 452 Adductor magnus, 452 Adenine Shiga/Shiga-like toxins and, 132 Adenocarcinomas carcinogens causing, 225 esophagus, 378 gastric, 216, 226 lung, 224, 684 nomenclature for, 220 nonbacterial thrombotic endocarditis and, 228
Additive effect of drugs, 235 Adduction arm (rotator cuff), 446 hand, 450 hip, 451 passive, abnormal, 454 thigh, 452 Adductor brevis, 452 Adductor longus, 451, 452 Adductor magnus, 452 Adductor magnus, 452 Adenine Shiga/Shiga-like toxins and, 132 Adenocarcinomas carcinogens causing, 225 esophagus, 378 gastric, 216, 226 lung, 224, 684 nomenclature for, 220 nonbacterial thrombotic endocarditis and, 228 pancreas, 226, 368, 398
Additive effect of drugs, 235 Adduction arm (rotator cuff), 446 hand, 450 hip, 451 passive, abnormal, 454 thigh, 452 Adductor brevis, 452 Adductor longus, 451, 452 Adductor magnus, 452 Adenine Shiga/Shiga-like toxins and, 132 Adenocarcinomas carcinogens causing, 225 esophagus, 378 gastric, 216, 226 lung, 224, 684 nomenclature for, 220 nonbacterial thrombotic endocarditis and, 228 pancreas, 226, 368, 398 paraneoplastic syndromes, 228
Additive effect of drugs, 235 Adduction arm (rotator cuff), 446 hand, 450 hip, 451 passive, abnormal, 454 thigh, 452 Adductor brevis, 452 Adductor longus, 451, 452 Adductor magnus, 452 Adenine Shiga/Shiga-like toxins and, 132 Adenocarcinomas carcinogens causing, 225 esophagus, 378 gastric, 216, 226 lung, 224, 684 nomenclature for, 220 nonbacterial thrombotic endocarditis and, 228 pancreas, 226, 368, 398 paraneoplastic syndromes, 228 pectinate line, 366
Additive effect of drugs, 235 Adduction arm (rotator cuff), 446 hand, 450 hip, 451 passive, abnormal, 454 thigh, 452 Adductor brevis, 452 Adductor longus, 451, 452 Adductor magnus, 452 Adenine Shiga/Shiga-like toxins and, 132 Adenocarcinomas carcinogens causing, 225 esophagus, 378 gastric, 216, 226 lung, 224, 684 nomenclature for, 220 nonbacterial thrombotic endocarditis and, 228 pancreas, 226, 368, 398 paraneoplastic syndromes, 228 pectinate line, 366
Additive effect of drugs, 235 Adduction arm (rotator cuff), 446 hand, 450 hip, 451 passive, abnormal, 454 thigh, 452 Adductor brevis, 452 Adductor longus, 451, 452 Adductor magnus, 452 Adenine Shiga/Shiga-like toxins and, 132 Adenocarcinomas carcinogens causing, 225 esophagus, 378 gastric, 216, 226 lung, 224, 684 nomenclature for, 220 nonbacterial thrombotic endocarditis and, 228 pancreas, 226, 368, 398 paraneoplastic syndromes, 228 pectinate line, 366 prostatic, 654
Additive effect of drugs, 235 Adduction arm (rotator cuff), 446 hand, 450 hip, 451 passive, abnormal, 454 thigh, 452 Adductor brevis, 452 Adductor longus, 451, 452 Adductor magnus, 452 Adenine Shiga/Shiga-like toxins and, 132 Adenocarcinomas carcinogens causing, 225 esophagus, 378 gastric, 216, 226 lung, 224, 684 nomenclature for, 220 nonbacterial thrombotic endocarditis and, 228 pancreas, 226, 368, 398 paraneoplastic syndromes, 228 pectinate line, 366 prostatic, 654 stomach, 379
Additive effect of drugs, 235 Adduction arm (rotator cuff), 446 hand, 450 hip, 451 passive, abnormal, 454 thigh, 452 Adductor brevis, 452 Adductor longus, 451, 452 Adductor magnus, 452 Adenine Shiga/Shiga-like toxins and, 132 Adenocarcinomas carcinogens causing, 225 esophagus, 378 gastric, 216, 226 lung, 224, 684 nomenclature for, 220 nonbacterial thrombotic endocarditis and, 228 pancreas, 226, 368, 398 paraneoplastic syndromes, 228 pectinate line, 366 prostatic, 654 stomach, 379 Adenohypophysis, 327
Additive effect of drugs, 235 Adduction arm (rotator cuff), 446 hand, 450 hip, 451 passive, abnormal, 454 thigh, 452 Adductor brevis, 452 Adductor longus, 451, 452 Adductor magnus, 452 Addenine Shiga/Shiga-like toxins and, 132 Adenocarcinomas carcinogens causing, 225 esophagus, 378 gastric, 216, 226 lung, 224, 684 nomenclature for, 220 nonbacterial thrombotic endocarditis and, 228 pancreas, 226, 368, 398 paraneoplastic syndromes, 228 pectinate line, 366 prostatic, 654 stomach, 379 Adenohypophysis, 327 embryologic derivatives, 613
Additive effect of drugs, 235 Adduction arm (rotator cuff), 446 hand, 450 hip, 451 passive, abnormal, 454 thigh, 452 Adductor brevis, 452 Adductor longus, 451, 452 Adductor magnus, 452 Adenine Shiga/Shiga-like toxins and, 132 Adenocarcinomas carcinogens causing, 225 esophagus, 378 gastric, 216, 226 lung, 224, 684 nomenclature for, 220 nonbacterial thrombotic endocarditis and, 228 pancreas, 226, 368, 398 paraneoplastic syndromes, 228 pectinate line, 366 prostatic, 654 stomach, 379 Adenohypophysis, 327

Adenomas
bone, 464
colorectal, 389 nomenclature for, 220
salivary gland, 376
thyroid, 342 Adenomatous colonic polyps, 387
Adenomyosis (endometrial), 648
uterine bleeding from, 633 Adenopathy
Kawasaki disease, 314
Adenosine as antiarrhythmic drug, 324
blood flow regulation, 297
pacemaker action potential and, 292 Adenosine deaminase deficiency,
37, 117
Adenosine triphosphate (ATP) electron transport chain, 78
production of, 74, 78
in TCA cycle, 77 in urea cycle, 82
Adenosine triphosphate (ATP)
synthase inhibitors, 78 Adenoviruses
characteristics of, 164
conjunctivitis, 534 pneumonia, 683
Adherens junctions, 474
Adhesions, 386 Adipose lipolysis, 320
Adipose tissue
estrogen production, 630 in starvation, 91
Adjustment disorder, 564
Adnexal (ovarian) torsion, <b>625</b> Adoption studies, 256
ADPKD (Autosomal dominant
polycystic kidney disease) saccular aneurysms and, 516
ADP receptor inhibitors, 437
ADP ribosyltransferases, 132 Adrenal adenomas
Cushing syndrome, 348
hyperaldosteronism, 349 Adrenal carcinomas
Li-Fraumeni syndrome, 224
P-glycoprotein in, 227 Adrenal cortex, <b>327</b>
progesterone production, 630
Adrenal hemorrhage Waterhouse-Friderichsen
syndrome, 349
Adrenal hyperplasia Cushing syndrome, 348
hyperaldosteronism and, 349
Adrenal insufficiency adrenoleukodystrophy, 47
anovulation with, 645
fludrocortisone for, 354 mechanism and types of, <b>349</b>
vitamin B <sub>5</sub> deficiency, 67
Adrenal medulla, <b>327</b> neuroblastomas of, 350
pheochromocytomas in, 350
Adrenal steroids, <b>335</b> Adrenal zona fasciculata, 336
Adrenocortical atrophy
Addison disease, 349 exogenous corticosteroids, 348
Adrenocortical insufficiency
drug reaction and, 249 Adrenocorticotropic hormone (ACTH)
adrenal cortex regulation of, 327
in Cushing syndrome, 228, 348

	secretion of, 327
	signaling pathways of, 337
	Adrenoleukodystrophy, 47, 524
	Adults
	common causes of death, 272
	primary brain tumors, 526
	Adult T-cell leukemia, 226
	Adult T-cell lymphoma, 430
	Advance directives, <b>266</b>
	Aedes mosquitoes
	yellow fever transmission, 168
	Aerobes, 126
	Aerobic metabolism
202	ATP production, 74
292	fed state, 91
	vitamin B <sub>1</sub> (thiamine), 66
	Aerobic organisms
	culture requirements, 126 Afferent arteriole, 580
	ANP/BNP effect on, 588
	constriction of, 583
	Afferent nerves, 296
	Aflatoxins, 153
	as carcinogen, 225
	AFP, 117, 653
	African sleeping sickness, 156
	Afterload
	cardiac output, 284
	hydralazinė, 318
	in shock, 310
	Agammaglobulinemia
	chromosome affected, 64
	Agars (bacterial culture), 126
	Agenesis, 613
	Müllerian, 622
	uterovaginal, 639
	Age-related amyloidosis, 212
	Age-related macular degeneration
)	(ARMD), <b>536</b>
	Aging changes, 270 Agnosia, 511
	Agonists
	indirect cholinomimetic, 234
	indirect general, 242
	indirect sympathomimetics, 242
	partial, 234
	potency and efficacy, 234
	Agoraphobia, 563
	Agranulocytosis, 573
	drug reaction and, 250
	sulfa drug allergies, 252
	thionamides, 354
	Agraphia, 511
	AIDS (acquired immunodeficiency
	syndrome)
	bacillary angiomatosis, 478
	brain abscess, 180
	Candida albicans, 153
	cryptococcal meningitis, 199
	Cryptosporidium, 155
	Cytomegalovirus (CMV), 165 human herpesvirus 8, 165
	marijuana for, 571
	mycobacteria, 140
	Pneumocystis jirovecii, 154
	primary central nervous system
	lymphoma, 430
	retinitis, 165
	retroviruses, 167
	time course (untreated), 176
	Air emboli, 672
	Airways (conducting zone), 662
H)	Akathisia, 499, 519
	antipsychotic drugs and, 573
	Akinesia, 520

ALA dehydratase, 419, 425
Alanine
ammonia transport, 82 gluconeogenesis in starvation, 91
pyruvate dehydrogenase complex
deficiency, 77
Alanine aminotransferase (ALT), 77
hepatitis viruses, 172
in liver damage, 390
toxic shock syndrome, 135
Alar plate, 490
Albendazole
cestodes, 160
Albinism, 476 locus heterogeneity, 57
ocular, 61
Albumin, 213
calcium and, 333
as liver marker, 390
Albuminocytologic dissociation
(CSF), 524
Albuterol, 242
asthma, 687
Alcohol dehydrogenase, 72
Alcohol exposure
in utero, 300 Alcoholic cirrhosis, <b>391</b>
cholelithiasis and, 396
Alcoholic hepatitis, 391
Alcoholic liver disease, <b>391</b>
Alcoholism, 145
anemia, 420
cataracts and, 535
cirrhosis and, 389
common organisms affecting, 179
esophageal cancer, 378
ethanol metabolism and, 72
folate deficiency, 420 gastritis in, 379
hepatitis, 367
hypertension and, 300
ketone bodies in, 90
Korsakoff syndrome, 558
liver serum markers in, 390
magnesium levels in, 332
Mallory-Weiss syndrome in, 377
osteonecrosis in, 463
pancreatitis, 249, 397
porphyria, 425 sideroblastic anemia, 419
vitamin B <sub>1</sub> deficiency, 66
vitamin B <sub>1</sub> deficiency, 68
Alcohol-related disorders
readmissions with, 272
Alcohol use
essential tremor, 519
gout and, 467
head and neck cancer, 671
intoxication and withdrawal, 570
sleep, 497
teratogenic effects, 614 Alcohol use disorder, <b>571</b>
Alcohol withdrawal, 570
drug therapy, 546, 572
hallucinations in, 559, 570
Aldesleukin, 121
Aldolase B, 80
Aldose reductase, 81
Aldosterone, 588, 590
adrenal cortex secretion of, 327
SIADH, 338
signaling pathways for, 337
Aldosterone antagonists, 316
Aldosterone antagonists, 316 Aldosterone resistance, 593
Aldosterone antagonists, 316
Aldosterone antagonists, 316 Aldosterone resistance, 593

FAS1\_2019\_21\_Index\_749-806.indd 750 11/21/19 12:27 PM

Alemtuzumab, 122 Alendronate, 486 Alexia, 515 Alirocumab, 320 Aliskiren, 610 Alkaline phosphatase (ALP), 390, 463 bone disorder lab values, 464 hyperparathyroidism and, 345 Paget disease of bone, 463 in thyroid storm, 342 as tumor marker, 226 Alkalosis, 592 contraction, 60 diuretic effects, 609 hypokalemia with, 590 metabolic, 349 Alkaptonuria, 84 ALK gene, 224 lung cancer, 684 Alkylating agents, 441 as carcinogens, 225 targets of, 438 teratogenicity of, 614 Allantois, 618 Allelic heterogeneity, 57 Allergic bronchopulmonary aspergillosis (ABPA), 153 Allergic contact dermatitis, 477 Allergic reactions, 112 blood transfusion, 114 All-trans retinoic acid for promyelocytic leukemia, 66 Allopurinol for gout, 487 kidney stones, 598 Lesch-Nyhan syndrome, 37 rash with, 250 Alopecia doxorubicin, 439 etoposide/teniposide, 442 minoxidil for, 658 syphilis, 147 tinea capitis, 152 vitamin A toxicity, 66 vitamin B<sub>5</sub> deficiency, 67 vitamin B<sub>7</sub> deficiency, 68 α-1,4-glucosidase glycogen metabolism, 86  $\alpha_1$ -antagonists BPH treatment, 654  $\alpha_1$ -antitrypsin, 52  $\alpha_1$ -antitrypsin deficiency, 51, 392 emphysema, 674  $\alpha_1$ -blockers tamsulosin, example of, 237  $\alpha_1$  selective blockers, 244  $\alpha_2$ -agonists, 243  $\alpha_2$ -antagonists, 576  $\alpha_2$  selective blockers, 244 α-adrenergic agonists, 686 α-agonists glaucoma treatment, 552 muscle spasm treatment, 551 α-amanitin RNA polymerase inhibition, 42 α-amylase, 373 α-antagonists for pheochromocytomas, 350 α-blockers, 244 Beers criteria, 247 for cocaine overdose, 571 nonselective, 244 α cells, 328 glucagonomas in, 351 glucagon production by, 333

α-dystroglycan muscular dystrophy, 61 α-fetoprotein as tumor marker, 226 in hepatocellular carcinoma, 392 neural tube defects, 491 α-galactosidase A Fabry disease, 88 α-glucosidase inhibitors, 353 α-hemolytic cocci viridans group streptococci, 136 α-hemolytic bacteria Streptococcus pneumoniae, 136 α-intercalated cells, 593 α-ketoglutarate hyperammonemia and, 82 α-ketoglutarate dehydrogenase metabolic pathways, 74 TCA cycle, 7 vitamin B<sub>1</sub> and, 66 α-methyldopa, 243 anemia and, 423 α-oxidation, 47 Alpha rhythm (EEG), 497 α-synuclein, 520 α-thalassemia, 418 Alpha toxin, 133 α-toxin Clostridium botulinum, 138 α (type I) error, 263 Alport syndrome, 596 cataracts and, 535 collagen deficiency in, 50 Alprazolam, 546 Alteplase (tPA), 413, 437 Alternative hypothesis, 262 Alternative splicing, 43 Altitude sickness, 670 Altruism, 555 Aluminum hydroxide, 399 Alveolar cell types, 661 Alveolar dead space, 664 Alveolar gas equation, 668 Alveolar macrophages, 661, 662 Alveolar PO<sub>2</sub>, 668 Alveolar sacs, 662 Alveolar stage (development), 660 Alveolar ventilation, 664 Alveoli, 660 pneumocytes, 661 Alzheimer disease, 520 amyloidosis in, 212 drug therapy for, 240, 549 neurotransmitters for, 495 Amanita phalloides necrosis caused by, 42, 249 RNA polymerase inhibition, 42 Amantadine, 548 Ambiguous genitalia 46,XY DSD, 639 ovotesticular disorder of sex development, 638 placental aromatase deficiency, 639 Amebiasis Entamoeba histolytica amebiasis, 155 antiandrogens, 658 cystic fibrosis, 60 ectopic pregnancy and, 641 functional hypothalamic, 645 menopause diagnosis, 636

Müllerian agenesis, 622

pituitary prolactinomas, 328

Amides (local anesthetics), 550

Amikacin, 191 Amiloride, 609 for diabetes insipidus, 338 Amines MAO inhibitors, 575 Amine whiff test, 148 Amino acids blood-brain barrier and, 496 branched, 84 classification of,  $\bf 81$ codons for, 37 derivatives of, 83 genetic code for, 37 in histones, 34 metabolism, 90 purine synthesis, 35 tRNA, 44 urea cycle, 82 Aminoacyl-tRNA, 45 Aminoglycosides, 191 magnesium levels and, 332 pregnancy use, 204 Pseudomonas aeruginosa, 143 teratogenicity, 614 toxicity of, 251 Aminopenicillins mechanism and use, 188 Amiodarone, 323 hypothyroidism, 249 hypothyroidism with, 341 photosensitivity, 250 pulmonary fibrosis, 251 Amitriptyline, 575 migraine headaches, 518 Amlodipine, 318 Ammonia Ornithine transcarbamylase deficiency, 83 Ammonia transport, 82 Ammonium chloride overdose treatment, 233 Ammonium magnesium phosphate (kidney stones), 598 Amnesia brain lesions, 511 classification of, 558 Amnionitis Listeria monocytogenes, 139 Amniotic fluid abnormalities, 641 Amniotic fluid emboli, 672 Amniotic fluid tests AChE in, 491 with neural tube defects, 491 Amoxapine, 575 Amoxicillin clinical use, 188 Haemophilus influenzae, 142 Helicobacter pylori, 146 Lyme disease, 146 prophylaxis, 198 Amphetamines, 242 intoxication and withdrawal, 570 narcolepsy treatment, 568 norepinephrine and, 239 as weak bases, 233 Amphotericin B clinical use, 199 Cryptococcus neoformans, 153 Naegleria fowleri, 156 opportunistic fungal infections, systemic mycoses, 151 Ampicillin Ĉlostridium difficile, 138 Listeria monocytogenes, 139

mechanism and use, 188 meningitis, 180 prophylaxis, 198 Ampulla of Vater, 368 Amygdala lesions of, 511 limbic system, 499 Amylase in pancreatitis, 397 Amylin analogs, 353 Amyloid angiopathy intraparenchymal hemorrhage, 513 Amvloidosis cardiomyopathy with, 308 carpal tunnel syndrome, 459 classification, 212 kidney deposition in, 597 with rheumatoid arthritis, 466 Amyloid precursor protein (APP), 520 Amyotrophic lateral sclerosis (ALS) drug therapy for, 549, 551 spinal cord lesions, 530 Anabolic steroids hepatic adenomas and, 392 Anaerobic metabolism glycolysis, 74 pyruvate metabolism, 77 Anaerobic organisms aspiration and, 179 clindamycin, 192 Clostridia (with exotoxins), 138 culture requirements, 127 glycyclines, 192 metronidazole, 195 Nocardia vs Actinomyces, 139 overgrowth in vagina, 148 pneumonia caused by, 179 Anal atresia, 614 Anal cancer HIV and, 177 oncogenic microbes and, 226 Anal fissures, 366 Anal wink reflex, 510 Anaphase, 46 Anaphylaxis, 112 blood transfusion, 114 complement and, 106 epinephrine for, 242 IgA-containing products, 116 shock with, 310 Anaplasma spp Gram stain, 125 transmission, 146, 149 Anaplasmosis Anaplasma spp, 150 Anaplastic thyroid carcinomas, 343 Anastomoses, 503 Anastrozole, 656 Anatomic dead space, 664 Anatomic snuff box, 449 Anatomy endocrinal, 327-328 gastrointestinal, 360-369 of heart, 276, **283** hematologic/oncologic, 406–409 musculoskeletal, 446–454 nervous system, 493–510 renal, 580 reproductive, 624-627 respiratory, 662–663 "anchovy paste" exudate, 155 Ancylostoma, 159 diseases associated with, 161 infection routes, 158 microcytic anemia, 161 Androblastoma, 653

FAS1\_2019\_21\_Index\_749-806.indd 751 11/21/19 12:27 PM

Androgen-binding protein Sertoli cell secretion, 628 Androgenetic alopecia, 658 Androgenic steroid abuse, 636 Androgen insensitivity syndrome, 639 Androgen receptor defect, 639 Androgens, source and functions, 636 Androstenedione, 335, 636 Anemia, 417 amphotericin B, 199 Ancylostoma, 161 babesiosis, 157 bacterial endocarditis, 311 blood oxygen content, 666 blood transfusion therapy, 429 blood viscosity in, 286 cephalosporins, 189 chloramphenicol, 192 colorectal cancer, 388 cytarabine and, 440 dapsone, 194 Diphyllobothrium latum, 160 drug reaction and, 250 Escherichia coli, 145 ESR in, 214 extrinsic hemolytic, 423 G6PD deficiency, 79 hookworms, 159 in hypertensive emergency, 300 intrinsic hemolytic, 422 isoniazid, 197 kwashiorkor, 71 lab values, 419 macrocytic, 419 malaria, 157 megaloblastic, 420 microcytic, hypochromic, 418 nonhemolytic, normocytic, 421 normocytic, normochromic, 421 NRTIs, 203 oxygen deprivation and, 669 penicillin G, V, 189 pernicious anemia, 372, 379 pregnancy and, 633 pure red cell aplasia, 228 recombinant cytokines for, 121 renal failure, 603 sideroblastic, 67, 419 spherocytes in, 415 in sulfa drug allergies, 252 taxonomy, 417 thioamides causing, 354 trimethoprim, 194 tropical sprue, 381 vitamin B<sub>12</sub> deficiency, 69 vitamin B<sub>9</sub> deficiency, 68 Weil disease, 147 Wilson disease, 395 Anemia of chronic disease, 421 rheumatoid arthritis, 466 Anencephaly, 491 polyhydramnios and, 641 Anergy, 110 Anesthetics general principles, **549** inhaled, 550 intravenous, 550 local, 550 Aneuploidy, 638 Aneurysms, 516 atherosclerosis, 302 coarctation of aorta, 299 Ehlers-Danlos syndrome, 51 superior vena cava syndrome, 685

ventricular, 305, 307

Angelman syndrome chromosome association, 64 Angina aortic stenosis, 291 atherosclerosis, 302 cocaine causing, 571 contraindicated drugs, **323** drug therapy for, 318, 324 glycoprotein IIb/IIIa inhibitors for, 438 ischemic disease and, 304 unstable/NSTEMI treatment, 307 Angina, "intestinal," 386 Angina pectoris  $\check{\beta}$ -blockers for, 245 Angiodysplasia, 386 Angioedema, 610 C1 esterase inhibitor deficiency, scombroid poisoning, 247 Angiogenesis bevacizumab and, 442 wound healing and, 216 Angiokeratomas, 88 Angiomas, 117 Angiosarcomas, 392, 478 carcinogens causing, 225 nomenclature for, 220 Angiotensin-converting enzyme (ACE) inhibitors, **610** Angiotensin II, 588, 590 ACE inhibitor effects on, 610 signaling pathways for, 337 Angiotensin II receptor blockers, **610** heart failure, 309 hypertension, 316 naming convention for, 253 preload/afterload effects, 284 Anhedonia, 561 Anhidrosis Horner syndrome, 540 Anidulafungin, 200 Aniline dyes, 606 transitional cell carcinoma and, 606 Anisocytosis, 407 Anitschkow cells, 312 Ankle sprains, 455 Ankylosing spondylitis, 469 HLA-B27 and, 100 therapeutic antibodies for, 122 TNF- $\alpha$  inhibitors for, 487 Annular pancreas, 360 Anopheles mosquito, 157 Anopia visual field defects, 542 Anorectal varices portal circulation, 365 Anorexia hypothalamus and, 498 liver cancer/tumors, 392 pancreatic adenocarcinoma, 398 renal failure, 603 Anorexia nervosa anovulation with, 645 characteristics of, 567 Anosmia zinc deficiency, 71 ANOVA tests, 264 Anovulation common causes, 645 Antacids, 399

Antagonists

ADH, 254

endothelin receptor, 254

ethanol antidote, for, 235

 $H_2$ , 254 nonselective, 245 of drugs, 235 Anterior cerebral artery cingulate herniation, 529 cortical distribution, 502 stroke, 514 Anterior circulation strokes, 514 Anterior communicating artery saccular aneurysm, 516 Anterior corticospinal tract, 508 Anterior cruciate ligament (ACL) iniury anterior drawer sign in, 454 "unhappy triad," 460 Anterior drawer sign, 454 Anterior hypothalamus, 498 Anterior inferior cerebellar artery, 514 Anterior inferior tibiofibular ligament, 455 Anterior pituitary gland, 327, 331 Anterior spinal artery complete occlusion, 530 stroke, 514 Anterior talofibular ligament, 455 Anterograde amnesia, 558 benzodiazepines, 550 brain lesions, 511 Anthracosis, 677 Anthracyclines, 439 cardiomyopathy from, 248 Anthrax, 132, 137 Anthrax toxin Bacillus anthracis and, 137 Anti-ACh receptor antibody, 115 Antiandrogen drugs, **658** Antianginal therapy, 307, 318, 319, 324 Antiapoptotic molecule oncogene product, 224 Antiarrhythmic drugs mechanisms and clinical uses, 322-324 torsades de pointes, 248 Antibiotics, 153 acne treatment, 477 Clostridium difficile with, 138 Jarisch-Herxheimer reaction with, long QT interval, 294 selective growth media, 126 torsades de pointes, 248 Antibodies in adaptive immunity, 99 antibody diversity generation, 104 antibody specificity generation, 104 exo- and endotoxins, 131, 133 hepatitis viruses, 174 hypersensitivity mediation, 112 structure and function, 104 therapeutic, 122 Antibody-dependent cell-mediated cytotoxicity, 101 Anticardiolipin antiphospholipid syndrome, 470 Anticardiolipin antibody, 115 Anti-CCP antibody, 115 Anti-centromere antibodies scleroderma, 473 Anticentromere autoantibody, 115 Anticholinergic drugs delirium with, 558 toxicity treatment for, 248 Anticholinesterase drugs, 240 Anticholinesterase poisoning, 240 Anticipation (genetics), 56

Anticoagulant drugs acute coronary syndromes, 307 antiphospholipid syndrome, 470 atrial fibrillation, 295 coagulation cascade and, 412 Anticoagulation coagulation cascade and, 413 Anticonvulsant drugs, 471 Antidepressant drugs, **574**–576 atypical, 576 for fibromyalgia, 471 long OT interval with, 294 torsades de pointes, 248 Anti-desmoglein (anti-desmosome) autoantibody, 115 Anti-digoxin Fab fragments, 248 for cardiac glycoside toxicity, 321 Antidiuretic hormone (ADH), 329, 588, 590 antagonist naming conventions, 254 antagonists, 338, 354 in diabetes insipidus, 338 function of, 328 hypothalamus synthesis, 498 pituitary gland and, 327 SIADH and, 338 signaling pathways of, 337 Anti-DNA topoisomerase I autoantibody, 115 Anti-dsDNA antibody, 115 Antiemetic drugs aprepitant, 401 long QT interval with, 294 marijuana, 571 metoclopramide, 400 ondansetron, 400 torsades de pointes, 248 Antiepileptic drugs Cytochrome P-450 interactions, for fibromyalgia, 471 rash from, 250 teratogenicity, 614 Antifungal drugs griseofulvin, 48 mechanism and use, 198-200 seborrheic dermatitis, 476 tinea versicolor, 152 Antigenic shift/drift, 169 Antigen-presenting cells (APCs) B cells as, 409 CD28, 110 MHC I and II and, 100 naive T-cell activation, 103 in spleen, 98 Antigens active immunity, 110 antibody structure and function, 104 chronic mucocutaneous candidiasis, 116 for self, 102 HLA I and II, 100 lymphocyte recognition of, 98 type and memory, 105 Anti-glomerular basement membrane autoantibody, 115 Anti-glutamic acid decarboxylase autoantibody, 115 Antigout drugs colchicine, 48 Anti-HBc, 174 Anti-HBe, 174 Anti-HBs, 174 Anti-helicase autoantibody, 115

FAS1\_2019\_21\_Index\_749-806.indd 752 11/21/19 12:27 PM

stimulants and, 570

Antihelminthic drugs, 200
mebendazole, 48
naming convention, 253 Anti-hemidesmosome autoantibody,
115
Antihistamines, 686 for scombroid poisoning, 247
Anti-histone antibody, 115
Antihypertensive drugs
hypertension in pregnancy, 643 Anti-IgE monoclonal therapy, 687
Anti-IL-5 monoclonal therapy, 687
Anti-inflammatory drugs, 485
Anti-intrinsic factor autoantibody, 115 Anti-La/SSB autoantibody, 115
Antileukotrienes
for asthma, 687 Antimetabolites, <b>440</b>
Antimicrobial drugs
highly resistant bacterial treatment,
198 mechanisms of action summary,
<b>187</b> –204
naming conventions for, 253 pregnancy contraindications, <b>204</b>
prophylaxis, 198
Antimicrosomal autoantibody, 115
Anti-mite/louse therapy, <b>200</b> Antimitochondrial autoantibody, 115
Antimuscarinic drugs
Parkinson disease, 548 reactions to, 251
toxicity treatment for, 248
Antimycin A electron transport chain, 78
Antimycobacterial therapy, <b>196</b>
Anti-NMDA receptor paraneoplastic
syndrome encephalitis, 228 Antinuclear (ANA) antibody, 115
Sjögren syndrome, 468
Antioxidants free radical elimination by, 210
Antiparasitic drugs
naming convention for, 253 Antiparietal cell autoantibody, 115
Anti-phospholipase A2 receptor
autoantibody, 115
Antiphospholipid syndrome, <b>470</b> autoantibody in, 115
Antiplatelet antibodies
abciximab as, 122 Antiplatelet drugs
for acute coronary syndromes, 307
Anti-presynaptic voltage-gated calcium channel
autoantibody, 115
Antiprogestin drugs, 657
Antiprotozoan drugs, <b>200</b> Antipseudomonal drugs
cephalosporins, 189
fluoroquinolones, 195 penicillins, <b>188</b>
Antipsychotic drugs
adverse effects/events, 573 antimuscarinic reaction, 251
atypical, 573
dopaminergic pathways, 499
dystonia with, 569 long QT interval with, 294
Parkinson-like syndrome, 251
tardive dyskinesia, 251 torsades de pointes, 248
Tourette syndrome, 572
typical, 573
Antiribonucleoprotein antibodies Sjögren syndrome, 468

Anti-Ro/SSA autoantibody, 115
Anti-Scl-70 autoantibody, 115
Anti-Smith autoantibody, 115 Anti-smooth muscle autoantibody,
Antisocial personality disorder, 565
early-onset disorder, 557 Antispasmodics, 551
Anti-SRP autoantibody, 115
Anti-streptolysin O (ASO) titers, 312 Antisynthetase autoantibody, 115
Antithrombin coagulation cascade and, 413
deficiency of, 428
Antitoxins as passive immunity, 110
Anti-TSH receptor autoantibody, 115
Antitumor antibiotics, <b>439</b> Anti-U1 RNP antibodies, 115, 470
Antiviral therapy hepatitis C, 203, 204
mechanism and use, 201
Anti- $\beta_2$ glycoprotein antiphospholipid syndrome, 470
autoantibody, 115
Anxiety drug therapy, 546, 563, 575
neurotransmitters, 495 Aorta
branches, 363
coarctation of, 299, 300 congenital heart disease, 298
diaphragm, 663 ECG and, 293
retroperitoneal, 360
in syphilitic heart disease, 312 traumatic rupture of, 303
"tree bark" appearance, 312
Aortic aneurysm, 302 Ehlers-Danlos syndrome, 51
hypertension, 300 Marfan syndrome, 300
syphilitic heart disease, 312
Aortic arch derivatives, <b>619</b> Aortic arch receptors, 296
Aortic dissection, <b>303</b>
hypertension, 300 Marfan syndrome, 300
Aortic insufficiency syphilitic heart disease, 312
Aorticopulmonary septum, 281
embryologic derivatives, 613 Aortic regurgitation, 288
heart murmurs with, 291 Marfan syndrome, 300
Aortic root dilation
heart murmur with, 291 Aortic stenosis, 288
heart murmurs, 291
macroangiopathic anemia, 423 Williams syndrome, 300
Aortic valve cardiac cycle, 287
embryological development of,
281 Aortitis
syphilis, 147, 184 Apalutamide, 658
APC gene, 224
adenomatous colonic polyps and, 387
colorectal cancer and, 389
familial adenomatous polyposis and, 387
"Ape hand," 447, 451 Apgar score, <b>634</b>

Apgar score, 634

Aphasia
MCA stroke, 514
types of, <b>516</b>
Aphthous stomatitis
Crohn disease, 382
Apixaban
factor Xa inhibitors, 437 Aplasia, 613
Aplasia cutis
methimazole, 354
Aplastic anemia, 421
chloramphenicol, 192
drug reaction and, 250
neutropenia with, 424
thionamides, 354
Aplastic crisis
hereditary spherocytosis, 422 sickle cell anemia, 422
Apolipoproteins
functions of, 93
Apoptosis, 208
corticosteroids, 424
Appendages (bacterial), 124
Appendicitis, 383
mittelschmerz vs, 631
Appetite regulation, <b>336</b> , 371
"Apple core" lesion (X-ray), 388
Apraclonidine, 552
Aprepitant, <b>401</b> Aqueous humor pathway, <b>535</b>
Arabinofuranosyl cytidine, 440
Arabinogalactan synthesis, 196
Arabinosyltransferase, 197
Arachidonic acid pathway, 485
Arachnodaetyly, 52
Arachnoid granulations, 503, 504, 522
Arachnoid mater
meninges, 496
meningioma, 526 ventricular system, 504
Arcuate fasciculus
aphasia and, 516
diagram, 501
Area postrema, 498
Area under the curve, 231
Arenaviruses, characteristics of, 167
Argatroban, 435
Arginine classification, 81
cystinuria, 85
kidney stones and, 598
Argininosuccinate,, 82
Argyll Robertson pupils
in syphilis, 184
tabes dorsalis, 530
Aripiprazole, 573
Arm abduction, <b>446</b>
Armadillos (disease vectors), 149 Aromatase, 636
in pathway, 335
Aromatase inhibitors, <b>656</b>
Aromatic amines
carcinogenicity of, 225
Arrhythmias
amphotericin B, 199
diabetic ketoacidosis, 347
diphtheria, 139 drug reactions and, 248
hypokalemia and, 591
local anesthetics and, 550
macrolides, 193
McArdle disease, 87
muscular dystrophy, 61
myocardial infarction and, 305, 307
shock caused by, 310
sleep apnea and, 679

```
TCA toxicity, 569
   thyroid hormones and, 354
Arsenic
   angiosarcomas, 392, 478
   carcinogenicity of, 225
   glycolysis and, 74
   toxicity symptoms, 76
   toxicity treatment, 248
Artemether, 200
Arterial oxygen saturation, 666
Arterial PCO<sub>2</sub>, 668
Arteries, anatomy of, 283
Arteriolosclerosis, 301, 346
Arteriosclerosis, 301
Arteriovenous malformations (AVMs)
   hereditary hemorrhagic
          telangiectasia, 316
Arteriovenous shunts, 463
Arteritis
   giant cell (temporal), 314, 518
   headaches, 518
Artesunate
   malaria, 157, 200
Arthralgias
   alkaptonuria, 84
   coccidiomycosis, 151
   Henoch-Schönlein purpura, 315
   hepatitis viruses, 172
   in alkaptonuria, 84
   rubella, 169, 182
   serum sickness, 113
   vitamin A toxicity, 66
Arthritis, 457, 466
azathioprine for, 440
Campylobacter jejuni, 145
   carpal tunnel syndrome and, 459
   celecoxib for, 486
   chlamydiae, 148, 184
   Crohn disease, 382
   gonococcal, 468
gonorrhea, 142, 180, 184
   immunosuppressants, 120
   inflammatory bowel disease, 100
   lupus, 470
   Lyme disease, 146 psoriatic, 469
   reactive arthritis, 469
   septic, 468
Staphylococcus aureus, 135
   Takayasu arteritis, 314
therapeutic antibodies, 122
   ulcerative colitis, 382
Arthropathy
   hemochromatosis, 395
Arthus reaction, 113
Arylsulfatase A
   metachromatic leukodystrophy, 88
 Arytenoids, 620
Asbestos
carcinogenicity, 225
Asbestosis, 677, 678
Ascaris lumbricoides, 159
Ascaris spp, 158
Ascending cholangitis, 397
Ascending colon, 360
Aschoff bodies, 312
Ascites
   Budd-Chiari syndrome, 392
   hepatocellular carcinoma, 392
   spontaneous bacterial peritonitis, 390
Ascorbic acid, 69
Asenapine, 573
Aseptic meningitis
   mumps, 170
   picornaviruses, 167
```

FAS1\_2019\_21\_Index\_749-806.indd 753 11/21/19 12:27 PM

A.L		ECC 1 205	A
Asherman syndrome, 648	opsoclonus-myoclonus syndrome,	ECG tracings, 295	Autonomic ganglia, 236 Autonomic insufficiency, 242
Ashkenazi Jews	228 prion disease, 178	Lyme disease, 146 Atrioventricular canals, 281	
disease incidence, 88	psychoactive drug intoxication, 570	Atrioventricular node	Autonomic nervous system (ANS) delirium tremens, 569
ASO titer, 136 Aspart, 352	streptomycin, 197	AV node, 292	dysregulation in inflammatory
Aspart, 372	sueptomychi, 197 syphilis, 147	conduction pathway, 293	demyelinating
Aspartame, 84	tabes dorsalis, 530	ECG and, 293	polyradiculopathy, 524
Aspartate urea cycle, 82	trinucleotide repeat expansion	Atrioventricular valves	limbic system in, 499
	disease, 62	embryologic development of, 281	male sexual response, <b>627</b>
Aspartate aminotransferase (AST), 390	truncal, 511	1	
hepatitis, 172	vitamin B <sub>12</sub> deficiency, 530	Atrophic gastritis gastrin in, 371	receptors in, <b>236</b>
toxic shock syndrome, 135	vitamin E deficiency, 70	Atrophy, 206	in serotonin syndrome, 569 Autonomy (ethics), 265
Aspartic acid, 81	Wernicke-Korsakoff syndrome,	motor neuron signs, 529, 531	Autoregulation of blood flow, <b>297</b>
Aspergillosis	511, 571		Autosomal dominant diseases, <b>60</b>
Aspergillus fumigatus, 153	Ataxia-telangiectasia, 40, <b>117</b>	neurodegenerative disorders, 520 optic disc/nerve, 536	ADPKD, 516
bronchiectasis, 674, 675	9		,
echinocandins, 200	Atazanavir, 203 Atelectasis, <b>680</b>	ventriculomegaly, 522	Brugada syndrome, 294
Aspergillus fumigatus, 153	Atenolol, 245, 323	Atropine, <b>241</b> antimuscarinic reaction, 251	Charcot-Marie-Tooth disease, 524
HIV-positive adults, 177		for β-blocker overdose, 323	elastin syndrome, 52
Aspergillus spp	Atherosclerosis, <b>302</b>	effects of, 241	Huntington disease, 520
chronic granulomatous disease, 109	abdominal aortic aneurysms and, 302		hyper-IgE syndrome, 116
Aspiration	diabetes mellitus and, 346	toxicity treatment, 248	hypertrophic cardiomyopathy, 308 malignant hyperthermia
ARDS and, 678	familial dyslipidemias, 94	Attention-deficit hyperactivity disorder	0 71
in utero "breathing," 660	homocystinuria, 84	(ADHD), 557	susceptibility, 550
lung abscess, 685		drug therapy for, 557, 572	neurofibromatosis, 525
reflux-related, 359, 377	renovascular disease, 604	Tourette syndrome, 557	porphyrias, 425
Zenker diverticulum, 384	stable angina with, 304	Attributable risk (AR), 258	Romano-Ward syndrome, 294
Aspiration pneumonia	transplant rejection, 119	Atypical antidepressants, <b>576</b>	tuberous sclerosis, 525
alcoholics, 179	Athetosis, 511, 519	Atypical antipsychotic drugs, <b>573</b>	von Hippel-Lindau disease, 525
clindamycin, 192	Atomoxetine, 557	postpartum psychosis, 562	Autosomal dominant polycystic kidney
nosocomial infections, 185	Atonic seizures, 517	Atypical depression, 575	disease (ADPKD), 604
Aspirin, <b>486</b>	Atopic dermatitis (eczema), 477	Atypical pneumonias	chromosome association, 64
acute coronary syndromes, 307	Atopic reactions, 112	chlamydiae, 148	Autosomal dominant tubulointerstitial
cyclooxygenase, 411	Atovaquone	macrolides, 193	kidney disease, 604
hemolysis in G6PD deficiency, 250	babesiosis, 157	typical organisms, 683	Autosomal recessive diseases, 60
for ischemic stroke, 512	malaria, 157	Auditory cortex	abetalipoproteinemia, 94
Kawasaki disease, 314	P. falciparum, 200	diagram, 501	adenosine deaminase deficiency,
thrombogenesis and, 411	for Pneumocystis jirovecii, 154	thalamic relay, 498	117
uncoupling agent, 78	ATPase, 395	Auditory hallucinations, 559	alkaptonuria, 84
as weak acid, 233	ATP production, <b>74</b>	Auditory physiology, <b>533</b>	Chédiak-Higashi syndrome, 117
zero-order elimination of, 232	Atresia	Auerbach plexus, 376, 384	cystic fibrosis, 60
Asplenia	anal, 614	Auer rods	5α-reductase deficiency, 639
Streptococcus pneumoniae, 136	duodenal, 359	in AML, 432	Friedreich ataxia, 531
target cells, 415	esophageal, 359	Auramine-rhodamine stain, 125	hemochromatosis, 395
Asterixis, 519	intestinal, 359	Auscultation of heart, <b>290</b>	hereditary hyperbilirubinemias,
hepatic encephalopathy, 391	jejunal/ileal, 359	Auspitz sign, 477	394
renal failure, 603	Atria	Autism spectrum disorder, 557	IL-12 receptor deficiency, 116
Asteroid bodies, 676	cardiac tumors, 316	double Y males and, 638	Jervell and Lange-Nielsen
Asthma, 674	depolarization/repolarization of,	fragile X syndrome, 62	syndrome, 294
albuterol for, 242	293	Autoantibodies, 115	Kartagener syndrome, 49
β-blockers and, 245	embryologic development of, 281	Autoclaves	leukocyte adhesion deficiency, 117
breast milk and, 636	Atrial fibrillation	disinfection/sterilization, 204	maple syrup urine disease, 84
cromolyn sodium for, 408	β-blockers for, 323	Autodigestion, 397	severe combined
drug therapy, <b>687</b>	calcium channel blockers for, 324	Autoimmune diseases	immunodeficiency, 117
epinephrine for, 242	cardiac glycosides for, 321	acute pericarditis, 313	spinal muscular atrophy, 530
gastroesophageal reflux disease, 377	ECG tracing of, 295	blistering skin, <b>480</b>	Wilson disease, 395
hypertension treatment with, 316	hypertension, 300	collagen and, 50	Autosomal recessive polycystic kidney
immunosuppressants, 120	jugular venous pulse in, 287	Dressler syndrome, 307	disease (ARPKD), 604
muscarinic antagonists for, 241	potassium channel blockers for,	myocarditis with, 313	Potter sequence caused by, 578
omalizumab for, 122	323	rheumatoid arthritis, 466	Autosomal trisomies, <b>63</b>
pulsus paradoxus in, 310	Atrial flutter	self-antigen in, 102	Down syndrome (trisomy 21), 63
salmeterol for, 242	β-blockers for, 323	Sjögren syndrome, 468	Edwards syndrome (trisomy 18), 63
type I hypersensitivity, 112	ECG tracing of, 295	SLE, 470	karyotyping for, 55
Astigmatism, 535	potassium channel blockers for,	Autoimmune gastritis, 379	Patau syndrome (trisomy 13), 63
Astrocytes, <b>493</b>	323 "Atrial kick," 287	Autoimmune hemolytic anemia, 423 cephalosporins, 189	Avascular necrosis
foot processes, 496			femoral head, 461
origin of, 490	Atrial natriuretic peptide (ANP), <b>296</b> , 588, 590	Autoimmune hepatitis type 1	Avascular necrosis, <b>463</b>
Ataxia		autoantibody, 115 Autoimmune hypothyroidism, 173	scaphoid bone, 449
abetalipoproteinemia, 94	in SIADH 228	AND DEFINITION OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY OF THE PROPERTY	sickle cell anemia, 422
	in SIADH, 338		
	signaling pathways for, 337	Autoimmune lymphoproliferative	Aversive stimulus (positive
cerebellar hemisphere lesions, 511	signaling pathways for, 337 Atrial septal defect (ASD), 299	Autoimmune lymphoproliferative syndrome, 208	Aversive stimulus (positive punishment), 554
cerebellar hemisphere lesions, 511 Friedreich, 62, 64, 531	signaling pathways for, 337 Atrial septal defect (ASD), 299 congenital rubella, 300	Autoimmune lymphoproliferative syndrome, 208 Autoimmune regulator (AIRE), 102	Aversive stimulus (positive punishment), 554 Avoidant personality disorder, 566
cerebellar hemisphere lesions, 511 Friedreich, 62, 64, 531 hypnotics, 546	signaling pathways for, 337 Atrial septal defect (ASD), 299 congenital rubella, 300 Down syndrome, 300	Autoimmune lymphoproliferative syndrome, 208 Autoimmune regulator (AIRE), 102 Autoimmune thrombocytopenia, 121	Aversive stimulus (positive punishment), 554 Avoidant personality disorder, 566 Axilla/lateral thorax, 455
cerebellar hemisphere lesions, 511 Friedreich, 62, 64, 531 hypnotics, 546 lithium toxicity, 569	signaling pathways for, 337 Atrial septal defect (ASD), 299 congenital rubella, 300 Down syndrome, 300 fetal alcohol syndrome, 300	Autoimmune lymphoproliferative syndrome, 208 Autoimmune regulator (AIRE), 102 Autoimmune thrombocytopenia, 121 Autonomic drugs, 236–245	Aversive stimulus (positive punishment), 554 Avoidant personality disorder, 566 Axilla/lateral thorax, 455 Axillary nerve
cerebellar hemisphere lesions, 511 Friedreich, 62, 64, 531 hypnotics, 546 lithium toxicity, 569 metachromatic leukodystrophy, 88	signaling pathways for, 337 Atrial septal defect (ASD), 299 congenital rubella, 300 Down syndrome, 300 fetal alcohol syndrome, 300 Atrioventricular (AV) block	Autoimmune lymphoproliferative syndrome, 208 Autoimmune regulator (AIRE), 102 Autoimmune thrombocytopenia, 121 Autonomic drugs, 236–245 actions of, 239	Aversive stimulus (positive punishment), 554 Avoidant personality disorder, 566 Axilla/lateral thorax, 455 Axillary nerve arm abduction, 446
cerebellar hemisphere lesions, 511 Friedreich, 62, 64, 531 hypnotics, 546 lithium toxicity, 569	signaling pathways for, 337 Atrial septal defect (ASD), 299 congenital rubella, 300 Down syndrome, 300 fetal alcohol syndrome, 300	Autoimmune lymphoproliferative syndrome, 208 Autoimmune regulator (AIRE), 102 Autoimmune thrombocytopenia, 121 Autonomic drugs, 236–245	Aversive stimulus (positive punishment), 554 Avoidant personality disorder, 566 Axilla/lateral thorax, 455 Axillary nerve

FAS1\_2019\_21\_Index\_749-806.indd 754 11/21/19 12:27 PM

Axonal injury, 495	Bacterial infections	B-cell lymphomas	Berkson bias, 260
Axonal trafficking, 48	with immunodeficiency, 118	HIV-positive adults, 177	Bernard-Soulier syndrome, 411, 427
Axonemal dynein, 49	myocarditis with, 313	B cells, <b>409</b>	Berry aneurysm, 516
Azathioprine	skin, 479	activation, 103, 105	Berylliosis, 677
antimetabolites, 440	Bacterial peritonitis (spontaneous),	adaptive immunity, 99	β <sub>1</sub> -blockade, 284
for Crohn disease, 382	389, 390	anergy, 110	β <sub>2</sub> -agonists
immunosuppressant, 120	Bacterial toxin mechanisms	cell surface proteins, 110	naming convention for, 253
pancreatitis caused by, 249	inhibit release of neurotransmitter,	class switching, 103	β <sub>2</sub> -agonists
Azithromycin	132	disorders of, 116, 117	asthma, 687
atypical pneumonia treatment,	lysogenic phage encoding of, 130	function of, 409	insulin and, 334
148	Bacterial vaginosis	functions of, 101	β-adrenergic agonist
babesiosis, 157	characteristics of, 158, 181	glucocorticoid effects, 120	potassium shifts, 590
chlamydiae, 148	Gardnerella vaginalis, 148	immunodeficiency infections, 118	β-blockers, 245, <b>323</b>
in cystic fibrosis, 60	Bacteroides fragilis, 178	in lymph node, 96	acute coronary syndromes, 307
gonorrhea treatment, 142	Bacteroides spp	neoplasms, 430	angina, 319
macrolides, 193	alcoholism, 179	non-Hodgkin lymphoma, 429	aortic dissections, 303
Mycobacterium avium-	clindamycin, 192	sirolimus effect, 120	Cardiomyopathy (hypertrophic),
intracellulare, 140, 196	culture requirements of, 127	spleen, 98	245
prophylaxis in HIV, 198	metronidazole, 195	BCG vaccine	cocaine overdose, 571
Azoles, 153, <b>199</b>	nosocomial infections, 185	false positives from, 140	diabetes and, 245
vaginal infections, 181	"Bag of worms," 651	IL-12 receptor deficiency and, 116	dilated cardiomyopathy, 308
Azotemia	Baker cyst, 460	BCL-2 gene, 224	essential tremor, 519
acute interstitial nephritis, 601	tibial nerve injury, 453	Bcl-2 protein, 208	for cocaine overdose, 242
Aztreonam, 190	BAK protein, 208	BCR-ABL gene, 224	for pheochromocytomas, 350
_	Balancing (quality measurement), 273	Bead-like costochondral junctions, 463	for thyroid storm, 342
В	Bamboo spine, 469	Becker muscular dystrophy, 61	glaucoma treatment, 552
Babesia spp, 146, 157	Band cells, 406	Beck triad (cardiac tamponade), 310	heart failure, 309
Babesiosis, 157	Barbiturates	Beckwith-Wiedemann syndrome,	hyperkalemia, 590
Babinski reflex, 635	intoxication and withdrawal, 570	358, 606	hypertension, 316
motor neuron signs, 529	intravenous anesthetics, 550	Beers criteria, 247	hypertrophic cardiomyopathy, 308
primitive reflexes, 510	mechanism and use, 546	Behavioral therapy, 572	juxtaglomerular apparatus effects,
Bachmann bundle, 293	naming convention for, 253	Behavior modulation	589
Bacillary angiomatosis, 478	sleep alterations, 497	frontal lobe lesions and, 511	migraine headaches, 518
animal transmission, 149	Barlow maneuver, 461	limbic system and, 499	naming convention for, 253
HIV-positive adults, 177	Baroreceptors, 296	Behçet syndrome, 314	overdose treatment, 323
Bacillus anthracis, 137	Barr bodies, 34	Bell palsy, 532, 676	phobias, 563
exotoxin production, 132	in x-inactivation, 61	Bell-shaped distribution, 262	selectivity, 245
Bacillus cereus, 138	Barrett esophagus, 378	Bendazoles, 159	toxicity treatment for, 248
food poisoning, 178	Bartholin cyst/abscess, 644	Bends, 463	β cells, 328
Bacitracin	Bartonella henselae	Beneficence (ethics), 265	diabetes mellitus type 1 and 2, 347
gram-positive antibiotic test, 134	bacillary angiomatosis, 478	Benign breast disease, <b>649</b>	insulinomas of, 351
sensitivity to, 134, 136	Bartonella quintana, 161	Benign paroxysmal positional vertigo	insulin production by tumors, 351
Baclofen, 551	Bartonella spp	(BPPV), 534	insulin secretion by, 334
multiple sclerosis, 523	animal transmission, 149	Benign prostatic hyperplasia (BPH),	β-dystroglycan, 61
Bacteremia	Gram Stain, 125	237, <b>654</b>	β-galactosidase, 144
brain abscesses, 180	Bartter syndrome, 586	$\alpha_1$ -blockers for, 244	β-glucan, 200
cutaneous anthrax, 137	markers in, 591	epididymitis and orchitis with, 654	β-glucuronidase, 406
daptomycin, 195	Basal cell carcinomas, 484	tamsulosin for, 658	β-hCG, 653
Staphylococcus gallolyticus, 137	5-fluorouracil for, 440	treatment of, 237	as tumor marker, 226
Streptococcus bovis, 137	Basal ganglia, <b>500</b>	Benign tumors, 220	β-hemolysis, 133
Bacteria	intraparenchymal hemorrhage, 513	bones, 464	β-hemolytic bacteria, 135
biofilm-producing, 128	lesions in, <b>511</b>	breast, 649	common colonization sites, 135
culture requirements, 126	movement disorders, 519	Benralizumab, 687	Staphylococcus aureus, 135
encapsulated, 127	thalamic connections, 498	Benzathine penicillin G, 198	Staphylococcus epidermidis, 135
genetics, <b>130</b> , 131	Basal lamina, 50	Benzene	Staphylococcus saprophyticus, 136
hemolytic, 135	Basal nucleus of Meynert, 495	aplastic anemia, 250	Streptococcus agalactiae (Group B
highly resistant, 198	Basal plate, 490	Benzidine as carcinogen, 225	strep), 137
normal flora, 178	Base excision repair, 40	Benznidazole, 158	Streptococcus pyogenes (Group A
phage infection of, 130	Basement membrane, 98	Benzocaine, 550	strep), 136
pigment-producing, 128	blood-brain barrier, 496	Benzodiazepines	β-hydroxybutyrate, 90
spore-forming, 129	collagen in, 50	addictive risk, 546	β-interferon
stains for, 125	glomerular filtration barrier, 581	alcohol withdrawal, 572	multiple sclerosis, 523
structures and functions, 124	Basic amino acids, 81	Beers criteria, 247	β-lactam antibiotics, 187
virulence factors, 127, <b>129</b> , 135,	Basilar artery	clinical use and adverse effects, <b>546</b>	β-lactamase inhibitors, 189
143, 144, 145	herniation syndromes, 529	cocaine overdose, 571	$\beta_2$ -microglobulin
zoonotic, 149	stroke effects, 515	epilepsy treatment, 544	MHC I and II and, 100
Bacterial capsules, 124	Basilar membrane (cochlea), 533	intoxication and withdrawal, 570	β-oxidation of very-long-chain fatty
Bacterial endocarditis, 311	Basiliximab	naming convention for, 253	acids (VLCFA), 47
daptomycin, 195	immunosuppressant, 120	phobias, 563	β-prophage
Staphylococcus aureus, 135	Basophilia, 408	sleep effects, 497	Corynebacterium exotoxin
Bacterial exotoxin mechanisms	Basophilic stippling, 416	toxicity treatment for, 248	encoding, 139
increase fluid secretion, 132	lead poisoning, 419	Benzoyl peroxide for acne, 477	Beta rhythm (EEG), 497
inhibit phagocytic ability, 132	sideroblastic anemia, 419	Benztropine, 241, 548	β-thalassemia, 418
inhibit protein synthesis, 132	Basophils, 408	Berger disease, 596	allelic heterogeneity, 57
lyse cell membranes, 133	IgE antibody, 105	Beriberi	Betaxolol, 245, 552
superantigens causing shock, 133	BAX protein, 208	vitamin B <sub>1</sub> deficiency, 66	Bethanechol, 240

FAS1\_2019\_21\_Index\_749-806.indd 755 11/21/19 12:27 PM

Bevacizumab, 122, 442 Bezafibrate, 320 Bias and study errors, 260-262 Bicalutamide, 658 Bicarbonate carbon dioxide transport, 670 GI secretion, 372 overdose treatment, 233 pancreatic insufficiency, 381 salicylate toxicity, 248 TCA toxicity, 233, 248 Biceps brachii muscle Erb palsy, 448 Biceps femoris, 452, 453 Biceps reflex, 510 Biceps tendon, 446 Bicornuate uterus, 623 Bicuspid aortic valve aortic dissection and, 303 coarctation of aorta and, 299 heart murmur with, 291 thoracic aortic aneurysms and, 302 Turner syndrome, 300 Bifid ureter, 579 Bifurcation external landmarks, 663 Biguanide drugs, 353 Bilaminar disc, 612 Bilateral adenopathy, 676 Bilateral renal agenesis oligohydramnios and, 641 Potter sequence, 578 pulmonary hypoplasia and, 660 Bile, **374** hereditary hyperbilirubinemias, secretin effect on, 371 Bile acid resins, 320 lipid transport and, 92 reabsorption of, 320 synthesis of, 47 Bile canaliculus, 367 Bile ducts, 367, 368 Bile salts, 374 in cholelithiasis, 396 Biliary atresia, 393 Biliary cholangitis, primary autoantibody, 115 Biliary cirrhosis, 389, 393 cystic fibrosis, 60 Biliary colic, 396 Biliary structures, 368 Biliary tract disease, 395 Clonorchis sinensis, 161 gallstones, 368 hyperbilirubinemia with, 393 Biliary tract infections Enterococci, 137 Bilirubin, 375 bile, 374 cholelithiasis, 396 hereditary hyperbilirubinemias, liver marker, 390 toxic shock syndrome, 135 Bimatoprost, 552 Bimodal distribution, 262 Binge-eating disorder, 567, 575 Binge-eating/purging, anorexia nervosa, 567 Bioavailability, 231 area under the curve from, 231 Biochemistry cellular, 46-52 genetics, 56

laboratory techniques, 52-94

metabolism, 72-94 molecular, 34 nutrition, 65 Biochemistry laboratory techniques blotting procedures, 53 Cre-lox system, 56 CRISPR/Cas9, 53 enzyme-linked immunosorbent assay, 54 flow cytometry, 54 fluorescence in situ hybridization, free light chain (FLC) assay, 431 gene expression modifications, 56 karyotyping, 55 microarrays, 54 molecular cloning, 55 polymerase chain reaction, 52 reverse transcriptase polymerase chain reaction, 52 RNA interference, 56 serum protein electrophoresis, 431 Biofilm-producing bacteria, 128 Staphylococcus epidermidis, 135 Biologic agents naming conventions for, 254 Biomarkers α-fetoprotein, 491 astrocytes, 493 neurons, 493 Biostatistics/epidemiology, 256-262 Biotin, 68 Bipolar disorder, 561 drug therapy for, 572 lithium for, 574 Birbeck granules Langerhans cell histiocytosis, 434 "Bird's beak" sign (X-ray), 376 Birds (disease vectors), 148, 149 Bismuth, 399 Bisoprolol, 245 Bisphosphonates, 462, 486 esophagitis with, 249 naming convention for, 254 osteogenesis imperfecta treatment, Bitemporal hemianopia, 542 craniopharyngioma, 528 hypopituitarism, 339 optic chiasm compression, 516 Bitot spots, 66 Bivalirudin, 435 BK virus, 164 Black eschar, 137 Black lung disease, 677 Bladder, 160 bethanechol effect on, 240 BPH and, 654 development of, 618

exstrophy, 624

urachus, 618

Bladder cancer

"Blast crisis," 433

Blastomyces spp amphotericin B, 199

itraconazole, 199

outlet obstruction, 579

spasm treatment, 241

urgency in cystitis, 241

hematuria with, 594

Blastocyst implantation, 612

placenta percreta invasion, 640

cisplatin/carboplatin for, 442

hypercalcemia and, 228 Schistosoma haematobium, 161 Blastomycosis, 151 Bleeding, 642 adenomatous polyps, 387 direct factor Xa inhibitors, 437 direct thrombin inhibitors, 435 diverticulosis, 383 essential thrombocythemia, 433 glycoprotein IIb/IIIa inhibitors, 438 heparin, 436 inflammatory bowel disease, 382 peptic ulcer disease, 380 thrombolytics, 437 variceal, 371 warfarin, 436 Bleeding time, 427 Bleomycin antitumor antibiotics, 439 pulmonary fibrosis, 251 targets of, 438 toxicity, 444 Blepharospasm, 519 Blindness Chlamydia trachomatis, 149 giant cell arteritis, 314 neonatal, 142 Onchocerca volvulus, 159 Toxocara canis, 159 Blistering skin disorders, 480 Blood chocolate-colored, 666 coagulation and kinin pathways, hCG detection in, 633 oxygen content, 666 in placenta, 617 umbilical cord, 618 viscosity of, 668 Blood-brain barrier anesthetics, 549 astrocytes, 493 function and mechanism, 496 at hypothalamus, 498 L-DOPA, 549 Blood flow autoregulation, 297 exercise response, 670 Blood groups, 405 Blood-nerve permeability barrier, 495 Blood pH diuretic effects on, 609 Blood pressure angiotensin II effects, 588 antianginal therapy, 319 cortisol effect on, 336 fenoldopam and, 318 renal disorders and, 591 sympathomimetic effect on, 243 Blood-testis barrier, 628 Blood transfusions, 429 reactions, 114 therapy, 429 Blood vessels collagen in, 50 Ehlers-Danlos syndrome, 50 hereditary hemorrhagic telangiectasia, 316 Blood volume atrial natriuretic peptide release, 296 regulation, 588 Bloody diarrhea, 179 Campylobacter jejuni, 145, 149 Shigella, 144

Blotting procedures, 53 Blown pupil, 541 CN III damage, 541 saccular aneurysms, 516 "Blue babies," 298 Blueberry muffin rash cytomegalovirus, 182 rubella, 169, 182 Toxoplasma gondii, 182 "Blue bloater," 674 "Blue kids," 299 Blue sclerae, 51 Blumer shelf, 379 BMPR2 gene, 679 Body compartments, 231 Body dysmorphic disorder, 563 Boerhaave syndrome, 377 Bombesin, 350 Bone cancer, 464 primary bone tumors, 464 Bone cell biology, 458, 459 Bone crises, 88 Bone disorders adult T-cell lymphoma and, 430 lab values in, 464 Langerhans cell histiocytosis, 434 lytic ("punched out"), 431 osteogenesis imperfecta, 51 Bone formation, 458 Bone-in-bone (x-ray), 463 Bone marrow cytokine stimulation of, 121 lymphoid functions of, 96 suppression, 199 Bone mineral density scan, 462 Bone morphogenetic protein (BMP), Bones collagen in, 50 cortisol effect on, 336 lytic/blastic metastases, 223 primary bone tumors, 464 PTH effect on, 332 renal osteodystrophy, 603 Borderline personality disorder, Bordetella pertussis, 143 culture requirements, 126 exotoxin production, 132 macrolides, 193 vaccines, 143 Bordet-Gengou agar, 126 Borrelia burgdorferi animal transmission, 149 coinfection with, 157 facial nerve palsy, 186 Lyme disease, 146 tetracyclines, 192 Borrelia recurrentis animal transmission, 149 vectors, 161 Borrelia spp, 146 Bortezomib, 443 Bosentan, 686 Botulinum toxin lysogenic transduction, 130

Lyme disease, 146
tetracyclines, 192
Borrelia recurrentis
animal transmission, 149
vectors, 161
Borrelia spp, 146
Bortezomib, 443
Bosentan, 686
Botulinum toxin
lysogenic transduction, 130
passive antibodies for, 110
symptoms of, 138
toxin effects, 132
Bovine spongiform encephalopathy
(BSE), 178
Bowel stenosis, 383
Bowen disease, 651
Bowenoid papulosis, 651
Bow legs (genu varum), 463

ulcerative colitis, 382

Bloody stool, 366

Damman asserta 502
Bowman capsule, 583
Boxer's fracture, 459
BPH (benign prostatic hyperplasia)
hydronephrosis in, 599
nydronepinosis in, 777
Brachial artery, 455
Brachial plexus
Danagast tumas 605
Pancoast tumor, 685
Brachial plexus lesions, 448
Brachiocephalic syndrome, 685
Brachiocephalic vein, 685
Brachioradialis reflex, 510
,
Bradycardia
amiodarone and, 323
atropine for, 241
β-blockers and, 245, 323
dopamine for, 242
on ECG, 293
hypermagnesemia, 591
reflex, 588
sympatholytic drugs and, 243
Bradykinesia
with antipsychotic drugs, 573
Bradykinin
AĆE inhibitors and, 610
C1 esterase inhibitor deficiency,
107
Bradykinin, 610
BRAF gene, <b>224</b> , 387
melanomas and, 484
· · · · · · · · · · · · · · · · · · ·
papillary thyroid carcinoma and,
343
vemurafenib and, 444
Brain
blood flow autoregulation, 297
embryologic derivatives, 613
embryology of, 490
infarcts, 209
ischemia in, 210
metastasis to, 223
Brain abscesses
bacteremia, 180
bacteremia, 180 HIV-positive adults, 180
bacteremia, 180 HIV-positive adults, 180
bacteremia, 180 HIV-positive adults, 180 otitis media, 180
bacteremia, 180 HIV-positive adults, 180 otitis media, 180 Staphylococcus aureus, 180
bacteremia, 180 HIV-positive adults, 180 otitis media, 180 Staphylococcus aureus, 180
bacteremia, 180 HIV-positive adults, 180 otitis media, 180 Staphylococcus aureus, 180 Toxoplasma gondii, 177
bacteremia, 180 HIV-positive adults, 180 otitis media, 180 Staphylococcus aureus, 180 Toxoplasma gondii, 177 Viridans streptococci, 180
bacteremia, 180 HIV-positive adults, 180 otitis media, 180 Staphylococcus aureus, 180 Toxoplasma gondii, 177 Viridans streptococci, 180 Brain cysts, 161
bacteremia, 180 HIV-positive adults, 180 otitis media, 180 Staphylococcus aureus, 180 Toxoplasma gondii, 177 Viridans streptococci, 180 Brain cysts, 161
bacteremia, 180 HIV-positive adults, 180 otitis media, 180 Staphylococcus aureus, 180 Toxoplasma gondii, 177 Viridans streptococci, 180 Brain cysts, 161 Brain death, 269, 501, 502
bacteremia, 180 HIV-positive adults, 180 otitis media, 180 Staphylococcus aureus, 180 Toxoplasma gondii, 177 Viridans streptococci, 180 Brain cysts, 161 Brain death, 269, 501, 502 Brain injury
bacteremia, 180 HIV-positive adults, 180 otitis media, 180 Staphylococcus aureus, 180 Toxoplasma gondii, 177 Viridans streptococci, 180 Brain cysts, 161 Brain death, 269, 501, 502 Brain injury
bacteremia, 180 HIV-positive adults, 180 otitis media, 180 Staphylococcus aureus, 180 Toxoplasma gondii, 177 Viridans streptococci, 180 Brain cysts, 161 Brain death, 269, 501, 502 Brain injury gastritis with, 379
bacteremia, 180 HIV-positive adults, 180 otitis media, 180 Staphylococcus aureus, 180 Toxoplasma gondii, 177 Viridans streptococci, 180 Brain cysts, 161 Brain death, 269, 501, 502 Brain injury gastritis with, 379 hypopituitarism from, 339
bacteremia, 180 HIV-positive adults, 180 otitis media, 180 Staphylococcus aureus, 180 Toxoplasma gondii, 177 Viridans streptococci, 180 Brain cysts, 161 Brain death, 269, 501, 502 Brain injury gastritis with, 379 hypopituitarism from, 339 Brain lesions (common), 511
bacteremia, 180 HIV-positive adults, 180 otitis media, 180 Staphylococcus aureus, 180 Toxoplasma gondii, 177 Viridans streptococci, 180 Brain cysts, 161 Brain death, 269, 501, 502 Brain injury gastritis with, 379 hypopituitarism from, 339 Brain lesions (common), 511
bacteremia, 180 HIV-positive adults, 180 otitis media, 180 Staphylococcus aureus, 180 Toxoplasma gondii, 177 Viridans streptococci, 180 Brain cysts, 161 Brain death, 269, 501, 502 Brain injury gastritis with, 379 hypopituitarism from, 339 Brain lesions (common), 511 Brain natriuretic peptide (BNP), 296,
bacteremia, 180 HIV-positive adults, 180 otitis media, 180 Staphylococcus aureus, 180 Toxoplasma gondii, 177 Viridans streptococci, 180 Brain cysts, 161 Brain death, 269, 501, 502 Brain injury gastritis with, 379 hypopituitarism from, 339 Brain lesions (common), 511 Brain natriuretic peptide (BNP), 296, 588
bacteremia, 180 HIV-positive adults, 180 otitis media, 180 Staphylococcus aureus, 180 Toxoplasma gondii, 177 Viridans streptococci, 180 Brain cysts, 161 Brain death, 269, 501, 502 Brain injury gastritis with, 379 hypopituitarism from, 339 Brain lesions (common), 511 Brain natriuretic peptide (BNP), 296,
bacteremia, 180 HIV-positive adults, 180 otitis media, 180 Staphylococcus aureus, 180 Toxoplasma gondii, 177 Viridans streptococci, 180 Brain cysts, 161 Brain death, 269, 501, 502 Brain injury gastritis with, 379 hypopituitarism from, 339 Brain lesions (common), 511 Brain natriuretic peptide (BNP), 296, 588 in SIADH, 338
bacteremia, 180 HIV-positive adults, 180 otitis media, 180 Staphylococcus aureus, 180 Toxoplasma gondii, 177 Viridans streptococci, 180 Brain cysts, 161 Brain death, 269, 501, 502 Brain injury gastritis with, 379 hypopituitarism from, 339 Brain lesions (common), 511 Brain natriuretic peptide (BNP), 296, 588 in SIADH, 338 signaling pathways for, 337
bacteremia, 180 HIV-positive adults, 180 otitis media, 180 Staphylococcus aureus, 180 Toxoplasma gondii, 177 Viridans streptococci, 180 Brain cysts, 161 Brain death, 269, 501, 502 Brain injury gastritis with, 379 hypopituitarism from, 339 Brain lesions (common), 511 Brain natriuretic peptide (BNP), 296, 588 in SIADH, 338 signaling pathways for, 337 Brain stem
bacteremia, 180 HIV-positive adults, 180 otitis media, 180 Staphylococcus aureus, 180 Toxoplasma gondii, 177 Viridans streptococci, 180 Brain cysts, 161 Brain death, 269, 501, 502 Brain injury gastritis with, 379 hypopituitarism from, 339 Brain lesions (common), 511 Brain natriuretic peptide (BNP), 296, 588 in SIADH, 338 signaling pathways for, 337 Brain stem
bacteremia, 180 HIV-positive adults, 180 otitis media, 180 Staphylococcus aureus, 180 Toxoplasma gondii, 177 Viridans streptococci, 180 Brain cysts, 161 Brain death, 269, 501, 502 Brain injury gastritis with, 379 hypopituitarism from, 339 Brain lesions (common), 511 Brain natriuretic peptide (BNP), 296, 588 in SIADH, 338 signaling pathways for, 337 Brain stem dorsal view, 504
bacteremia, 180 HIV-positive adults, 180 otitis media, 180 Staphylococcus aureus, 180 Toxoplasma gondii, 177 Viridans streptococci, 180 Brain cysts, 161 Brain death, 269, 501, 502 Brain injury gastritis with, 379 hypopituitarism from, 339 Brain lesions (common), 511 Brain natriuretic peptide (BNP), 296, 588 in SIADH, 338 signaling pathways for, 337 Brain stem dorsal view, 504 ventral view, 504
bacteremia, 180 HIV-positive adults, 180 otitis media, 180 Staphylococcus aureus, 180 Toxoplasma gondii, 177 Viridans streptococci, 180 Brain cysts, 161 Brain death, 269, 501, 502 Brain injury gastritis with, 379 hypopituitarism from, 339 Brain lesions (common), 511 Brain natriuretic peptide (BNP), 296, 588 in SIADH, 338 signaling pathways for, 337 Brain stem dorsal view, 504 ventral view, 504 Brain stem/cerebellar syndromes
bacteremia, 180 HIV-positive adults, 180 otitis media, 180 Staphylococcus aureus, 180 Toxoplasma gondii, 177 Viridans streptococci, 180 Brain cysts, 161 Brain death, 269, 501, 502 Brain injury gastritis with, 379 hypopituitarism from, 339 Brain lesions (common), 511 Brain natriuretic peptide (BNP), 296, 588 in SIADH, 338 signaling pathways for, 337 Brain stem dorsal view, 504 ventral view, 504 Brain stem/cerebellar syndromes
bacteremia, 180 HIV-positive adults, 180 otitis media, 180 Staphylococcus aureus, 180 Toxoplasma gondii, 177 Viridans streptococci, 180 Brain cysts, 161 Brain death, 269, 501, 502 Brain injury gastritis with, 379 hypopituitarism from, 339 Brain lesions (common), 511 Brain natriuretic peptide (BNP), 296, 588 in SIADH, 338 signaling pathways for, 337 Brain stem dorsal view, 504 ventral view, 504 Brain stem/cerebellar syndromes multiple sclerosis, 523
bacteremia, 180 HIV-positive adults, 180 otitis media, 180 Staphylococcus aureus, 180 Toxoplasma gondii, 177 Viridans streptococci, 180 Brain cysts, 161 Brain death, 269, 501, 502 Brain injury gastritis with, 379 hypopituitarism from, 339 Brain lesions (common), 511 Brain natriuretic peptide (BNP), 296, 588 in SIADH, 338 signaling pathways for, 337 Brain stem dorsal view, 504 ventral view, 504 Brain stem/cerebellar syndromes multiple sclerosis, 523 Brain tumors
bacteremia, 180 HIV-positive adults, 180 otitis media, 180 Staphylococcus aureus, 180 Toxoplasma gondii, 177 Viridans streptococci, 180 Brain cysts, 161 Brain death, 269, 501, 502 Brain injury gastritis with, 379 hypopituitarism from, 339 Brain lesions (common), 511 Brain natriuretic peptide (BNP), 296, 588 in SIADH, 338 signaling pathways for, 337 Brain stem dorsal view, 504 ventral view, 504 Brain stem/cerebellar syndromes multiple sclerosis, 523 Brain tumors adult primary, 526-527
bacteremia, 180 HIV-positive adults, 180 otitis media, 180 Staphylococcus aureus, 180 Toxoplasma gondii, 177 Viridans streptococci, 180 Brain cysts, 161 Brain death, 269, 501, 502 Brain injury gastritis with, 379 hypopituitarism from, 339 Brain lesions (common), 511 Brain natriuretic peptide (BNP), 296, 588 in SIADH, 338 signaling pathways for, 337 Brain stem dorsal view, 504 ventral view, 504 Brain stem/cerebellar syndromes multiple sclerosis, 523 Brain tumors adult primary, 526-527
bacteremia, 180 HIV-positive adults, 180 otitis media, 180 Staphylococcus aureus, 180 Toxoplasma gondii, 177 Viridans streptococci, 180 Brain cysts, 161 Brain death, 269, 501, 502 Brain injury gastritis with, 379 hypopituitarism from, 339 Brain lesions (common), 511 Brain natriuretic peptide (BNP), 296, 588 in SIADH, 338 signaling pathways for, 337 Brain stem dorsal view, 504 ventral view, 504 Brain stem/cerebellar syndromes multiple sclerosis, 523 Brain tumors adult primary, 526–527 childhood primary, 528
bacteremia, 180 HIV-positive adults, 180 otitis media, 180 Staphylococcus aureus, 180 Toxoplasma gondii, 177 Viridans streptococci, 180 Brain cysts, 161 Brain death, 269, 501, 502 Brain injury gastritis with, 379 hypopituitarism from, 339 Brain lesions (common), 511 Brain natriuretic peptide (BNP), 296, 588 in SIADH, 338 signaling pathways for, 337 Brain stem dorsal view, 504 ventral view, 504 Brain stem/cerebellar syndromes multiple sclerosis, 523 Brain tumors adult primary, 526-527 childhood primary, 528 hallucinations with, 559
bacteremia, 180 HIV-positive adults, 180 otitis media, 180 Staphylococcus aureus, 180 Toxoplasma gondii, 177 Viridans streptococci, 180 Brain cysts, 161 Brain death, 269, 501, 502 Brain injury gastritis with, 379 hypopituitarism from, 339 Brain lesions (common), 511 Brain natriuretic peptide (BNP), 296, 588 in SIADH, 338 signaling pathways for, 337 Brain stem dorsal view, 504 ventral view, 504 ventral view, 504 Brain stem/cerebellar syndromes multiple sclerosis, 523 Brain tumors adult primary, 526-527 childhood primary, 528 hallucinations with, 559 incidence and mortality, 222
bacteremia, 180 HIV-positive adults, 180 otitis media, 180 Staphylococcus aureus, 180 Toxoplasma gondii, 177 Viridans streptococci, 180 Brain cysts, 161 Brain death, 269, 501, 502 Brain injury gastritis with, 379 hypopituitarism from, 339 Brain lesions (common), 511 Brain natriuretic peptide (BNP), 296, 588 in SIADH, 338 signaling pathways for, 337 Brain stem dorsal view, 504 ventral view, 504 ventral view, 504 Brain stem/cerebellar syndromes multiple sclerosis, 523 Brain tumors adult primary, 526-527 childhood primary, 528 hallucinations with, 559 incidence and mortality, 222
bacteremia, 180 HIV-positive adults, 180 otitis media, 180 Staphylococcus aureus, 180 Toxoplasma gondii, 177 Viridans streptococci, 180 Brain cysts, 161 Brain death, 269, 501, 502 Brain injury gastritis with, 379 hypopituitarism from, 339 Brain lesions (common), 511 Brain natriuretic peptide (BNP), 296, 588 in SIADH, 338 signaling pathways for, 337 Brain stem dorsal view, 504 ventral view, 504 Ventral view, 504 Brain stem/cerebellar syndromes multiple sclerosis, 523 Brain tumors adult primary, 526-527 childhood primary, 528 hallucinations with, 559 incidence and mortality, 222 metastatic source, 223
bacteremia, 180 HIV-positive adults, 180 otitis media, 180 Staphylococcus aureus, 180 Toxoplasma gondii, 177 Viridans streptococci, 180 Brain cysts, 161 Brain death, 269, 501, 502 Brain injury gastritis with, 379 hypopituitarism from, 339 Brain lesions (common), 511 Brain natriuretic peptide (BNP), 296, 588 in SIADH, 338 signaling pathways for, 337 Brain stem dorsal view, 504 ventral view, 504 Ventral view, 504 Brain stem/cerebellar syndromes multiple sclerosis, 523 Brain tumors adult primary, 526-527 childhood primary, 528 hallucinations with, 559 incidence and mortality, 222 metastatic source, 223 nitrosoureas for, 441
bacteremia, 180 HIV-positive adults, 180 otitis media, 180 Staphylococcus aureus, 180 Toxoplasma gondii, 177 Viridans streptococci, 180 Brain cysts, 161 Brain death, 269, 501, 502 Brain injury gastritis with, 379 hypopituitarism from, 339 Brain lesions (common), 511 Brain natriuretic peptide (BNP), 296, 588 in SIADH, 338 signaling pathways for, 337 Brain stem dorsal view, 504 ventral view, 504 Ventral view, 504 Brain stem/cerebellar syndromes multiple sclerosis, 523 Brain tumors adult primary, 526-527 childhood primary, 528 hallucinations with, 559 incidence and mortality, 222 metastatic source, 223
bacteremia, 180 HIV-positive adults, 180 otitis media, 180 Staphylococcus aureus, 180 Toxoplasma gondii, 177 Viridans streptococci, 180 Brain cysts, 161 Brain death, 269, 501, 502 Brain injury gastritis with, 379 hypopituitarism from, 339 Brain lesions (common), 511 Brain natriuretic peptide (BNP), 296, 588 in SIADH, 338 signaling pathways for, 337 Brain stem dorsal view, 504 ventral view, 504 Brain stem/cerebellar syndromes multiple sclerosis, 523 Brain tumors adult primary, 526–527 childhood primary, 528 hallucinations with, 559 incidence and mortality, 222 metastatic source, 223 nitrosoureas for, 441 Branched-chain ketoacid
bacteremia, 180 HIV-positive adults, 180 otitis media, 180 Staphylococcus aureus, 180 Toxoplasma gondii, 177 Viridans streptococci, 180 Brain cysts, 161 Brain death, 269, 501, 502 Brain injury gastritis with, 379 hypopituitarism from, 339 Brain lesions (common), 511 Brain natriuretic peptide (BNP), 296, 588 in SIADH, 338 signaling pathways for, 337 Brain stem dorsal view, 504 ventral view, 504 Brain stem/cerebellar syndromes multiple sclerosis, 523 Brain tumors adult primary, 526–527 childhood primary, 528 hallucinations with, 559 incidence and mortality, 222 metastatic source, 223 nitrosoureas for, 441 Branched-chain ketoacid dehydrogenase, 66
bacteremia, 180 HIV-positive adults, 180 otitis media, 180 Staphylococcus aureus, 180 Toxoplasma gondii, 177 Viridans streptococci, 180 Brain cysts, 161 Brain death, 269, 501, 502 Brain injury gastritis with, 379 hypopituitarism from, 339 Brain lesions (common), 511 Brain natriuretic peptide (BNP), 296, 588 in SIADH, 338 signaling pathways for, 337 Brain stem dorsal view, 504 ventral view, 504 Brain stem/cerebellar syndromes multiple sclerosis, 523 Brain tumors adult primary, 526–527 childhood primary, 528 hallucinations with, 559 incidence and mortality, 222 metastatic source, 223 nitrosoureas for, 441 Branched-chain ketoacid
bacteremia, 180 HIV-positive adults, 180 otitis media, 180 Staphylococcus aureus, 180 Toxoplasma gondii, 177 Viridans streptococci, 180 Brain cysts, 161 Brain death, 269, 501, 502 Brain injury gastritis with, 379 hypopituitarism from, 339 Brain lesions (common), 511 Brain natriuretic peptide (BNP), 296, 588 in SIADH, 338 signaling pathways for, 337 Brain stem dorsal view, 504 ventral view, 504 Brain stem/cerebellar syndromes multiple sclerosis, 523 Brain tumors adult primary, 526-527 childhood primary, 528 hallucinations with, 559 incidence and mortality, 222 metastatic source, 223 nitrosoureas for, 441 Branched-chain ketoacid dehydrogenase, 66 Branching enzyme (glycogen
bacteremia, 180 HIV-positive adults, 180 otitis media, 180 Staphylococcus aureus, 180 Toxoplasma gondii, 177 Viridans streptococci, 180 Brain cysts, 161 Brain death, 269, 501, 502 Brain injury gastritis with, 379 hypopituitarism from, 339 Brain lesions (common), 511 Brain natriuretic peptide (BNP), 296, 588 in SIADH, 338 signaling pathways for, 337 Brain stem dorsal view, 504 ventral view, 504 Ventral view, 504 Brain stem/cerebellar syndromes multiple sclerosis, 523 Brain tumors adult primary, 526-527 childhood primary, 528 hallucinations with, 559 incidence and mortality, 222 metastatic source, 223 nitrosources for, 441 Branched-chain ketoacid dehydrogenase, 66 Branching enzyme (glycogen metabolism), 86
bacteremia, 180 HIV-positive adults, 180 otitis media, 180 Staphylococcus aureus, 180 Toxoplasma gondii, 177 Viridans streptococci, 180 Brain cysts, 161 Brain death, 269, 501, 502 Brain injury gastritis with, 379 hypopituitarism from, 339 Brain lesions (common), 511 Brain natriuretic peptide (BNP), 296, 588 in SIADH, 338 signaling pathways for, 337 Brain stem dorsal view, 504 ventral view, 504 Brain stem/cerebellar syndromes multiple sclerosis, 523 Brain tumors adult primary, 526-527 childhood primary, 528 hallucinations with, 559 incidence and mortality, 222 metastatic source, 223 nitrosoureas for, 441 Branched-chain ketoacid dehydrogenase, 66 Branching enzyme (glycogen metabolism), 86 BRCA1/BRCA2 genes, 224
bacteremia, 180 HIV-positive adults, 180 otitis media, 180 Staphylococcus aureus, 180 Toxoplasma gondii, 177 Viridans streptococci, 180 Brain cysts, 161 Brain death, 269, 501, 502 Brain injury gastritis with, 379 hypopituitarism from, 339 Brain lesions (common), 511 Brain natriuretic peptide (BNP), 296, 588 in SIADH, 338 signaling pathways for, 337 Brain stem dorsal view, 504 ventral view, 504 Ventral view, 504 Brain stem/cerebellar syndromes multiple sclerosis, 523 Brain tumors adult primary, 526-527 childhood primary, 528 hallucinations with, 559 incidence and mortality, 222 metastatic source, 223 nitrosources for, 441 Branched-chain ketoacid dehydrogenase, 66 Branching enzyme (glycogen metabolism), 86
bacteremia, 180 HIV-positive adults, 180 otitis media, 180 Staphylococcus aureus, 180 Toxoplasma gondii, 177 Viridans streptococci, 180 Brain cysts, 161 Brain death, 269, 501, 502 Brain injury gastritis with, 379 hypopituitarism from, 339 Brain lesions (common), 511 Brain natriuretic peptide (BNP), 296, 588 in SIADH, 338 signaling pathways for, 337 Brain stem dorsal view, 504 ventral view, 504 ventral view, 504 Brain stem/cerebellar syndromes multiple sclerosis, 523 Brain tumors adult primary, 526-527 childhood primary, 528 hallucinations with, 559 incidence and mortality, 222 metastatic source, 223 nitrosoureas for, 441 Branched-chain ketoacid dehydrogenase, 66 Branching enzyme (glycogen metabolism), 86 BRCA1/BRCA2 genes, 224 DNA repair in, 40
bacteremia, 180 HIV-positive adults, 180 otitis media, 180 Staphylococcus aureus, 180 Toxoplasma gondii, 177 Viridans streptococci, 180 Brain cysts, 161 Brain death, 269, 501, 502 Brain injury gastritis with, 379 hypopituitarism from, 339 Brain lesions (common), 511 Brain natriuretic peptide (BNP), 296, 588 in SIADH, 338 signaling pathways for, 337 Brain stem dorsal view, 504 ventral view, 504 Brain stem/cerebellar syndromes multiple sclerosis, 523 Brain tumors adult primary, 526-527 childhood primary, 528 hallucinations with, 559 incidence and mortality, 222 metastatic source, 223 nitrosoureas for, 441 Branched-chain ketoacid dehydrogenase, 66 Branching enzyme (glycogen metabolism), 86 BRCA1/BRCA2 genes, 224

Breastfeeding, 636
Breast milk
IgA antibodies in, 105
oxytocin's role in, 328 prolactin and, 330
Breast/ovarian cancer
BRCA1 mutation, 64
BRCA2 mutation, 64 incomplete penetrance, 56
Breast pathology, <b>649</b>
benign disorders, 649
invasive carcinomas, <b>650</b> noninvasive carcinomas, <b>650</b>
Breast cancer
aromatase inhibitors for, 656
breastfeeding and, 636 hormonal contraception
contraindication, 657
hypercalcemia and, 228
incidence/mortality of, 222 oncogenes and, 224
paclitaxel for, 441
paraneoplastic cerebellar
degeneration and, 228 tamoxifen for, 443
trastuzumab for, 443
tumor suppressor genes and, 224
Breathing
mechanics of, 675 with pneumothorax, 682
Breath sounds
bronchial, 680, 682
diminished, 682 physical findings, 680
Brenner tumor, 646
Brief psychotic disorder, 560
Brimonidine, 552 Brittle bone disease, gene defects
in, 51
Broad-base budding (blastomycosis), 151
Broad ligament, 625
Broca area, 501
aphasia, 516
MCA stroke, 514 Bromocriptine, 548
Bronchi, 662
Bronchial carcinoid tumor, 684
Bronchiectasis Aspergillus fumigatus, 153
cystic fibrosis, 60
Kartagener syndrome, 49
Bronchioles, 662 histamine receptors and, 238
Bronchiolitis obliterans, 119, 683
organizing pneumonia (BOOP),
683 Bronchitis
cystic fibrosis, 60
Haemophilus influenzae, 142
Bronchoconstriction, 687 Bronchodilation, 687
sympathetic receptors and, 238
Bronchogenic carcinomas
asbestosis and, 677
carcinogens causing, 225 Bronchogenic cysts, 660
Bronchopneumonia, 683
Bronchopulmonary dysplasia, 210 free radical injury, 210
neonatal respiratory distress
syndrome, 661
Brown Saguard condrome 521

syndrome, 661 Brown-Séquard syndrome, **531** Horner syndrome, 531 "Brown tumors," 464

Brucella spp, 127
transmission and treatment of, <b>143</b>
zoonotic infections, 149
Brucellosis, 149
Brugada syndrome, <b>294</b> , 304
Danisia s
Bruising
scurvy, 69
Brunner glands
bicarbonate product, 372
duodenum, 362
Bruton agammaglobulinemia, 61, 116
Bruxism, 497
BTK gene, 116
B-type natriuretic peptide, <b>296</b>
Buckle (torus fracture), 462
Budd-Chiari syndrome, <b>392</b>
Budesonide, 687
Buerger disease, 314
Bugs
affecting unvaccinated children, <b>186</b>
causing diarrhea, <b>179</b>
causing food-borne illness, 178
hints, <b>186</b>
Bulbar (spongy) urethra injury, 627
Bulbus cordis, 281
Bulimia nervosa, 567
anovulation and, 645
drug therapy for, 572
laxative abuse by, 401
Mallory-Weiss syndrome and, 377
SSRIs for, 575
Bulk-forming laxatives, 401
Bullae, 475
impetigo, 479
necrotizing fasciitis, 479
skin lesions, 475
Bull neck lymphadenopathy, 132
Bullous impetigo, 479
Bullous pemphigoid, 475, 480
autoantibody, 115
Bulls-eye erythema, 146
Bumetanide, 608
BUN (blood urea nitrogen)
ornithine transcarbamylase
deficiency, 83
Bundled payment, 271
Bundle of His, 293
Bundle of Kent, 294
Bunyaviruses, 167–168
Bupivacaine, 550
Buprenorphine, 551
heroin detoxification, 576
morphine and, 234
Bupropion 576
Bupropion, 576
seizures with, 251
seizures with, 251 Burkholderia cepacia
seizures with, 251 Burkholderia cepacia cystic fibrosis, 179
seizures with, 251 Burkholderia cepacia cystic fibrosis, 179 Burkitt lymphoma, 430
seizures with, 251 Burkholderia cepacia cystic fibrosis, 179 Burkitt lymphoma, 430 chromosomal translocations and,
seizures with, 251 Burkholderia cepacia cystic fibrosis, 179 Burkitt lymphoma, 430 chromosomal translocations and, 434
seizures with, 251 Burkholderia cepacia cystic fibrosis, 179 Burkitt lymphoma, 430 chromosomal translocations and,
seizures with, 251 Burkholderia cepacia cystic fibrosis, 179 Burkitt lymphoma, 430 chromosomal translocations and, 434
seizures with, 251 Burkholderia cepacia cystic fibrosis, 179 Burkitt lymphoma, 430 chromosomal translocations and, 434 EBV, 165
seizures with, 251 Burkholderia cepacia cystic fibrosis, 179 Burkitt lymphoma, 430 chromosomal translocations and, 434 EBV, 165 oncogenes and, 224 oncogenic microbes and, 226
seizures with, 251 Burkholderia cepacia cystic fibrosis, 179 Burkitt lymphoma, 430 chromosomal translocations and, 434 EBV, 165 oncogenes and, 224 oncogenic microbes and, 226 Burnout (medical errors), <b>274</b>
seizures with, 251 Burkholderia cepacia cystic fibrosis, 179 Burkitt lymphoma, 430 chromosomal translocations and, 434 EBV, 165 oncogenes and, 224 oncogenic microbes and, 226 Burnout (medical errors), 274 Burns
seizures with, 251 Burkholderia cepacia cystic fibrosis, 179 Burkitt lymphoma, 430 chromosomal translocations and, 434 EBV, 165 oncogenes and, 224 oncogenic microbes and, 226 Burnout (medical errors), 274 Burns classification, 483
seizures with, 251 Burkholderia cepacia cystic fibrosis, 179 Burkitt lymphoma, 430 chromosomal translocations and, 434 EBV, 165 oncogenes and, 224 oncogenic microbes and, 226 Burnout (medical errors), 274 Burns classification, 483 shock with, 310
seizures with, 251 Burkholderia cepacia cystic fibrosis, 179 Burkitt lymphoma, 430 chromosomal translocations and, 434 EBV, 165 oncogenes and, 224 oncogenic microbes and, 226 Burnout (medical errors), 274 Burns classification, 483 shock with, 310 sunburn, 482
seizures with, 251 Burkholderia cepacia cystic fibrosis, 179 Burkitt lymphoma, 430 chromosomal translocations and, 434 EBV, 165 oncogenes and, 224 oncogenic microbes and, 226 Burnout (medical errors), 274 Burns classification, 483 shock with, 310 sunburn, 482 testosterone/methyltestosterone
seizures with, 251 Burkholderia cepacia cystic fibrosis, 179 Burkitt lymphoma, 430 chromosomal translocations and, 434 EBV, 165 oncogenes and, 224 oncogenic microbes and, 226 Burnout (medical errors), 274 Burns classification, 483 shock with, 310 sunburn, 482 testosterone/methyltestosterone for, 658
seizures with, 251 Burkholderia cepacia cystic fibrosis, 179 Burkitt lymphoma, 430 chromosomal translocations and, 434 EBV, 165 oncogenes and, 224 oncogenic microbes and, 226 Burnout (medical errors), 274 Burns classification, 483 shock with, 310 sunburn, 482 testosterone/methyltestosterone for, 658 "Burr cells," 414
seizures with, 251 Burkholderia cepacia cystic fibrosis, 179 Burkitt lymphoma, 430 chromosomal translocations and, 434 EBV, 165 oncogenes and, 224 oncogenic microbes and, 226 Burnout (medical errors), 274 Burns classification, 483 shock with, 310 sunburn, 482 testosterone/methyltestosterone for, 658 "Burr cells," 414 Bursitis
seizures with, 251 Burkholderia cepacia cystic fibrosis, 179 Burkitt lymphoma, 430 chromosomal translocations and, 434 EBV, 165 oncogenes and, 224 oncogenic microbes and, 226 Burnout (medical errors), 274 Burns classification, 483 shock with, 310 sunburn, 482 testosterone/methyltestosterone for, 658 "Burr cells," 414 Bursitis prepatellar, 460
seizures with, 251 Burkholderia cepacia cystic fibrosis, 179 Burkitt lymphoma, 430 chromosomal translocations and, 434 EBV, 165 oncogenes and, 224 oncogenic microbes and, 226 Burnout (medical errors), 274 Burns classification, 483 shock with, 310 sunburn, 482 testosterone/methyltestosterone for, 658 "Burr cells," 414 Bursitis

Buspirone
mechanism and clinical use, <b>574</b> Busulfan, 441
pulmonary fibrosis and, 251
toxicity, 444 Butorphanol, 551, 552
*
C
C1 esterase inhibitor deficiency, 107 C3 deficiency, 107
C5a receptor, 406
C5-C9 deficiencies, 107
CA 15-3/CA27-29 (tumor markers), 226
CA 19-9 (tumor marker), 226, 398
CATT have 41
CAAT box, 41 Cachexia, <b>227</b>
TNF- $\alpha$ and, 108
Café-au-lait spots
McCune-Albright syndrome, 57 Caffeine intoxication and withdrawal,
570
Cahill cycle, 82 Calcarine sulcus
thalamic relay to, 498
Calciferol (vitamin D), 589
Calcification, 211
dystrophic, 227 Calcineurin, 120
Calcinosis cutis, 473
Calcitonin, <b>333</b>
medullary thyroid carcinoma production, 343
tumor marker, 226
Calcitriol, 589 Calcium
in bone disorders, 464
calcitonin and, 333
in cardiac muscle, 292 in osteomalacia/rickets, 463
in Paget disease of bone, 463
Vitamin D and, 337
Calcium carbonate, 399 Calcium channels
ethosuximide effect on, 544
glucose and, 334 Lambert-Eaton myasthenic
syndrome, 228
myocardial action potential, 292
opioid effect on, 551 pacemaker action potential, 292
Calcium channel blockers
angina, 318
antiarrhythmic drugs, <b>324</b> contractility in, 284
cutaneous flushing, 248
gingival hyperplasia, 250
hypertension, 316 hypertrophic cardiomyopathy, 308
mechanism and clinical use, 318
migraine headaches, 518
Raynaud phenomenon, 472 Calcium homeostasis, 333
Calcium (kidney stones), 598
calcium oxalate nephrolithiasis, 69
Calcium pyrophosphate deposition disease, <b>467</b>
Calcium-sensing receptor (CaSR), 355
Calculation bioavailability of, 231
reabsorption and secretion rate, <b>584</b>
Calculous cholecystitis, 396
Caliciviruses, 163 characteristics of, 167
characteristics of, 107

FAS1\_2019\_21\_Index\_749-806.indd 757 11/21/19 12:27 PM

INDEX

California encephalitis, 167 Calluses (dermatology), 475 cAMP (cyclic adenosine monophosphate) endocrine hormone messenger, fructose bisphosphatase-2 and, 76 heat-labile/heat-stable toxin effects, hyperparathyroidism, 345 PTH effect on, 332 Vibrio cholerae, 146 CAMP factor, 137 Campylobacter spp animal transmission, 149 bloody diarrhea, 179 jejuni, 145 reactive arthritis and, 469 Canagliflozin, 353 Canalicular stage (development), 660 common metastases, 223 deaths from, 272 ESR in, 214 hallmarks of, 221 immune evasion in, 221 mortality of, 222 pneumoconioses, 676, 677 Cancer drugs cell cycle, **438** targets, 438 Cancer epidemiology, 222 Candesartan, 610 Candida albicans, 153 HIV-positive adults, 177 T cell dysfunction, 116 Candida spp amphotericin B, 199 azoles, 199 echinocandins, 200 immunodeficiency infections, 118 osteomyelitis, 180 tricuspid valve endocarditis and, vulvovaginitis, 181 Candidiasis Candida albicans, 153 chronic mucocutaneous, 116 cortisol and, 336 nystatin, 199 Cannibalism, 178 "Cannonball" metastases, 642 Capecitabine 5-F-dUMP, 36 "Cape-like" sensory loss, 492 Capillary fluid exchange, 297 Capitate bone, 449 Capitation, 271 Caplan syndrome, 466, 677 Capsules (bacterial), 124 Captain's wheel Paracoccidioidomycosis, 151 Captopril, 610 Caput medusae, 365 Carbachol, 240, 552 Carbamazepine agranulocytosis, 250 aplastic anemia, 250 cytochrome P-450 and, 252 epilepsy, 544 SIADH and, 249 Carbamoyl phosphate, 82 Carbamoyl phosphate synthetase, 73 Carbapenems mechanism and use, 190 Pseudomonas aeruginosa, 143

Carbidopa, 549 Carbohydrate absorption, 373 Carbohydrate metabolism inborn errors of, 80 Carbol fuchsin, 125 Carbon dioxide (CO2) production in tissues, 127 retention, 679 transport, 670 Carbonic anhydrase, 670 Carbon monoxide (CO) vs cyanide poisoning, 667 electron transport inhibition, 78 poisoning, 666 teratogenicity, 614 toxicity treatment, 248 Carbon tetrachloride free radical injury and, 210 Carboplatin mechanism and clinical use, 442 toxicities of, 444 Carboplatin toxicity, 444 Carboxylases, 73 Carboxypeptidase, 373 Carcinoembryonic antigen (CEA) (tumor marker), 226 Carcinogens, 225 griseofulvin, 200 Carcinoid syndrome, 352 bronchial carcinoid tumors, 684 somatostatin in treatment, 371 Carcinoid tumors biomarkers for, 226 immunohistochemical stains for, octreotide for, 400 stomach, 379 Carcinoma in situ, 219 cervical dysplasia, 645 ductal, 650 neoplastic progression, 219 penis, 651 vulvar, 644 Carcinomas bone, 464 colorectal, 388 invasive, 219 metastases of, 219, 223 nomenclature of, 220 thyroid, 343 Cardiac arrest antacid adverse effects, 399 hypermagnesemia, 591 Cardiac cycle, 287 Cardiac depression, 318 Cardiac function curves, 286 Cardiac glycosides mechanism and clinical use, 321 sodium-potassium pump inhibition, 49 Cardiac looping, 280 Cardiac output exercise and, 670 in pregnancy, 633 variables in, 284 V/Q mismatch and, 669 Cardiac output equations, 285 Cardiac pressures (normal), 297 Cardiac tamponade, 310 aortic dissection and, 303 jugular venous pulse in, 287 MĬ, 305, 307 shock, 310

Cardiac therapy, 317

Cardiac tumors, 316

Cardinal veins, 281

Cardiogenic shock, 310 etiology, 310 Cardiomegaly Pompe disease, 87 Cardiomyopathy, 308 β-blockers, 245 Chagas disease, 158 drug reaction and, 248 familial amyloid, 212 glycogen storage diseases, 87 heart failure with, 309 hemochromatosis and, 395 hypertrophic, 245 Kussmaul sign in, 316 Starling curves, 285 sudden cardiac death, 304 Cardiotoxicity doxorubicin, 439 drugs causing, 444 methylxanthines, 687 TCA adverse effects, 575 trastuzumab, 443 Cardiovascular drugs naming conventions for, 253 reactions to, 248 Cardiovascular system, 281-323 anatomy, 283 embryology, 281–283 pathology, 298–313 pharmacology, 316–322 physiology, 284–299 sclerosis of, 473 Carditis Lyme disease, 146 rheumatic fever, 312 Carfilzomib, 443 Carina (trachea), 663 Carmustine, 441 pulmonary fibrosis, 251 Carnitine acyltransferase I, 73, 89 Carotid artery atherosclerosis in, 302 cavernous sinus, 542 emboli from, 538 embryonic development, 619 giant cell arteritis and, 314 Carotid massage, 296 Carotid sinus, 296 Carpal bones, 449 Carpal tunnel syndrome, 459 lunate dislocation, 449 nerve injury, 447 rheumatoid arthritis, 466 Carteolol, 552 Cartilage collagen in, 50 fluoroquinolone damage to, 250 Cartilage damage, 204 Carvedilol, 245, 323 Casal necklace, 67 Caseating granulomas in tuberculosis, 140 Case-control studies, 256 Caseous necrosis, 209 Caspases, 208 Caspofungin echinocandins, 200 Casts in urine, 594 Catabolism of amino acids, 82 Catalase, 210 Catalase-positive organisms, 128 Cataplexy, 568 Cataracts, 535 corticosteroid toxicity, 120 diabetes mellitus and, 346

muscular dystrophy, 61 rubella, 182 sorbitol, 81 Catecholamines adrenal medulla secretion, 327 amphetamines and, 242 contractility effects of, 284 ephedrine and, 242 heart contractility, 284 pacemaker action potential, 292 pheochromocytoma and, 350 Catecholamine synthesis tyrosine catabólism, 83 Cats (disease vectors) Campylobacter jejuni, 145 Cat scratch disease, 149 Pasteurella multocida, 149, 186 Tinea corporis, 152 Toxoplasma gondii, 156, 182 Cauda equina, 507 Cauda equina syndrome, 530 Caudal fold closure defects, 358 Caudal regression syndrome, 614 Caudate basal ganglia, 500 Huntington disease, 520 Cavernous hemangiomas liver, 392 Cavernous hemangiomas (liver), 392 Cavernous sinus, 542 dural venous sinuses, 503 syndrome, 542 thrombosis with mucormycosis, CCR5 protein HIV and, 175 maraviroc, 203 viral receptor, 166 CD4+ cell count disease associations by levels, 177 CD4 protein, 101 viral receptor, 166 CD4+ T cells (HIV), 176 CD5 protein, 432 CD8 protein, 101 CD16 protein, 101 CD20 protein, 110 in CLL, 432 CD21 protein, 110 viral receptor, 166 CD25 protein cell surface protein, 110 regulatory T cells and, 102 CD28 protein, 110 CD34 protein, 110 leukocyte extravasation and, 215 CD40 protein, 110 CDKN2A gene, 224 CEA tumor marker, 388 Cefaclor, 189 Cefazolin mechanism and use, 189 prophylaxis, 198 Cefepime mechanism and use, 189 Pseudomonas aeruginosa, 143 Cefotaxime, 189 Cefotetan mechanism and use, 189 Cefoxitin mechanism and use, 189

Cefpodoxime

MRSA, 198

Ceftaroline

mechanism and use, 189

mechanism and use, 189

FAS1\_2019\_21\_Index\_749-806.indd 758 11/21/19 12:27 PM

galactosemia, 80

○ 6 · 11		0 1	
Ceftazidime	Central tendon (diaphragm), 663	Cestodes, 160	Childbirth
mechanism and use, 189	Central vertigo, 534	Cetirizine, 686	brachial plexus injury in, 448
Pseudomonas aeruginosa, 143	Centriacinar emphysema, 674	Cetuximab, 442	Budd-Chiari syndrome and, 392
Ceftriaxone	Cephalexin	CFTR gene	Graves disease and, 342
Chlamydia spp, 148	mechanism and use, 189	chronic pancreatitis and, 397	low birth weight, 635
for gonococci, 142	Cephalosporins	cGMP (cyclic guanosine	
			misoprostol induction, 399
for Haemophilus influenzae, 142	disulfiram-like reaction, 251	monophosphate)	neonatal flora, 178
mechanism and use, 189	mechanism and use, 189	atrial natriuretic peptide and, 296	oxytocin and uterine contractions,
meningitis, 180	pseudomembranous colitis, 249	endocrine hormone messenger,	328, 636
meningococci, 142	Pseudomonas aeruginosa, 143	337	postpartum mood disturbances,
typhoid fever, 144	Ceramide trihexoside	male sexual response, 627	562
Cefuroxime	in sphingolipidoses, 88	Chagas disease, 158	preterm, as common cause of
mechanism and use, 189	Cerebellar degeneration	achalasia in, 376	death, 272
Celecoxib, 252, <b>486</b>	paraneoplastic, 228	Chalk-stick fractures, 463	progesterone levels after, 630
Celiac artery	Cerebellar lesions	Chancroids, 184	Sheehan syndrome after, 339
mesenteric ischemia, 386	hemisphere, 511	Changes in the elderly, <b>270</b>	stress incontinence and, 599
structures supplied, 364	lateral, 499	Chaperone protein, 45	Childhood disorders, <b>557</b>
Celiac disease, 381	medial, 499	Charcoal yeast extract culture	Childhood musculoskeletal
autoantibody, 115	tonsillar herniation, 492, 529	Legionella pneumophila, 126, 143	conditions, <b>461</b>
HLA genes and, 100	vermis lesions, 511	Charcot-Bouchard microaneurysm,	Childhood primary brain tumors, <b>528</b>
IgA deficiency, 116	Cerebellum	516	Child neglect, <b>556</b>
Celiac sprue, 381	development of, 490	Charcot joints	Children
Celiac trunk, <b>364</b>	input/output of, <b>499</b>	syphilis, 147	causes of death, 272
Cell biology of bone, 459	tonsils, 492	tabes dorsalis and, 530	Chi-square tests, 264
Cell cycle phases, <b>46</b>	Cerebral aqueduct of Sylvius, 504	Charcot-Leyden crystals, 674	Chlamydia spp, <b>148</b> , 184
Cell envelope (bacterial), 124	Cerebral artery distributions, <b>502</b>	Charcot-Marie-Tooth disease, 524	atypical infections, 179
Cell injury, <b>207</b>	Cerebral cortex	Charcot triad, 397	diagnostic tests for, 148
		,	
Cell lysis, 590	aphasia, 514	Charging, tRNA, 44	Giemsa stain, 125
Cell membrane in apoptosis, 208	arterial distribution, <b>502</b>	Chédiak-Higashi syndrome, 117	Gram stain, 125
Cell surface proteins	dominant parietal lesions, 511	Cheilosis, 67	intracellular organism, 127
association and functions, 110	functional areas of, 501	Chelation	macrolides, 193
leukocyte adhesion deficiency, 117	hemineglect, 514	hemochromatosis, 395	pneumonia, 683
T cells and, 101	nondominant parietal lesions, 511	lead poisoning, 419	reactive arthritis, 469
Cell trafficking, <b>47</b>	visual field defects, 514	Chemokines, 108	sulfonamides for, 194
Cell types	Cerebral edema	delayed hypersensitivity, 112	tetracyclines, 192
labile, 46	diabetic ketoacidosis and, 347	Chemoreceptors, 296	Chlamydia trachomatis
permanent, 46	therapeutic hyperventilation, 501	Chemoreceptor trigger zone (CTZ),	eosinophilia, 149
stable (quiescent), 46	Cerebral hemispheres, 490	496	pelvic inflammatory disease, 149
Cellular biochemistry, 46–52	Cerebral palsy, 551	Chemotherapy	pneumonia, 179
Cellular injury	Cerebral perfusion pressure (CPP),	AML and, 432	serotypes, 149
cellular adaptations, <b>206</b>	501	MDR1 and responsiveness to,	UTIs, 600
irreversible, 207	"Cerebriform" nuclei, 430	227	Chlamydophila pneumoniae, 148
reversible, 207	Cerebrospinal fluid (CSF)	neutropenia with, 424	pneumonia, 179
Cellulitis, 136, 479	albuminocytologic dissociation,	ondansetron, 400	Chlamydophila psittaci
Pasteurella multocida, 149	524	paclitaxel, 48	atypical pneumonia, 148
Cell walls (bacterial), 124	blood-brain barrier and, 496	pancreatic cancer, 398	transmission, 149
Central clearing	circulation of, 496, 503	readmissions with, 272	Chloasma (melasma), 476
nuclei, 343	findings in meningitis, 180	treatments for vomiting, 401	Chloramphenicol
rash, 152	Guillain-Barré syndrome, 524	vincristine/vinblastine, 48	aplastic anemia and, 250
Central diabetes insipidus, 338	hydrocephalus, 522	Chemotoxicities, 444	
Central/downward transtentorial	Hydrocephalus, 722		
LEITOTOPATALLI LETTATORIA			gray baby syndrome, 250
	multiple sclerosis, 523	Cherry hemangiomas, 478	gray baby syndrome, 250 mechanism and use, <b>192</b>
herniation, 529	multiple sclerosis, 523 neurodegenerative disorders, 521	Cherry hemangiomas, 478 "Cherry red" epiglottis, 142	gray baby syndrome, 250 mechanism and use, <b>192</b> pregnancy contraindications, 204
herniation, 529 Central nervous system (CNS)	multiple sclerosis, 523 neurodegenerative disorders, 521 origins, 490	Cherry hemangiomas, 478 "Cherry red" epiglottis, 142 Cherry-red spot (macula), 538	gray baby syndrome, 250 mechanism and use, <b>192</b> pregnancy contraindications, 204 protein synthesis inhibition, 191
herniation, 529 Central nervous system (CNS) anesthetic principles for, 549	multiple sclerosis, 523 neurodegenerative disorders, 521 origins, 490 poliomyelitis, 531	Cherry hemangiomas, 478 "Cherry red" epiglottis, 142 Cherry-red spot (macula), 538 lysosomal storage disease, 88	gray baby syndrome, 250 mechanism and use, <b>192</b> pregnancy contraindications, 204 protein synthesis inhibition, 191 Chlordiazepoxide, 546
herniation, 529 Central nervous system (CNS) anesthetic principles for, 549 antiarrhythmic adverse effects,	multiple sclerosis, 523 neurodegenerative disorders, 521 origins, 490 poliomyelitis, 531 production, 493	Cherry hemangiomas, 478 "Cherry red" epiglottis, 142 Cherry-red spot (macula), 538 lysosomal storage disease, 88 Chest pain	gray baby syndrome, 250 mechanism and use, <b>192</b> pregnancy contraindications, 204 protein synthesis inhibition, 191
herniation, 529 Central nervous system (CNS) anesthetic principles for, 549	multiple sclerosis, 523 neurodegenerative disorders, 521 origins, 490 poliomyelitis, 531	Cherry hemangiomas, 478 "Cherry red" epiglottis, 142 Cherry-red spot (macula), 538 lysosomal storage disease, 88	gray baby syndrome, 250 mechanism and use, <b>192</b> pregnancy contraindications, 204 protein synthesis inhibition, 191 Chlordiazepoxide, 546
herniation, 529 Central nervous system (CNS) anesthetic principles for, 549 antiarrhythmic adverse effects, 322, 323	multiple sclerosis, 523 neurodegenerative disorders, 521 origins, 490 poliomyelitis, 531 production, 493	Cherry hemangiomas, 478 "Cherry red" epiglottis, 142 Cherry-red spot (macula), 538 lysosomal storage disease, 88 Chest pain	gray baby syndrome, 250 mechanism and use, <b>192</b> pregnancy contraindications, 204 protein synthesis inhibition, 191 Chlordiazepoxide, 546 alcohol withdrawal, 572
herniation, 529 Central nervous system (CNS) anesthetic principles for, 549 antiarrhythmic adverse effects, 322, 323 cancer epidemiology, 222	multiple sclerosis, 523 neurodegenerative disorders, 521 origins, 490 poliomyelitis, 531 production, 493 ventricular system, 504 Cerebrovascular disease	Cherry hemangiomas, 478 "Cherry red" epiglottis, 142 Cherry-red spot (macula), 538 lysosomal storage disease, 88 Chest pain panic disorder, 563	gray baby syndrome, 250 mechanism and use, <b>192</b> pregnancy contraindications, 204 protein synthesis inhibition, 191 Chlordiazepoxide, 546 alcohol withdrawal, 572 Chlorhexidine, 204 Chloride channels
herniation, 529 Central nervous system (CNS) anesthetic principles for, 549 antiarrhythmic adverse effects, 322, 323 cancer epidemiology, 222 cell types in, 493–494	multiple sclerosis, 523 neurodegenerative disorders, 521 origins, 490 poliomyelitis, 531 production, 493 ventricular system, 504 Cerebrovascular disease diabetes mellitus, 346	Cherry hemangiomas, 478 "Cherry red" epiglottis, 142 Cherry-red spot (macula), 538 lysosomal storage disease, 88 Chest pain panic disorder, 563 pneumothorax, 682 Chest wall	gray baby syndrome, 250 mechanism and use, <b>192</b> pregnancy contraindications, 204 protein synthesis inhibition, 191 Chlordiazepoxide, 546 alcohol withdrawal, 572 Chlorhexidine, 204 Chloride channels cystic fibrosis, 60
herniation, 529 Central nervous system (CNS) anesthetic principles for, 549 antiarrhythmic adverse effects, 322, 323 cancer epidemiology, 222 cell types in, 493–494 depression, 546	multiple sclerosis, 523 neurodegenerative disorders, 521 origins, 490 poliomyelitis, 531 production, 493 ventricular system, 504 Cerebrovascular disease diabetes mellitus, 346 Certolizumab, 487	Cherry hemangiomas, 478 "Cherry red" epiglottis, 142 Cherry-red spot (macula), 538 lysosomal storage disease, 88 Chest pain panic disorder, 563 pneumothorax, 682 Chest wall elastic properties, 665	gray baby syndrome, 250 mechanism and use, <b>192</b> pregnancy contraindications, 204 protein synthesis inhibition, 191 Chlordiazepoxide, 546 alcohol withdrawal, 572 Chlorhexidine, 204 Chloride channels cystic fibrosis, 60 Chlorine, 204
herniation, 529 Central nervous system (CNS) anesthetic principles for, 549 antiarrhythmic adverse effects, 322, 323 cancer epidemiology, 222 cell types in, 493–494 depression, 546 drug name conventions, 253	multiple sclerosis, 523 neurodegenerative disorders, 521 origins, 490 poliomyelitis, 531 production, 493 ventricular system, 504 Cerebrovascular disease diabetes mellitus, 346 Certolizumab, 487 Ceruloplasmin	Cherry hemangiomas, 478 "Cherry red" epiglottis, 142 Cherry-red spot (macula), 538 lysosomal storage disease, 88 Chest pain panic disorder, 563 pneumothorax, 682 Chest wall elastic properties, 665 Chest X-rays	gray baby syndrome, 250 mechanism and use, <b>192</b> pregnancy contraindications, 204 protein synthesis inhibition, 191 Chlordiazepoxide, 546 alcohol withdrawal, 572 Chlorhexidine, 204 Chloride channels cystic fibrosis, 60 Chlorine, 204 Chloroprocaine, 550
herniation, 529 Central nervous system (CNS) anesthetic principles for, 549 antiarrhythmic adverse effects, 322, 323 cancer epidemiology, 222 cell types in, 493–494 depression, 546 drug name conventions, 253 nitrosoureas effect on, 441	multiple sclerosis, 523 neurodegenerative disorders, 521 origins, 490 poliomyelitis, 531 production, 493 ventricular system, 504 Cerebrovascular disease diabetes mellitus, 346 Certolizumab, 487 Ceruloplasmin free radical elimination by, 210	Cherry hemangiomas, 478 "Cherry red" epiglottis, 142 Cherry-red spot (macula), 538 lysosomal storage disease, 88 Chest pain panic disorder, 563 pneumothorax, 682 Chest wall elastic properties, 665 Chest X-rays aortic dissections on, 303	gray baby syndrome, 250 mechanism and use, <b>192</b> pregnancy contraindications, 204 protein synthesis inhibition, 191 Chlordiazepoxide, 546 alcohol withdrawal, 572 Chlorhexidine, 204 Chloride channels cystic fibrosis, 60 Chlorine, 204 Chloroprocaine, 550 Chloroquine, <b>200</b>
herniation, 529 Central nervous system (CNS) anesthetic principles for, 549 antiarrhythmic adverse effects, 322, 323 cancer epidemiology, 222 cell types in, 493–494 depression, 546 drug name conventions, 253 nitrosoureas effect on, 441 origins of, <b>490</b>	multiple sclerosis, 523 neurodegenerative disorders, 521 origins, 490 poliomyelitis, 531 production, 493 ventricular system, 504 Cerebrovascular disease diabetes mellitus, 346 Certolizumab, 487 Ceruloplasmin free radical elimination by, 210 Cervical cancer, 645	Cherry hemangiomas, 478 "Cherry red" epiglottis, 142 Cherry-red spot (macula), 538 lysosomal storage disease, 88 Chest pain panic disorder, 563 pneumothorax, 682 Chest wall elastic properties, 665 Chest X-rays aortic dissections on, 303 balloon heart on, 308	gray baby syndrome, 250 mechanism and use, <b>192</b> pregnancy contraindications, 204 protein synthesis inhibition, 191 Chlordiazepoxide, 546 alcohol withdrawal, 572 Chlorhexidine, 204 Chloride channels cystic fibrosis, 60 Chlorine, 204 Chloroprocaine, 550 Chloroquine, <b>200</b> malaria, 157
herniation, 529 Central nervous system (CNS) anesthetic principles for, 549 antiarrhythmic adverse effects, 322, 323 cancer epidemiology, 222 cell types in, 493–494 depression, 546 drug name conventions, 253 nitrosoureas effect on, 441 origins of, 490 posterior fossa malformations, 491,	multiple sclerosis, 523 neurodegenerative disorders, 521 origins, 490 poliomyelitis, 531 production, 493 ventricular system, 504 Cerebrovascular disease diabetes mellitus, 346 Certolizumab, 487 Ceruloplasmin free radical elimination by, 210 Cervical cancer, 645 carcinogens causing, 225	Cherry hemangiomas, 478 "Cherry red" epiglottis, 142 Cherry-red spot (macula), 538 lysosomal storage disease, 88 Chest pain panic disorder, 563 pneumothorax, 682 Chest wall elastic properties, 665 Chest X-rays aortic dissections on, 303 balloon heart on, 308 eggshell calcification, 677	gray baby syndrome, 250 mechanism and use, <b>192</b> pregnancy contraindications, 204 protein synthesis inhibition, 191 Chlordiazepoxide, 546 alcohol withdrawal, 572 Chlorhexidine, 204 Chloride channels cystic fibrosis, 60 Chlorine, 204 Chloroprocaine, 550 Chloroquine, <b>200</b> malaria, 157 Chlorpheniramine, 686
herniation, 529 Central nervous system (CNS) anesthetic principles for, 549 antiarrhythmic adverse effects, 322, 323 cancer epidemiology, 222 cell types in, 493–494 depression, 546 drug name conventions, 253 nitrosoureas effect on, 441 origins of, 490 posterior fossa malformations, 491, 492	multiple sclerosis, 523 neurodegenerative disorders, 521 origins, 490 poliomyelitis, 531 production, 493 ventricular system, 504 Cerebrovascular disease diabetes mellitus, 346 Certolizumab, 487 Ceruloplasmin free radical elimination by, 210 Cervical cancer, 645 carcinogens causing, 225 epidemiology of, 643	Cherry hemangiomas, 478 "Cherry red" epiglottis, 142 Cherry-red spot (macula), 538 lysosomal storage disease, 88 Chest pain panic disorder, 563 pneumothorax, 682 Chest wall elastic properties, 665 Chest X-rays aortic dissections on, 303 balloon heart on, 308 eggshell calcification, 677 notched ribs on, 299	gray baby syndrome, 250 mechanism and use, <b>192</b> pregnancy contraindications, 204 protein synthesis inhibition, 191 Chlordiazepoxide, 546 alcohol withdrawal, 572 Chlorhexidine, 204 Chloride channels cystic fibrosis, 60 Chlorine, 204 Chloroprocaine, 550 Chloroquine, <b>200</b> malaria, 157 Chlorpheniramine, 686 Chlorpromazine, 573
herniation, 529 Central nervous system (CNS) anesthetic principles for, 549 antiarrhythmic adverse effects, 322, 323 cancer epidemiology, 222 cell types in, 493–494 depression, 546 drug name conventions, 253 nitrosoureas effect on, 441 origins of, 490 posterior fossa malformations, 491,	multiple sclerosis, 523 neurodegenerative disorders, 521 origins, 490 poliomyelitis, 531 production, 493 ventricular system, 504 Cerebrovascular disease diabetes mellitus, 346 Certolizumab, 487 Ceruloplasmin free radical elimination by, 210 Cervical cancer, 645 carcinogens causing, 225	Cherry hemangiomas, 478 "Cherry red" epiglottis, 142 Cherry-red spot (macula), 538 lysosomal storage disease, 88 Chest pain panic disorder, 563 pneumothorax, 682 Chest wall elastic properties, 665 Chest X-rays aortic dissections on, 303 balloon heart on, 308 eggshell calcification, 677	gray baby syndrome, 250 mechanism and use, <b>192</b> pregnancy contraindications, 204 protein synthesis inhibition, 191 Chlordiazepoxide, 546 alcohol withdrawal, 572 Chlorhexidine, 204 Chloride channels cystic fibrosis, 60 Chlorine, 204 Chloroprocaine, 550 Chloroquine, <b>200</b> malaria, 157 Chlorpheniramine, 686
herniation, 529 Central nervous system (CNS) anesthetic principles for, 549 antiarrhythmic adverse effects, 322, 323 cancer epidemiology, 222 cell types in, 493–494 depression, 546 drug name conventions, 253 nitrosoureas effect on, 441 origins of, 490 posterior fossa malformations, 491, 492	multiple sclerosis, 523 neurodegenerative disorders, 521 origins, 490 poliomyelitis, 531 production, 493 ventricular system, 504 Cerebrovascular disease diabetes mellitus, 346 Certolizumab, 487 Ceruloplasmin free radical elimination by, 210 Cervical cancer, 645 carcinogens causing, 225 epidemiology of, 643	Cherry hemangiomas, 478 "Cherry red" epiglottis, 142 Cherry-red spot (macula), 538 lysosomal storage disease, 88 Chest pain panic disorder, 563 pneumothorax, 682 Chest wall elastic properties, 665 Chest X-rays aortic dissections on, 303 balloon heart on, 308 eggshell calcification, 677 notched ribs on, 299 Wegener granulomatosis on, 315	gray baby syndrome, 250 mechanism and use, <b>192</b> pregnancy contraindications, 204 protein synthesis inhibition, 191 Chlordiazepoxide, 546 alcohol withdrawal, 572 Chlorhexidine, 204 Chloride channels cystic fibrosis, 60 Chlorine, 204 Chloroprocaine, 550 Chloroquine, <b>200</b> malaria, 157 Chlorpheniramine, 686 Chlorpromazine, 573 Chlorthalidone, 609
herniation, 529 Central nervous system (CNS) anesthetic principles for, 549 antiarrhythmic adverse effects, 322, 323 cancer epidemiology, 222 cell types in, 493–494 depression, 546 drug name conventions, 253 nitrosoureas effect on, 441 origins of, 490 posterior fossa malformations, 491, 492 regional specification of, 506 shock from injury, 310	multiple sclerosis, 523 neurodegenerative disorders, 521 origins, 490 poliomyelitis, 531 production, 493 ventricular system, 504 Cerebrovascular disease diabetes mellitus, 346 Certolizumab, 487 Ceruloplasmin free radical elimination by, 210 Cervical cancer, 645 carcinogens causing, 225 epidemiology of, 643 HIV-positive adults, 177 hydronephrosis with, 599	Cherry hemangiomas, 478 "Cherry red" epiglottis, 142 Cherry-red spot (macula), 538 lysosomal storage disease, 88 Chest pain panic disorder, 563 pneumothorax, 682 Chest wall elastic properties, 665 Chest X-rays aortic dissections on, 303 balloon heart on, 308 eggshell calcification, 677 notched ribs on, 299 Wegener granulomatosis on, 315 widened mediastinum on, 137	gray baby syndrome, 250 mechanism and use, <b>192</b> pregnancy contraindications, 204 protein synthesis inhibition, 191 Chlordiazepoxide, 546 alcohol withdrawal, 572 Chlorhexidine, 204 Chloride channels cystic fibrosis, 60 Chlorine, 204 Chloroprocaine, 550 Chloroquine, <b>200</b> malaria, 157 Chlorpheniramine, 686 Chlorpromazine, 573 Chlorthalidone, 609 Chocolate agar
herniation, 529 Central nervous system (CNS) anesthetic principles for, 549 antiarrhythmic adverse effects, 322, 323 cancer epidemiology, 222 cell types in, 493–494 depression, 546 drug name conventions, 253 nitrosoureas effect on, 441 origins of, 490 posterior fossa malformations, 491, 492 regional specification of, 506 shock from injury, 310 Central nervous system stimulants,	multiple sclerosis, 523 neurodegenerative disorders, 521 origins, 490 poliomyelitis, 531 production, 493 ventricular system, 504 Cerebrovascular disease diabetes mellitus, 346 Certolizumab, 487 Ceruloplasmin free radical elimination by, 210 Cervical cancer, 645 carcinogens causing, 225 epidemiology of, 643 HIV-positive adults, 177 hydronephrosis with, 599 oncogenic microbes and, 226	Cherry hemangiomas, 478 "Cherry red" epiglottis, 142 Cherry-red spot (macula), 538 lysosomal storage disease, 88 Chest pain panic disorder, 563 pneumothorax, 682 Chest wall elastic properties, 665 Chest X-rays aortic dissections on, 303 balloon heart on, 308 eggshell calcification, 677 notched ribs on, 299 Wegener granulomatosis on, 315 widened mediastinum on, 137 Cheyne-Stokes respirations, 679	gray baby syndrome, 250 mechanism and use, <b>192</b> pregnancy contraindications, 204 protein synthesis inhibition, 191 Chlordiazepoxide, 546 alcohol withdrawal, 572 Chlorhexidine, 204 Chloride channels cystic fibrosis, 60 Chlorine, 204 Chloroprocaine, 550 Chloroquine, <b>200</b> malaria, 157 Chlorpheniramine, 686 Chlorpromazine, 573 Chlorthalidone, 609 Chocolate agar Haemophilus influenzae, 126, 142
herniation, 529 Central nervous system (CNS) anesthetic principles for, 549 antiarrhythmic adverse effects, 322, 323 cancer epidemiology, 222 cell types in, 493–494 depression, 546 drug name conventions, 253 nitrosoureas effect on, 441 origins of, 490 posterior fossa malformations, 491, 492 regional specification of, 506 shock from injury, 310 Central nervous system stimulants, 572	multiple sclerosis, 523 neurodegenerative disorders, 521 origins, 490 poliomyelitis, 531 production, 493 ventricular system, 504 Cerebrovascular disease diabetes mellitus, 346 Certolizumab, 487 Ceruloplasmin free radical elimination by, 210 Cervical cancer, 645 carcinogens causing, 225 epidemiology of, 643 HIV-positive adults, 177 hydronephrosis with, 599 oncogenic microbes and, 226 papillomaviruses, 164	Cherry hemangiomas, 478 "Cherry red" epiglottis, 142 Cherry-red spot (macula), 538 lysosomal storage disease, 88 Chest pain panic disorder, 563 pneumothorax, 682 Chest wall elastic properties, 665 Chest X-rays aortic dissections on, 303 balloon heart on, 308 eggshell calcification, 677 notched ribs on, 299 Wegener granulomatosis on, 315 widened mediastinum on, 137 Cheyne-Stokes respirations, 679 Chiari malformations, 492	gray baby syndrome, 250 mechanism and use, <b>192</b> pregnancy contraindications, 204 protein synthesis inhibition, 191 Chlordiazepoxide, 546 alcohol withdrawal, 572 Chlorhexidine, 204 Chloride channels cystic fibrosis, 60 Chlorine, 204 Chloroprocaine, 550 Chloroquine, <b>200</b> malaria, 157 Chlorpheniramine, 686 Chlorpromazine, 573 Chlorthalidone, 609 Chocolate agar Haemophilus influenzae, 126, 142 Cholangiocarcinomas
herniation, 529 Central nervous system (CNS) anesthetic principles for, 549 antiarrhythmic adverse effects, 322, 323 cancer epidemiology, 222 cell types in, 493–494 depression, 546 drug name conventions, 253 nitrosoureas effect on, 441 origins of, 490 posterior fossa malformations, 491, 492 regional specification of, 506 shock from injury, 310 Central nervous system stimulants, 572 Central pontine myelinolysis, 524	multiple sclerosis, 523 neurodegenerative disorders, 521 origins, 490 poliomyelitis, 531 production, 493 ventricular system, 504 Cerebrovascular disease diabetes mellitus, 346 Certolizumab, 487 Ceruloplasmin free radical elimination by, 210 Cervical cancer, 645 carcinogens causing, 225 epidemiology of, 643 HIV-positive adults, 177 hydronephrosis with, 599 oncogenic microbes and, 226 papillomaviruses, 164 Cervical rib, 448	Cherry hemangiomas, 478 "Cherry red" epiglottis, 142 Cherry-red spot (macula), 538 lysosomal storage disease, 88 Chest pain panic disorder, 563 pneumothorax, 682 Chest wall elastic properties, 665 Chest X-rays aortic dissections on, 303 balloon heart on, 308 eggshell calcification, 677 notched ribs on, 299 Wegener granulomatosis on, 315 widened mediastinum on, 137 Cheyne-Stokes respirations, 679 Chiari malformations, 492 Chickenpox	gray baby syndrome, 250 mechanism and use, <b>192</b> pregnancy contraindications, 204 protein synthesis inhibition, 191 Chlordiazepoxide, 546 alcohol withdrawal, 572 Chlorhexidine, 204 Chloride channels cystic fibrosis, 60 Chlorine, 204 Chloroprocaine, 550 Chloroprocaine, 550 Chloropromazine, 573 Chlorpheniramine, 686 Chlorpromazine, 573 Chlorthalidone, 609 Chocolate agar Haemophilus influenzae, 126, 142 Cholangiocarcinomas Clonorchis sinensis, 160, 161
herniation, 529 Central nervous system (CNS) anesthetic principles for, 549 antiarrhythmic adverse effects, 322, 323 cancer epidemiology, 222 cell types in, 493–494 depression, 546 drug name conventions, 253 nitrosoureas effect on, 441 origins of, 490 posterior fossa malformations, 491, 492 regional specification of, 506 shock from injury, 310 Central nervous system stimulants, 572 Central pontine myelinolysis, 524 Central post-stroke pain syndrome,	multiple sclerosis, 523 neurodegenerative disorders, 521 origins, 490 poliomyelitis, 531 production, 493 ventricular system, 504 Cerebrovascular disease diabetes mellitus, 346 Certolizumab, 487 Ceruloplasmin free radical elimination by, 210 Cervical cancer, 645 carcinogens causing, 225 epidemiology of, 643 HIV-positive adults, 177 hydronephrosis with, 599 oncogenic microbes and, 226 papillomaviruses, 164 Cervical rib, 448 Cervicitis	Cherry hemangiomas, 478 "Cherry red" epiglottis, 142 Cherry-red spot (macula), 538 lysosomal storage disease, 88 Chest pain panic disorder, 563 pneumothorax, 682 Chest wall elastic properties, 665 Chest X-rays aortic dissections on, 303 balloon heart on, 308 eggshell calcification, 677 notched ribs on, 299 Wegener granulomatosis on, 315 widened mediastinum on, 137 Cheyne-Stokes respirations, 679 Chiari malformations, 492 Chickenpox rash, 183	gray baby syndrome, 250 mechanism and use, <b>192</b> pregnancy contraindications, 204 protein synthesis inhibition, 191 Chlordiazepoxide, 546 alcohol withdrawal, 572 Chlorhexidine, 204 Chloride channels cystic fibrosis, 60 Chlorine, 204 Chloroprocaine, 550 Chloroprocaine, 550 Chloropromazine, 573 Chlorpheniramine, 686 Chlopromazine, 573 Chlorthalidone, 609 Chocolate agar Haemophilus influenzae, 126, 142 Cholangiocarcinomas Clonorchis sinensis, 160, 161 hyperbilirubinemia, 393
herniation, 529 Central nervous system (CNS) anesthetic principles for, 549 antiarrhythmic adverse effects, 322, 323 cancer epidemiology, 222 cell types in, 493–494 depression, 546 drug name conventions, 253 nitrosoureas effect on, 441 origins of, 490 posterior fossa malformations, 491, 492 regional specification of, 506 shock from injury, 310 Central nervous system stimulants, 572 Central pontine myelinolysis, 524 Central post-stroke pain syndrome, 515	multiple sclerosis, 523 neurodegenerative disorders, 521 origins, 490 poliomyelitis, 531 production, 493 ventricular system, 504 Cerebrovascular disease diabetes mellitus, 346 Certolizumab, 487 Ceruloplasmin free radical elimination by, 210 Cervical cancer, 645 carcinogens causing, 225 epidemiology of, 643 HIV-positive adults, 177 hydronephrosis with, 599 oncogenic microbes and, 226 papillomaviruses, 164 Cervical rib, 448 Cervicitis sexually transmitted infections, 184	Cherry hemangiomas, 478 "Cherry red" epiglottis, 142 Cherry-red spot (macula), 538 lysosomal storage disease, 88 Chest pain panic disorder, 563 pneumothorax, 682 Chest wall elastic properties, 665 Chest X-rays aortic dissections on, 303 balloon heart on, 308 eggshell calcification, 677 notched ribs on, 299 Wegener granulomatosis on, 315 widened mediastinum on, 137 Cheyne-Stokes respirations, 679 Chiari malformations, 492 Chickenpox rash, 183 VZV, 165	gray baby syndrome, 250 mechanism and use, <b>192</b> pregnancy contraindications, 204 protein synthesis inhibition, 191 Chlordiazepoxide, 546 alcohol withdrawal, 572 Chlorhexidine, 204 Chloride channels cystic fibrosis, 60 Chlorine, 204 Chloroprocaine, 550 Chloroprocaine, 550 Chloropromazine, 573 Chlorpheniramine, 686 Chlorpromazine, 573 Chlorthalidone, 609 Chocolate agar Haemophilus influenzae, 126, 142 Cholangiocarcinomas Clonorchis sinensis, 160, 161 hyperbilirubinemia, 393 oncogenic microbes and, 226
herniation, 529 Central nervous system (CNS) anesthetic principles for, 549 antiarrhythmic adverse effects, 322, 323 cancer epidemiology, 222 cell types in, 493–494 depression, 546 drug name conventions, 253 nitrosoureas effect on, 441 origins of, 490 posterior fossa malformations, 491, 492 regional specification of, 506 shock from injury, 310 Central nervous system stimulants, 572 Central pontine myelinolysis, 524 Central post-stroke pain syndrome, 515 Central precocious puberty, 637	multiple sclerosis, 523 neurodegenerative disorders, 521 origins, 490 poliomyelitis, 531 production, 493 ventricular system, 504 Cerebrovascular disease diabetes mellitus, 346 Certolizumab, 487 Ceruloplasmin free radical elimination by, 210 Cervical cancer, 645 carcinogens causing, 225 epidemiology of, 643 HIV-positive adults, 177 hydronephrosis with, 599 oncogenic microbes and, 226 papillomaviruses, 164 Cervical rib, 448 Cervicitis sexually transmitted infections, 184 Cervix	Cherry hemangiomas, 478 "Cherry red" epiglottis, 142 Cherry-red spot (macula), 538 lysosomal storage disease, 88 Chest pain panic disorder, 563 pneumothorax, 682 Chest wall elastic properties, 665 Chest X-rays aortic dissections on, 303 balloon heart on, 308 eggshell calcification, 677 notched ribs on, 299 Wegener granulomatosis on, 315 widened mediastinum on, 137 Cheyne-Stokes respirations, 679 Chiari malformations, 492 Chickenpox rash, 183 VZV, 165 Chief cells (parathyroid), 332	gray baby syndrome, 250 mechanism and use, 192 pregnancy contraindications, 204 protein synthesis inhibition, 191 Chlordiazepoxide, 546 alcohol withdrawal, 572 Chlorhexidine, 204 Chloride channels cystic fibrosis, 60 Chlorine, 204 Chloroprocaine, 550 Chloroprocaine, 550 Chloropromazine, 570 Chloropheniramine, 686 Chlorpheniramine, 686 Chlorpheniramine, 699 Chocolate agar Haemophilus influenzae, 126, 142 Cholangiocarcinomas Clonorchis sinensis, 160, 161 hyperbilirubinemia, 393 oncogenic microbes and, 226 sclerosing cholangitis, 395
herniation, 529 Central nervous system (CNS) anesthetic principles for, 549 antiarrhythmic adverse effects, 322, 323 cancer epidemiology, 222 cell types in, 493–494 depression, 546 drug name conventions, 253 nitrosoureas effect on, 441 origins of, 490 posterior fossa malformations, 491, 492 regional specification of, 506 shock from injury, 310 Central nervous system stimulants, 572 Central pontine myelinolysis, 524 Central post-stroke pain syndrome, 515 Central precocious puberty, 637 Central retinal artery occlusion, 538	multiple sclerosis, 523 neurodegenerative disorders, 521 origins, 490 poliomyelitis, 531 production, 493 ventricular system, 504 Cerebrovascular disease diabetes mellitus, 346 Certolizumab, 487 Ceruloplasmin free radical elimination by, 210 Cervical cancer, 645 carcinogens causing, 225 epidemiology of, 643 HIV-positive adults, 177 hydronephrosis with, 599 oncogenic microbes and, 226 papillomaviruses, 164 Cervical rib, 448 Cervicitis sexually transmitted infections, 184	Cherry hemangiomas, 478 "Cherry red" epiglottis, 142 Cherry-red spot (macula), 538 lysosomal storage disease, 88 Chest pain panic disorder, 563 pneumothorax, 682 Chest wall elastic properties, 665 Chest X-rays aortic dissections on, 303 balloon heart on, 308 eggshell calcification, 677 notched ribs on, 299 Wegener granulomatosis on, 315 widened mediastinum on, 137 Cheyne-Stokes respirations, 679 Chiari malformations, 492 Chickenpox rash, 183 VZV, 165	gray baby syndrome, 250 mechanism and use, <b>192</b> pregnancy contraindications, 204 protein synthesis inhibition, 191 Chlordiazepoxide, 546 alcohol withdrawal, 572 Chlorhexidine, 204 Chloride channels cystic fibrosis, 60 Chlorine, 204 Chloroprocaine, 550 Chloroprocaine, 550 Chloropromazine, 573 Chlorpheniramine, 686 Chlorpromazine, 573 Chlorthalidone, 609 Chocolate agar Haemophilus influenzae, 126, 142 Cholangiocarcinomas Clonorchis sinensis, 160, 161 hyperbilirubinemia, 393 oncogenic microbes and, 226
herniation, 529 Central nervous system (CNS) anesthetic principles for, 549 antiarrhythmic adverse effects, 322, 323 cancer epidemiology, 222 cell types in, 493–494 depression, 546 drug name conventions, 253 nitrosoureas effect on, 441 origins of, 490 posterior fossa malformations, 491, 492 regional specification of, 506 shock from injury, 310 Central nervous system stimulants, 572 Central pontine myelinolysis, 524 Central post-stroke pain syndrome, 515 Central precocious puberty, 637	multiple sclerosis, 523 neurodegenerative disorders, 521 origins, 490 poliomyelitis, 531 production, 493 ventricular system, 504 Cerebrovascular disease diabetes mellitus, 346 Certolizumab, 487 Ceruloplasmin free radical elimination by, 210 Cervical cancer, 645 carcinogens causing, 225 epidemiology of, 643 HIV-positive adults, 177 hydronephrosis with, 599 oncogenic microbes and, 226 papillomaviruses, 164 Cervical rib, 448 Cervicitis sexually transmitted infections, 184 Cervix	Cherry hemangiomas, 478 "Cherry red" epiglottis, 142 Cherry-red spot (macula), 538 lysosomal storage disease, 88 Chest pain panic disorder, 563 pneumothorax, 682 Chest wall elastic properties, 665 Chest X-rays aortic dissections on, 303 balloon heart on, 308 eggshell calcification, 677 notched ribs on, 299 Wegener granulomatosis on, 315 widened mediastinum on, 137 Cheyne-Stokes respirations, 679 Chiari malformations, 492 Chickenpox rash, 183 VZV, 165 Chief cells (parathyroid), 332	gray baby syndrome, 250 mechanism and use, 192 pregnancy contraindications, 204 protein synthesis inhibition, 191 Chlordiazepoxide, 546 alcohol withdrawal, 572 Chlorhexidine, 204 Chloride channels cystic fibrosis, 60 Chlorine, 204 Chloroprocaine, 550 Chloroprocaine, 550 Chloropromazine, 570 Chloropheniramine, 686 Chlorpheniramine, 686 Chlorpheniramine, 699 Chocolate agar Haemophilus influenzae, 126, 142 Cholangiocarcinomas Clonorchis sinensis, 160, 161 hyperbilirubinemia, 393 oncogenic microbes and, 226 sclerosing cholangitis, 395
herniation, 529 Central nervous system (CNS) anesthetic principles for, 549 antiarrhythmic adverse effects, 322, 323 cancer epidemiology, 222 cell types in, 493–494 depression, 546 drug name conventions, 253 nitrosoureas effect on, 441 origins of, 490 posterior fossa malformations, 491, 492 regional specification of, 506 shock from injury, 310 Central nervous system stimulants, 572 Central pontine myelinolysis, 524 Central post-stroke pain syndrome, 515 Central precocious puberty, 637 Central retinal artery occlusion, 538 Central sleep apnea, 679	multiple sclerosis, 523 neurodegenerative disorders, 521 origins, 490 poliomyelitis, 531 production, 493 ventricular system, 504 Cerebrovascular disease diabetes mellitus, 346 Certolizumab, 487 Ceruloplasmin free radical elimination by, 210 Cervical cancer, 645 carcinogens causing, 225 epidemiology of, 643 HIV-positive adults, 177 hydronephrosis with, 599 oncogenic microbes and, 226 papillomaviruses, 164 Cervicitis sexually transmitted infections, 184 Cervix anatomy of, 625 epithelial histology, 626	Cherry hemangiomas, 478 "Cherry red" epiglottis, 142 Cherry-red spot (macula), 538 lysosomal storage disease, 88 Chest pain panic disorder, 563 pneumothorax, 682 Chest wall elastic properties, 665 Chest X-rays aortic dissections on, 303 balloon heart on, 308 eggshell calcification, 677 notched ribs on, 299 Wegener granulomatosis on, 315 widened mediastinum on, 137 Cheyne-Stokes respirations, 679 Chiari malformations, 492 Chickenpox rash, 183 VZV, 165 Chief cells (parathyroid), 332 Chief cells (stomach), 372 Child abuse, <b>556</b>	gray baby syndrome, 250 mechanism and use, <b>192</b> pregnancy contraindications, 204 protein synthesis inhibition, 191 Chlordiazepoxide, 546 alcohol withdrawal, 572 Chlorhexidine, 204 Chloride channels cystic fibrosis, 60 Chlorine, 204 Chloroprocaine, 550 Chloroprocaine, 550 Chloropromazine, 573 Chlorpheniramine, 686 Chlorpromazine, 573 Chlorthalidone, 609 Chocolate agar Haemophilus influenzae, 126, 142 Cholangiocarcinomas Clonorchis sinensis, 160, 161 hyperbilirubinemia, 393 oncogenic microbes and, 226 sclerosing cholangitis, 395 Cholangitis, 368, 382, 393, 397 Cholecalciferol, 70
herniation, 529 Central nervous system (CNS) anesthetic principles for, 549 antiarrhythmic adverse effects, 322, 323 cancer epidemiology, 222 cell types in, 493–494 depression, 546 drug name conventions, 253 nitrosoureas effect on, 441 origins of, 490 posterior fossa malformations, 491, 492 regional specification of, 506 shock from injury, 310 Central nervous system stimulants, 572 Central pontine myelinolysis, 524 Central post-stroke pain syndrome, 515 Central precocious puberty, 637 Central retinal artery occlusion, 538	multiple sclerosis, 523 neurodegenerative disorders, 521 origins, 490 poliomyelitis, 531 production, 493 ventricular system, 504 Cerebrovascular disease diabetes mellitus, 346 Certolizumab, 487 Ceruloplasmin free radical elimination by, 210 Cervical cancer, 645 carcinogens causing, 225 epidemiology of, 643 HIV-positive adults, 177 hydronephrosis with, 599 oncogenic microbes and, 226 papillomaviruses, 164 Cervical rib, 448 Cervicitis sexually transmitted infections, 184 Cervix anatomy of, 625	Cherry hemangiomas, 478 "Cherry red" epiglottis, 142 Cherry-red spot (macula), 538 lysosomal storage disease, 88 Chest pain panic disorder, 563 pneumothorax, 682 Chest wall elastic properties, 665 Chest X-rays aortic dissections on, 303 balloon heart on, 308 eggshell calcification, 677 notched ribs on, 299 Wegener granulomatosis on, 315 widened mediastinum on, 137 Cheyne-Stokes respirations, 679 Chiari malformations, 492 Chickenpox rash, 183 VZV, 165 Chief cells (parathyroid), 332 Chief cells (stomach), 372	gray baby syndrome, 250 mechanism and use, 192 pregnancy contraindications, 204 protein synthesis inhibition, 191 Chlordiazepoxide, 546 alcohol withdrawal, 572 Chlorhexidine, 204 Chloride channels cystic fibrosis, 60 Chlorine, 204 Chloroprocaine, 550 Chloroprocaine, 550 Chloroprocaine, 570 Chloropheniramine, 686 Chlorpromazine, 573 Chlorthalidone, 609 Chocolate agar Haemophilus influenzae, 126, 142 Cholangiocarcinomas Clonorchis sinensis, 160, 161 hyperbilirubinemia, 393 oncogenic microbes and, 226 sclerosing cholangitis, 395 Cholangitis, 368, 382, 393, 397

FAS1\_2019\_21\_Index\_749-806.indd 759 11/21/19 12:27 PM

Cholecystokinin (CCK) polyposis syndrome, 387 secretory cell location, 373 renal cell carcinoma, 605 Choledocholithiasis, 396 Robertsonian translocation, 64 Cholelithiasis, 395, 396, 397 von Hippel-Lindau disease, 525 acute pancreatitis, 397 Wilson disease, 395 bile ducts and, 368 Chronic bronchitis, 674 biliary cirrhosis and, 396 Chronic disease, anemia of, 421 Chronic gastritis, 379 Crohn disease, 382 hyperbilirubinemia and, 393 Chronic granulomatous disease octreotide and, 400 (CGD) Cholera toxin catalase-positive microbes, 186 lysogenic phage infection, 130 mechanism, 132 immunodeficiencies and, 117 recombinant cytokines for, 121 Cholestasis serum markers, 390 respiratory burst in, 109 Cholesteatomas, 533 Chronic inflammation, 216 Cholesterol Chronic ischemic heart disease, 304 atherosclerosis, 302 Chronic kidney disease in bile, 374 erythropoietin in, 589 cholelithiasis and, 396 hypertension and, 300 lipid-lowering agents, 320 Chronic lymphocytic leukemia synthesis of, 47, 73, 79 (CLL), 432 vitamin B3 effects, 67 immunosuppressants, 120 Cholesteryl ester transfer protein, 93 rituximab for, 443 Cholestyramine, 320 Chronic mesenteric ischemia, 386 Cholinergic agonists, 253 Chronic mucocutaneous candidiasis, Cholinergic effects, 321 cardiac glycosides, 321 Chronic myelogenous leukemia Cholinesterase inhibitors (CML), 433 basophilia caused by, 408 diarrhea with, 249 busulfan for, 441 neuromuscular blockade reversal, chromosomal translocations and, Cholinomimetic agents, 240 glaucoma treatment, 552 imatinib for, 443 oncogenes and, 224 Chondrocalcinosis, 467 Chondrocytes, 458, 462 Chronic myeloproliferative disorders, osteoarthritis, 466 Chondroma, 464 Chronic obstructive pulmonary Chondrosarcoma, 465 disease (COPD) albuterol for, 242 Chordae rupture, 291 B-blockers and, 245 Chorea muscarinic antagonists for, 241 brain lesions, 511 Huntington disease, 520 salmeterol for, 242 movement disorders, 519 Chronic pancreatitis, 397 Choriocarcinoma, 642 pancreatic insufficiency from, 381 Chronic placental insufficiency, hCG in, 633 methotrexate for, 440 Chronic pyelonephritis, 600 testicular, 653 theca-lutein cysts and, 646 Chronic renal failure, 603 Chorionic plate, 617 hyperphosphatemia with, 345 Chorionic somatomammotropin, 634 Chronic respiratory diseases Chorionic villi bronchitis, 674 hydatidiform moles, 642 with chronic inflammatory placenta, 617 diseases, 683 Chorioretinitis death in children, 272 congenital toxoplasmosis, 182 obstructive diseases, 674 pneumoconioses, 675 Choristomas, 220 Choroid layer (ophthalmology) sinusitis, 674 thromboembolism, 679 inflammation, 536 neovascularization, 536 Chronic thromboembolic pulmonary Choroid plexus (CNS), 504 hypertension, 679 Christmas tree distribution, 482 Chronic transplant rejection, 119 Chromaffin cells Churg-Strauss syndrome, 315 autoantibody, 115 diagram, 327 Chvostek sign pheochromocytomas, 350 Chromatin structure, 34 hypocalcemia, 591 Chromatolysis, 495 hypoparathyroidism, 344 Chromogranin, 226, 684 Chylomicrons, 92, 94 Chymotrypsin, 373 Cidofovir, **202** Chromosomal translocations, 434 Chromosome abnormalities congenital microdeletion, 64 Cigarette smoke (carcinogen), 225 gene associations with, 64 Ciguatoxin, 247 hemochromatosis, 395 Cilastatin karyotyping for, 55 imipenem and, 190 nephroblastoma, 606 seizures with, 251 nondisjunction (meiosis), 63 Ciliary ganglia, 539 omphaloceles, 358 Cilia structure, 49

Ciliated cells, 662 Cimetidine, 399 cytochrome P-450 and, 252 gynecomastia and, 649 Cinacalcet, 355 Cinchonism antiarrhythmic causing, 322 neurologic drug reaction, 251 Cingulate gyrus limbic system, 499 Cingulate (subfalcine) herniation, Ciprofloxacin for Crohn disease, 382 cytochrome P-450 and, 252 fluoroquinolones, 195 meningococci, 142 Mycobacterium aviumintracellulare, 196 prophylaxis, 198 Pseudomonas aeruginosa, 143 Circadian rhythm hypothalamic control, 498 sleep physiology, 497 Circle of Willis, **503** saccular aneurysms, 516 Circulatory system fetal, 282 kidneys and, 580 Circumflex femoral artery, 463 Circumoral pallor group A streptococcal pharyngitis, Cirrhosis  $\alpha_1$ -antitrypsin deficiency, 392 alcoholic, 71, 391 bacterial peritonitis (spontaneous), 390 cholelithiasis and, 396 cystic fibrosis, 60 encephalopathy with, 391 esophageal varices and, 377 fructose intolerance, 80 gynecomastia, 649 hemochromatosis, 395 with hepatitis, 389 hepatocellular carcinomas, 392 hyperbilirubinemia in, 393 non-alcoholic fatty liver disease, portal hypertension, 389 serum markers for, 390 Cisplatin mechanism and clinical use, 442 targets of, 438 toxicities of, 251, 444 Citalopram, 575 Citrate synthase, 74 Citrulline, 82 c-KIT gene, 224 CK-MB, 304, 306 Cladribine, 440 for hairy cell leukemia, 432 Clara cells, 661, 662 Clarithromycin Helicobacter pylori, 146 HIV prophylaxis, 198 macrolides, 193 Mycobacterium avium $intracellulare,\,196$ pregnancy use, 204 Clasp knife spasticity, 529 Class IA antiarrhythmics, 322 Class IB antiarrhythmics, 322 Class IC antiarrhythmics, 322

Class III antiarrhythmics, 323 Class IV antiarrhythmics, 324 Classical conditioning, 554 Class switching CD40, 103 thymus-dependent antigens, 105 Clathrin, 47 Claudication atherosclerosis, 302 Buerger disease, 314 giant cell arteritis, 314 Clavicle fractures, 460 Clavulanate Haemophilus influenzae, 142 Clavulanic acid, 189 Clawing (hand), 451 Klumpke palsy, 448 Clearance (CL) of drugs, 231 Clear cell adenocarcinoma, 644 DES and, 656 Cleavage in collagen synthesis, 50 Cleft lip and palate development, 621 Patau syndrome, 63 Pierre Robin sequence, 620 Clevidipine, 318 for hypertensive emergency, 318 Clindamycin bacterial vaginosis, 148 Clostridium difficile and, 138 mechanism and use, 192 metronidazole vs, 192 protein synthesis inhibition, 191 pseudomembranous colitis with, 249 Clinical reflexes, 510 Clinical trials, 256 Clinical vignette strategies, 23 "Clock-face" chromatin, 409, 431 Clofazimine Hansen disease, 141 Mycobacterium leprae, 196 Clomiphene estrogen receptor modulators, 656 hot flashes with, 249 Clonipramine, 575 Clonidine, 240, 243 Cloning methods (laboratory technique), 55 Clonorchis sinensis cholangiocarcinoma, 226 diseases association, 161 trematodes, 160 Clopidogrel, 437 acute coronary syndromes, 307 for ischemic stroke, 512 thrombogenesis and, 411 Closed-angle glaucoma, 536 pilocarpine for, 240 Clostridium botulinum exotoxin production, 132 food poisoning, 178 therapeutic uses, 138 Clostridium difficile antibiotic use, 185 metronidazole, 195 nosocomial infection, 185 PPI association, 138 proton pump inhibitor use, 399 toxins and effects of, 138 vancomycin, 190 watery diarrhea, 179 Clostridium perfringens clindamycin, 192 exotoxin production, 133

FAS1\_2019\_21\_Index\_749-806.indd 760 11/21/19 12:27 PM

Class II antiarrhythmics, 323

food poisoning, 178
toxins produced, 138
traumatic open wound, 186
watery diarrhea, 179
Clostridium spp, 138
anaerobic organism, 127 exotoxins, 138
Clostridium tetani, 138
exotoxin production, 132
Clotrimazole, 199
Clotting factors, 71
Clozapine, 573
agranulocytosis with, 250
Clubbing (digital), 675
cystic fibrosis, 60
Eisenmenger syndrome, 299 Club cells, <b>661</b>
Clue cells
bacterial vaginosis, 148, 181
Cluster A personality disorders
characteristics of, 565
schizoid, 565
schizotypal, 565
Cluster B personality disorders
antisocial, <b>565</b>
borderline, 565 histrionic, 565
narcissistic, 565
Cluster C personality disorders
avoidant, <b>566</b>
dependent, 566
obsessive-compulsive, 566
Cluster headaches, 518, 547
c-MYC gene, 224
CN III, IV, VI palsies, <b>541</b>
CNS (central nervous system) cancer epidemiology, 222
CNS lymphomas
HIV-positive adults, 177
oncogenic microbes and, 226
$CO_2$
production in tissues, 127
Coagulation, 71
Coagulation disorders, <b>426</b>
hemophilia, 426 hereditary thrombosis syndromes,
428
mixed platelet/coagulation, 428
vitamin K and, 426
Coagulation pathways, 412
Coagulative necrosis, 209
MI, 305
Coagulopathy
postpartum hemorrhage, 641 preeclampsia, 643
uterine bleeding with, 633
Coal workers' pneumoconiosis, 677
CoA production, 67, 72
Coarctation of aorta, 299, 300
Cobalamin, 69
Cobblestone mucosa, 382
Cocaine
β-blockers and, 245
coronary vasospasm, 248 intoxication and withdrawal, 571
liver processing of, 367
sympathomimetic action, 242
teratogenicity, 614
Coccidioides spp
silver stain, 125
treatment, 199
Coccidioidomycosis, 151
erythema nodosum and, 482 Coccobacilli, 141
Cocci bacteria
antibiotic tests, 134

Cochlea
CN VIII, 506
inner ear, 533
presbycusis, 533
Codeine, 551 Codman triangle (x-ray), 465
Codominance, 56
Codons
amino acid specification, 37
genetic code features, 37
start and stop, 44 Cofactors
apolipoproteins, 93
biotin, 68, 73
cobalamin, 69
copper, 51
Menkes disease, 51
pantothenic acid, 67 phenylketonuria, 84
pyridoxine, 67
pyruvate dehydrogenase complex,
76
riboflavin, 67
TCA cycle, 77
thiamine, 74 vitamin K, 71
"Coffee bean sign" (X-ray), 386
Cognitive behavioral therapy (CBT),
557, 572
ADHD, 557
anxiety disorders, 562
atypical depression, 561 bipolar disorder, 561
body dysmorphic disorder, 563
obsessive-compulsive disorder, 563
panic disorder, 563
phobias, 563
postpartum depression, 562 PTSD, 563
Cohort studies, 256
Coin lesion (X-ray), 684
x-ray signs, 684
Cola-colored urine, 596
Colchicine, 55
agranulocytosis, 250 calcium pyrophosphate deposition
disease, 467
diarrhea with, 249
gout, 467, 487
microtubules and, 48
myopathy with, 250 "Cold enrichment," 139
Colectomy
adenomatous polyposis, 387
inflammatory bowel disease, 382
Colesevelam, 320
Colestipol, 320 Colistin
polymyxin E, 193
Pseudomonas aeruginosa, 143
Colitis
Clostridium difficile, 138
oral vancomycin, 190
pseudomembranous, <b>179</b> , 188, 192 Collagen, <b>50</b>
decreased/faulty production, 51
epithelial cell junctions and, 474
osteoblast secretion of, 459
polyostotic fibrous dysplasia and, 57
scar formation, 218
synthesis and structure, <b>50</b> in systemic sclerosis, 473
types of, 50
vitamin C in synthesis, 69

vitamin C in synthesis, 69

Collagenase in neutrophils, 406

wound healing, 216

Collapsing pressure (alveoli), 661
Collecting tubules
potassium-sparing diuretics and, 609
Colles fracture, 462
Colliculi, 504
Colon
histology of, 362
ischemia in, 210 Colon cancer, <b>388</b>
adenomatous polyposis and, 387
bevacizumab for, 442
cetuximab for, 442
5-fluorouracil for, 440 incidence/mortality in, 222
irinotecan/topotecan for, 442
Lynch syndrome, 40
molecular pathogenesis of, 389
oncogenes and, 224
serrated polyps and, 387 Staphylococcus gallolyticus and,
137
tumor suppressor genes and, 224
Colonic ischemia, 363, 386
Colonic polyps, <b>387</b> Colony stimulating factor, 121
Colorado tick fever, 167
Color blindness, 197
Colovesical fistulas, 383
Coltivirus, 167
Coma hepatic encephalopathy, 391
herniation syndromes, 529
hyponatremia, 591
rabies, 171
thyroid storm, 342 Toxocara canis, 159
Trypanosoma brucei, 156
Comedones, 477
Commaless genetic code, 37
Comma-shaped rods, 141 Common bile duct, 361, 368
Common cold, 168
Common peroneal nerve, 452, 453
Common variable immunodeficiency
(CVID), 116 Communicating hydrocephalus, 522
Communicating hydrocepharus, 322 Communication with patient, 268
Compartment syndrome, 461
Competence (bacterial genetics), 130
Competitive agonists, 234 Competitive antagonist, 234
Competitive inhibitors, 230
Complement
activation pathways and functions,
106
binding of, 104 disorders of, <b>107</b> –122
eculizumab, 122
endotoxin activation, 133
immunodeficiency infections, 118
immunoglobulin isotypes, 105 innate immunity, 99
splenic dysfunction, 98
transplant rejection, 119
Complement activation inhibition
β-hemolytic bacteria, 135
Complementation (viral), 162 Complete (third-degree) AV block,
295
Complex partial seizures, 517
Complex renal cysts, 604
Compliance (lung), 665 Comprehensive Basic Science
Delicitories Datate Deferies

Examination (CBSE), 11

Comprehensive Basic Science Self-Assessment (CBSSA), 11 Computer-Based Test (CBT) environment of, 3-4 exam schedule for, 7-8 structure of, 3 COMT inhibitors, 548 Conditioning (psychological), 554 Conduct disorder, 557 Conducting zone (respiratory tree), 662 Conduction aphasia, 516 Conductive hearing loss, 533 Condylomata acuminata, 477 sexual transmission, 184 Condylomata lata syphilis, 147, 184 Confidence intervals, 263 Confidentiality, 267 in abuse, 269 behavioral science ethics, 265 exceptions to, 267 Confluence of the sinuses, 503 Confounding bias, 261 Congenital adrenal hyperplasias, **335** Congenital heart disease, 298–300 defect associations, 300 maternal phenylketonuria, 84 pulmonary arterial hypertension, 679 rubella, 182 Congenital hydrocele (scrotal), 652 Congenital hypothyroidism (cretinism), 341 Congenital long QT syndrome, 294 Congenital lung malformations, 660 Congenital malformation mortality, Congenital nevus, 475 Congenital rubella cardiac defect associations, 300 heart murmur, 291 Congenital solitary functioning kidney, **579** Congenital syphilis, 147 Congestion (respiratory) with lobar pneumonia, 683 Congo red stain, 212 Conivaptan, 354 SIADH, 354 Conjoined tendon, 369 Conjugated (direct) hyperbilirubinemia, 393 Conjugate vaccines, 127 Conjugation (bacterial genetics), 130 Conjunctival suffusion/injection eye disorders, 147 Kawasaki disease, 314 Conjunctivitis, 148, 534 adenovirus, 164 chlamydia, 184 gonococcal prophylaxis, 198 Haemophilus influenzae, 142 reactive arthritis, 469 rubeola, 170, 183, 186 Zika virus, 171 Connective tissue diseases aortic dissection and, 303 pulmonary arterial hypertension, 679 thoracic aortic aneurysms and, 302 Connective tissue drug reactions, 250 Conn syndrome, 349, 591 Consensual light reflex, 539 Consent healthcare proxy, 269 minors, 265, 268

FAS1\_2019\_21\_Index\_749-806.indd 761 11/21/19 12:27 PM

Consolidation (lung finding), 680	pulmonary hypertension, 679	C-peptide	Cryptococcus neoformans, 153
lobar pneumonia, 683 Constipation	right ventricular failure, 668 Corpus cavernosum	insulin and, 334 with insulinomas, 351	HIV-positive adults, 177 stains for, 125
anal fissures, 366	lymphatic drainage of, 624	CpG island methylator phenotype	Cryptococcus spp
calcium channel blockers, 318	Corpus luteum	(CIMP), 387	meningitis, 180
Hirschsprung disease, 384	hCG and, 633	Crackles (physical findings), 680	treatment, 199
irritable bowel syndrome, 383	progesterone production, 630	Cranial nerve palsies	urease-positive, 127
laxative treatments, 401	Correlation coefficient, 264	osteopetrosis, 463	Cryptogenic organizing pneumonia,
loperamide, 400	Corticopanillary comotic gradient	Cranial nerves, <b>506</b>	Cryptorohidism 651
ondansetron, 400 ranolazine, 319	Corticopapillary osmotic gradient, 588	common lesions, <b>532</b> functions of, 506	Cryptorchidism, <b>651</b> Sertoli cells and, 628
vincristine, 441	Corticosteroid-binding globulin, 336	locations of, 504	Cryptosporidium spp, 155
Constrictive pericarditis	Corticosteroids	nerve and vessel pathways, <b>505</b>	fluorescent antibody stain, 125
jugular venous pulse in, 287	asthma, 687	nuclei of, <b>505</b>	watery diarrhea, 179
Kussmaul sign, 316	cataracts, 535	pharyngeal arch derivation, 620	Crypts of Lieberkühn, 362
Contact dermatitis, 113	Crohn disease, 382 Cushing syndrome, 348	reflexes of, <b>507</b>	C-section deliveries neonatal flora, 178
Contemplation stage, substance addiction, 568	giant cell arteritis, 314	Craniopharyngioma, 528, 613 hypopituitarism with, 339	neonatal flora with, 178
Continuous heart murmurs, 291	hyperglycemia with, 249	Craniotabes, 463	risk factors after, 640
Contraception	hypopituitarism, 339	C-reactive protein (CRP), 213	Culture requirements
isotretinoin teratogenicity, 614	lymphopenia with, 424	innate immunity and, 99	bacteria, 126
methods for, <b>657</b>	microscopic polyangiitis, 315	Creatine kinase, 203	Cuneiform cartilage, 620
parental consent for minors and, 265	neutrophilia from, 424	Creatinine ACE inhibitor effects, 610	Curling ulcers
progestins for, 657	osteonecrosis, 463 osteoporosis with, 250	glomerular filtration rate and,	gastritis, 379 "Currant jelly" stools, 385, 386
Contractility in cardiac output, 284	pancreatitis with, 249	582	"Currant jelly" sputum
Contraction alkalosis, 60, 587, 588,	for polymyalgia rheumatica, 470	proximal convoluted tubules,	Klebsiella spp, 186
609	Takayasu arteritis, 314	587	Curschmann spirals, 674
Coombs-positive hemolysis	thyroid storm, 342	Creatinine clearance, 582	Cushing disease, 348
α-methyldopa, 243	Wegener granulomatosis, 315	Cre-lox system, 56 Cremasteric muscle and fascia	Cushing-like symptoms, 203
anemia with, 423 Coombs test, 423	Corticotropin-releasing hormone (CRH)	inguinal canal and, 369	Cushing reflex, 296 Cushing syndrome, <b>348</b>
Cooperative kinetics, 230	adrenal cortex regulation of, 327	Cremasteric reflex, 452, 510	anovulation with, 645
COPI/COPII proteins, 47	cortisol regulation, 336	Crepitus	corticosteroids, 120
Copper deficiency, 419	function of, 328	esophageal perforation, 377	eosinopenia, 424
Copper intrauterine device, <b>657</b>	signaling pathways of, 337	in necrotizing fasciitis, 479	paraneoplastic syndrome, 228
Copper metabolism	Cortisol, <b>336</b>	soft tissue, 138	small cell lung cancer, 684
Wilson disease, 395 Copper toxicity, 248	congenital adrenal hyperplasias, 335	Crepitus in necrotizing fasciitis, 479 Crescentic glomerulonephritis, 596	Cushing ulcers gastritis, 379
Coprolalia, 557	in Cushing syndrome, 348	CREST syndrome, 473	Cutaneous anthrax, 137
Copy number variations (CNV), 54	signaling pathways for, 337	autoantibody, 115	edema toxin, 132
Cord factor, 140	Corynebacterium diphtheriae	sclerodermal esophageal	Cutaneous flushing
Cori cycle, 82	culture requirements for, 126	dysmotility, 377	drugs causing, 248
Cori disease, 87 Corkscrew fibers, 528	exotoxin effects, <b>139</b> exotoxin production, 132	Creutzfeldt-Jakob disease, 178, 521	Cutaneous laish maniasis, 159
"Corkscrew" hair, 69	Costovertebral angle tenderness, 601	"Crew cut" (skull X-ray), 422 Cricoid cartilage, 620	Cutaneous leishmaniasis, 158 Cutaneous mycoses, <b>152</b>
Cornea	Co-transporter 2 (SGLT2) inhibitors,	Cricothyroid muscle, 620	Cutaneous paraneoplastic syndromes,
astigmatism, 535	353	Cri-du-chat syndrome, <b>64</b>	228
collagen in, 50	Cough	Crigler-Najjar syndrome, 393, 394	Cutaneous small-vessel vasculitis,
Corneal arcus	ACE inhibitors, 251, 610	Crimean-Congo hemorrhagic fever,	314
familial hypercholesterolemia, 94 hyperlipidemia, 301	chronic bronchitis, 674 gastroesophageal reflux disease,	167 CRISPR/Cas9, <b>53</b>	Cutis aplasia Patau syndrome, 63
Corneal reflex, 507	377	Crohn disease, 382	CXCR4
Corneal vascularization, 67	guaifenesin, 686	azathioprine, 120	viral receptor, 166
Corniculate cartilage, 620	hypersensitivity pneumonitis, 675	B <sub>12</sub> deficiency, 420	CXCR4/CCR5 protein
Coronary arteries	lung cancer, 684	cholelithiasis and, 396	presence on cells, 110
anatomy of, <b>283</b>	nonproductive, 140	natalizumab, 122	Cyanide
atherosclerosis in, 302 Coronary artery disease	staccato, 149 Wegener granulomatosis, 315	spondyloarthritis and, 469 sulfasalazine for, 400	electron transport chain, 78 Cyanide poisoning
atrial fibrillation and, 295	whooping, 132, 143	vitamin B <sub>12</sub> deficiency, 69	vs carbon monoxide poisoning, <b>667</b>
diabetes mellitus and, 346	Councilman bodies	Cromolyn, 687	induced methemoglobinemia, 666
hormonal contraception with, 657	yellow fever, 168	Cross-linking in collagen synthesis, 50	nitroprusside, 318
hypertension and, 300	Countertransference, 554	Cross-over study, 256, 261	treatment for, 248
sudden cardiac death, 304	Courvoisier sign	Cross-sectional studies, <b>256</b>	Cyanosis
Coronary sinus anomalous pulmonary return, 298	pancreatic cancer, 398 Cowpox, 164	Croup, <b>170</b> paramyxoviruses, 167, 169	"blue babies," 298 "blue kids," 299
development, 281	Coxiella burnetii	pulsus paradoxus in, 310	Eisenmenger syndrome, 299
Coronary steal syndrome, 304	animal transmission, 149	CRP and ESR, 214	esophageal atresia, 359
Coronary vasospasm, 248	Q fever, 150	Crust (skin), 475	methemoglobinemia, 666
triptans and, 547	Coxiella spp	basal cell carcinoma, 484	patent ductus arteriosus, 299
Coronaviruses	intracellular organisms, 127	impetigo, 479	pulmonary hypertension, 679
characteristics of, 167 genomes of, 163	Coxsackievirus acute pericarditis, 313	varicella zoster virus, 479 Cryoprecipitate, 429	tetralogy of Fallot, 298 Cyclins, 46
Cor pulmonale, 309, 668	picornavirus, 168	Crypt hyperplasia, 381	Cyclobenzaprine, 551
from obstructive lung disease, 674	presentation, 167	Cryptococcal meningitis, 199	Cyclooxygenase
pneumoconioses, 677	rashes of childhood, 183	Cryptococcosis, 153	aspirin effect on, 411

FAS1\_2019\_21\_Index\_749-806.indd 762 11/21/19 12:27 PM

Cyclooxygenase inhibition	Cytoplasmic membrane (bacterial),	Decussation	De novo synthesis
irreversible, 486	124	in spinal tracts, 509	pyrimidine and purine, <b>36</b> , 73
reversible, 485, 486	Cytoplasmic processing bodies	Deep brachial artery, 455	Dense deposit disease, 596
selective, 486	(P-bodies), 41	Deep inguinal lymph nodes, 624	Dental plaque
Cyclophosphamide, 441	Cytoskeletal elements, <b>48</b>	Deep venous thrombosis (DVT), <b>671</b>	normal flora, 178
hemorrhagic cystitis with, 249 microscopic polyangiitis, 315	Cytotoxic T cells, <b>102</b> cell surface proteins, 110	direct factor Xa inhibitors for, 437 glucagonomas and, 351	viridans streptococci, 128 Dentate line, 366
SIADH with, 249	MHC I and II, 100	heparin for, 436	Dentate nucleus, 499
toxicities of, 444	Cytotrophoblast, 617	tamoxifen/raloxifene and, 443	Dentin
transitional cell carcinoma and,	-)	Deer flies (disease vectors), 159	collagen in, 50
606	D	Defense mechanisms	osteogenesis imperfecta, 51
Wegener granulomatosis, 315	Dabigatran, 435	immature, 554–555	Dentinogenesis imperfecta, 51
Cycloplegia	Dabrafenib, <b>444</b>	mature, 555	Denys-Drash syndrome, 606
atropine, 241	Daclizumab	Defensins, 99	Dependent personality disorder, 566
muscarinic antagonists for, 241 Cyclosporine	targets of, 121	Deferasirox, 248 Deferiprone, 248	Depersonalization/derealization disorder, 558
gingival hyperplasia, 250	Dacrocytes, 414 Dactinomycin, 439	Deferoxamine, 248	panic disorder, 563
gout, 250	RNA polymerase inhibition, 42	Deformation, 613	Depolarizing neuromuscular
immunosuppression, 120	targets of, 438	Degarelix, <b>656</b>	blocking drugs, 551
Cyclothymic disorder, 561	Dactylitis	Degenerate/redundant genetic code, 37	Depressants, intoxication and
Cystathionine, 67	seronegative spondyloarthritis, 469	Degmacytes, 414	withdrawal, 570
Cystathionine synthase deficiency, 84	sickle cell anemia, 422	G6PD deficiency, 79	Depression
Cyst disorders (renal), 604	Dalfopristin	Dehydration	atypical features in, <b>561</b>
Cysteine, 85 Cystic duct, 368	VRE, 198 Danazol, <b>658</b>	diabetic ketoacidosis, 347 filtration changes and, 583	benzodiazepine withdrawal, 570 dissociative identity disorder, 558
Cystic fibrosis, <b>60</b>	pseudotumor cerebri, 521	gout exacerbation, 467	drug therapy, 572
Aspergillus fumigatus, 153	"Dancing eyes, dancing feet," 228	loop diuretics and, 608	electroconvulsive therapy, 562
bronchiectasis, 675	Dandy-Walker syndrome, 492	mannitol and, 607	hyperparathyroidism, 345
chromosome association, 64	Dantrolene, 550, 551	osmotic laxatives, 401	metoclopramide, 400
common organisms, 179	Dapagliflozin, 353	salivary stones with, 376	mirtazapine for, 244
meconium ileus and, 386	Dapsone	shock, 310	neurotransmitters for, 495
N-acetylcysteine, 686	Hansen disease, 141	Dehydrogenases, 73	postpartum, 562
pancreatic insufficiency, 381	hemolysis in G6PD deficiency, 250	Delavirdine	seasonal pattern with, 561
vitamin deficiencies and, 65 Cystine, 598	mechanism and use, <b>194</b> <i>Mycobacterium leprae</i> , 196	HIV therapy, 203 Delirium, <b>558</b>	serotonin-norepinephrine reuptake inhibitors (SNRIs) for, 575
Cystinuria, <b>85</b>	Pneumocystis jirovecii, 154	barbiturate withdrawal, 570	SSRIs for, 575
Cystitis	Daptomycin	diabetic ketoacidosis, 347	Deprivation effects (infants), 556
acute bacterial, 594, 600	mechanism and use, 195	PCP, 571	De Quervain tenosynovitis, 461
squamous cell carcinoma risk, 606	MRSA, 198	thyroid storm, 342	De Quervain thyroiditis, 341
Cytarabine, 440	Darkfield microscopy	Delirium tremens (DTs), <b>569</b> , 570	Dermacentor tick (disease vector), 149
Cytochrome C, 208	for Treponema, 146	δ cells	Dermatitis
Cytochrome P-450 azoles, 199	Darunavir HIV therapy, 203	endocrine pancreas somatostatin production, 371	B-complex deficiency, 65 drug reactions and, 250
barbiturates and, 546	Dasabuvir, 204	somatostatin production, 371	glucagonomas, 351
cimetidine and, 399	Dasatinib, 443	Delta rhythm (EEG), 497	IPEX syndrome, 102
griseofulvin, 200	Datura, 241	Delta virus, 167	type IV hypersensitivity reaction, 113
interactions with, 252	Daunorubicin, 439	Deltoid muscle	vitamin B <sub>5</sub> deficiency, 67
macrolides, 193	dilated cardiomyopathy, 248	axillary nerve injury, 447	vitamin B <sub>7</sub> deficiency, 68
phenobarbital effect on, 544	DCC gene, 224	Erb palsy, 448	Dermatitis herpetiformis, 481
rifamycins, 196	Deacetylation	Delusional disorder, 560	celiac disease and, 381
ritonavir, 203 Cytokeratin, 227	histones, 34 Dead space (lung), 664	Delusions, 559 mesolimbic pathway, 499	Dermatologic lesion terms, <b>475</b> Dermatomes
Cytokines, 101, 108	Deafness	Demeclocycline	landmarks, 510
corticosteroids and, 120	Alport syndrome, 596	diabetes insipidus and, 249, 338	Dermatomyositis, 228
Graves disease and, 342	congenital long QT syndrome, 294	Dementia	autoantibody, 115
rejection reactions, 119	congenital syphilis, 147	HIV-positive adults, 177	Dermatomyositis/polymyositis, 471
type IV hypersensitivity, 113	rubella, 182	metachromatic leukodystrophy, 88	Dermatophytes, <b>152</b>
Cytokinesis, 46	syphilis, 182	neurodegenerative disorders, 520–521	Dermis, 473
Cytomegalovirus (CMV) AIDS retinitis, 165	Deamination base excision repair, 40	prion disease, 178	Descending colon, 360 Desert bumps, 151
cholecystitis and, 396	Death	vitamin B <sub>3</sub> deficiency, 67	Desert rheumatism
clinical significance, 165	aortic dissection in, 303	Demyelinating/dysmyelinating	Coccidioidomycosis, 151
esophagitis and, 377	children, explaining to, 269	disorders, <b>523</b>	Desflurane, 550
HIV-positive adults, 177	common causes, 272	lead poisoning (adult), 425	Desipramine, 575
hyper-IgM syndrome and, 117	sudden cardiac death, 304	metachromatic leukodystrophy, 88	Desloratadine, 686
immunodeficient patients, 118	thyroid storm, 342	progressive multifocal	Desmin, 48, 227
pneumonia, 683 TORCH infection, 182	Death receptor pathway, 207, 208 Debranching enzyme	leukoencephalopathy, 524	Desmopressin central DI, 329
treatment, 202	Cori disease, 87	vitamin B <sub>12</sub> deficiency, 530 Dendritic cells, <b>408</b>	DI treatment, 338
viral receptor, 166	glycogen metabolism, 86	IL-10, 108	for hemophilia, 426
Cytoplasm	Decay-accelerating factor (DAF), 106	innate immunity, 99	Desmosome, 474
cell cycle phase, 46	Deceleration injury, 303	T- and B-cell activation, 102, 103	Desquamation
cytoskeletal elements, 48	Decerebrate (extensor) posturing, 511	Dengue, 167	staphylococcal toxic shock
glycolysis, 76	Decidua basalis, 617	Denial, 554	syndrome, 135
HMP shunt, 79	Decision-making capacity, <b>266</b>	Denosumab, 122	Desvenlafaxine, 575
metabolism in, 72	Decorticate (flexor) posturing, 511	for osteoporosis, 462	Detached retina, 537

FAS1\_2019\_21\_Index\_749-806.indd 763 11/21/19 12:27 PM

Developmental delay fetal alcohol syndrome, 615 renal failure and, 603 Dexamethasone Cushing syndrome diagnosis, 348 Dexlansoprazole, 399 Dexrazoxane, 439 Dextroamphetamine, 572 Dextrocardia, 280 x-ray, 49 Dextromethorphan, 551, 686 DHT (dihydrotestosterone), 622, 636, 639 Diabetes insipidus, 338 antidiuretic hormone in, 329 drug reaction and, 249 lithium, 574 lithium toxicity, 569 potassium-sparing diuretics for, 609 thiazides for, 609 Diabetes mellitus, 346-347 atherosclerosis and, 302 β-blockers and, 245 carpal tunnel syndrome, 459 cataracts and, 535 chronic renal failure and, 603 CN III damage, 541 diabetic ketoacidosis, 347 diabetic retinopathy, 537 Friedreich ataxia, 531 fungal infections, 186 glucagonomas, 351 glucosuria in, 584 hemochromatosis, 395 hepatitis C, 173 hypertension and, 300, 316 management of, 352-353 naming conventions for, 253 nephropathy with, 597 opportunistic infections, 153 pancreatic cancer, 398 polyhydramnios and, 641 in pregnancy, 300 pyelonephritis and, 600 readmissions with, 272 tacrolimus and, 120 teratogenic potential of maternal, therapy management, 352 type 1 vs type 2, 347 urinary tract infections, 181 UTIs and, 600 Diabetes mellitus type 1, 347 autoantibody, 115 HLA subtypes with, 100 Diabetes mellitus type 2, 347 amyloidosis, 212 Diabetic ketoacidosis (DKA), 347 DM type 1 and, 346 ketone bodies, 90 Diabetic nephropathy ACE inhibitors for, 610 Diabetic neuropathy, 575 Diabetic retinopathy, 537 Diagnosis errors, 274 Diagnostic criteria, psychiatric grief, 562 panic disorder, 563 symptom duration and, 564 Diagnostic maneuvers/signs Gower sign, 61 Diagnostic test evaluation, 257 Diagnostic tests/maneuvers laboratory tests in bone disorders, 464 lower extremity, 491 wrist and hand injury, 459

Dialectical behavioral therapy, 565, Dialysis-related amyloidosis, 212 Diamond-Blackfan anemia, 420 Diapedesis, 215 Diaper rash Candida albicans, 153 nystatin, 199 Diaphoresis, 305 acromegaly, 339 Diaphragmatic hernia, 370 Diaphragm structures, 663 Diaphysis, 465 Diarrhea, 117 B-complex deficiency, 65 bismuth/sucralfate for, 399 Campylobacter jejuni, 145 cholera toxin, 132 clindamycin, 192 Clostridium difficile, 138 Cryptosporidium, 155 drug reaction and, 249 ezetimibe, 320 giardiasis, 155 graft-versus-host disease, 119 HIV-positive adults, 17' inflammatory bowel diseases, 382 irritable bowel syndrome, 383 lactase deficiency, 81 lactose intolerance, 381 as laxative adverse effect, 401 leflunomide, 486 loperamide for, 400 magnesium deficiency from, 332 magnesium hydroxide, 399 malabsorption syndromes, 381 metoclopramide, 400 misoprostol, 399 opioids for, 551 organisms causing, 179 pellagra, 67 rice-water, 132 rotavirus, 168 Salmonella, 144 Shigella, 144 thyroid storm and, 342 Vibrio cholerae, 146 VIPomas, 371 vitamin C toxicity, 69 watery, 132 Diastole cardiac cycle, 287 heart failure and, 309 heart murmurs of, 291 heart sounds of, 287 Diazepam, 546 alcohol withdrawal, 572 Diclofenac, 486 Dicloxacillin mechanism and use, 188 Dicrotic notch, 287 Dicyclomine, 241 Didanosine, 203 HIV therapy, 203 pancreatitis, 249 Diencephalon, 490 Diethylcarbamazine antihelminthic, 200 nematode infections, 159 Diethylstilbestrol (DES), 656

teratogenicity, 614

vaginal tumors, 644

Differential media, 126

Diffuse axonal injury, 515

Diffuse cortical necrosis, 602

Diffuse gastric cancer, 379 Diffuse glomerular disorders, 594 Diffuse large B-cell lymphoma (DLBCL), 430, 432 Diffuse partial seizures, 517 Diffuse proliferative glomerulonephritis (DPGN), 596 Diffuse scleroderma, 473 Diffuse stomach cancer, 379 Diffusion-limited gas exchange, 668 DiGeorge syndrome, 344 lymph node paracortex in, 96 thymic shadow in, 98 Digestion malabsorption syndromes, 381 secretory products for, 372-374 ulcerative colitis and, 382 Digestive tract anatomy and histology, 362 Digitalis arrhythmias induced by, 322 contractility effects, 284 hyperkalemia and, 590 toxicity treatment for, 248 Digoxin contractility effects of, 285, 286 for dilated cardiomyopathy, 308 mechanism and clinical use, 321 sodium-potassium pump inhibition, 49 therapeutic index of, 234 toxicity treatment, 324 leflunomide effects, 36, 486 blockers, 253 5α-reductase deficiency, 639 function, 636 sexual determination, 622 drug reaction and, 248 hemochromatosis, 395 muscular dystrophy, 61 wet beriberi, 66 with myocarditis, 313 for arsenic toxicity, 248 for lead poisoning, 248, 419 exotoxins, 130, 131, 132 unvaccinated children, 186 vaccine for, 139 disease association, 161 presentation, 160 vitamin B<sub>12</sub> deficiency, 69, 420 brain stem/cerebellar syndromes,

in botulism, 138 intracranial hypertension, 521 myasthenia gravis, 472 osmotic demyelination syndrome, Dipyridamole for coronary steal syndrome, 304 Direct bilirubin, 375 Direct cholinomimetic agonists, 240 Direct (conjugated) hyperbilirubinemia, 393 Direct Coombs test Type II hypersensitivity, 112 Direct factor Xa inhibitors, 437 Direct fluorescent antibody (DFA) microscopy for Treponema, 146 Direct inguinal hernia, 370 Direct light reflex, 539 Direct sympathomimetics, 242 Direct thrombin inhibitors, 435 Discharge planning, 272 Discolored teeth, 204 Discounted fee-for-service, 271 Disease associations, 161 Disease prevention, **270** Disease vectors Aedes mosquitoes, 168 Anopheles mosquito, 157 armadillos, 149 birds, 148, 149 cats, 149 dogs, 145, 149 fleas, 149, 150 flies, 144, 149 horse flies, 159 Ixodes ticks, 146 rodents, 167 ticks, 146, 150 zoonotic bacteria, 149 Disinfection/sterilization methods, 204 Disinhibited behavior Klüver-Bucy syndrome, 511 Disopyramide, 322 Disorganized thought, 559 Dispersion measures, 262 Displacement, 554 Disruption (morphogenesis), 613 Disruptive mood dysregulation disorder, 557 Disseminated candidiasis, 153 Disseminated intravascular coagulation (DIC), 428 Ebola, 171 endotoxins, 131, 133 meningococci, 142 microangiopathic anemia, 423 Waterhouse-Friderichsen syndrome, 349 Dissociation, 554 Dissociative disorders, 558 amnesia, 558 identity disorder, 558 Distal humerus, 455 Distal interphalangeal (DIP) joints,

Dihydroergotamine, 518 Dihydrofolic acid, 194 Dihydroorotate dehydrogenase Dihydropyridine calcium channel Dihydropyridine receptor, 456 Dihydrorhodamine test, 117 Dihydrotestosterone (DHT) Dihydroxyacetone-P, 80 Disinhibited social engagement, 556 Dilated cardiomyopathy, 308, 309 doxorubicin, 439 Diltiazem, 318 Dimenhydrinate, 686 Dimercaprol acute myelogenous leukemia, 432 for mercury poisoning, 248 Dinitrophenol, 78 Diphenhydramine, 686 Diphenoxylate, 551 Diphtheria Corynebacterium diphtheriae, 139 Diphyllobothrium latum Distal renal tubular acidosis (type 1), Diplococci, 142 Distributive shock, 310 Diplopia Disulfiram alcoholism treatment, 571 central vertigo, 534 ethanol metabolism and, 72 Diffuse esophageal spasm, 377 drug toxicity, 544 disulfiram-like reaction, 251

FAS1 2019 21 Index 749-806.indd 764 11/21/19 12:27 PM

-		_	
Diuresis	Dorsal columns (spinal cord), 508,	multiorgan, <b>251</b>	Dyskinesia
atrial natriuretic peptide, 296	509	musculoskeletal, <b>250</b>	tardive, 251
for shock, 310	thalamic relay for, 498	neurologic, <b>251</b>	Dyslipidemia
Diuretics	Dorsal interossei muscle, 450	renal/genitourinary, <b>251</b>	β-blocker adverse effects, 323
dilated cardiomyopathy, 308	Dorsal motor nucleus, 506	respiratory, <b>251</b>	β-blockers, <b>245</b>
electrolyte changes, <b>609</b>	Dorsal optic radiation, 542	Drug reaction with eosinophilia	familial, 94
glaucoma treatment, 552	Dorsal pancreatic bud, 360	and systemic symptoms	renal failure and, 603
hypertension treatment, 316	Dorsiflexion	(DRESS), 250	vitamin B <sub>3</sub> for, 67
magnesium levels and, 332	common peroneal nerve injury,	Drug-related disorders	Dysmenorrhea
mechanism and clinical use, <b>607</b>	453	myocarditis, 313	copper IUD, 657
pancreatitis, 249	Dosage calculations, <b>231</b>	Drug resistance	primary, 645
for SIADH, 338	Dosage interval, 231	plasmids in, 131	Dysmetria 524
Diverticula, <b>383</b>	Double-blinded studies, 256 Double stranded viruses, 163	Drugs	central vertigo, 534
Diverticulitis, 383 Diverticulosis, 383		cholinomimetic agents, 240	with strokes, 514
	Double Y males, 638	efficacy vs potency, 233	Dyspareunia, 567
Diverticulum, 383	Down syndrome, 63	elimination of, 232, 233 errors in, 274	Dysphagia achalasia, 376
Dizygotic ("fraternal") twins, 616 Dizziness	ALL and AML in, 432 cardiac defect association, 300	patient difficulty with, 268	esophageal pathologies and,
AChE inhibitors, 549	cataracts and, 535	phase I metabolism, 232	377–378
calcium channel blockers, 318	chromosome association, 64	reactions to, 248–251	in botulism, 138
dihydropyridine, 318	hCG in, 633	therapeutic index, 234	osmotic demyelination syndrome,
nitrates, 318	Hirschsprung disease and, 384	toxicities, 248	524
ramelteon, 547	intestinal atresia and, 359	Drug safety	Plummer-Vinson syndrome, 418
ranolazine, 319	Doxazosin, 244	therapeutic index, measurement,	stroke effects, 514
sacubitril, 319	Doxepin, 575	234	Zenker diverticulum, 384
vertigo and, 534	Doxorubicin	Drug trials, 256	Dysplasia
DMPK gene, 61	dilated cardiomyopathy, 248	Drunken sailor gait, 511	bronchopulmonary, 210
DNA	targets, 438	Drusen, 536	cellular adaptive response, 206
cloning methods, 55	toxicities, 444	Dry beriberi, 66	cervical, 645
free radical effect on, 210	Doxycycline	Dry cough with ACE inhibitors, 251	neoplastic progression, 219
introns vs exons, 43	chlamydiae, 148	Dry mouth	Dysplastic kidney
laddering in apoptosis, 208	in gonorrhea treatment, 142	Lambert-Eaton myasthenic	multicystic, 578, 579
methylation in, 34	lymphogranuloma venereum, 149	syndrome, 472	Dyspnea
mutations in, 39	MRSA, 198	Dry skin, 66	α <sub>1</sub> -antitrypsin deficiency, 392
plasmid transfer, 130	Mycoplasma pneumoniae, 150	Dubin-Johnson syndrome, 393, 394	aortic stenosis, 291
repair of, <b>40</b>	rickettsial/vector-borne disease,	Duchenne muscular dystrophy, 61	heart failure, 309
DNÂ ligase	150	inheritance, 61	hypersensitivity pneumonitis, 675
action of, 38	tetracyclines, 192	Ductal adenocarcinomas, 368	hypertrophic cardiomyopathy, 308
DNA mutations	Doxylamine, 686	Ductal carcinoma in situ (DCIS),	in botulism, 138
types of, 39	DPP-4 inhibitors, 353	650	Wegener granulomatosis, 315
DNA polymerase inhibitors, 253	Dressler syndrome, 305, 307, 313	Ductal carcinomas (invasive), 650	Dystonia
DNA polymerases	DRESS syndrome, 250	Ductus arteriosus, 282, 619	acute, 241
action of, 38	Drooling treatment, 241	Ductus deferens	antipsychotics/antiepileptics, 569
DNA repair, <b>40</b>	Drop metastases, 528	embryology, 622	benztropine for, 241
DNA replication, <b>38</b>	Drop seizures, 517	Ductus venosus, 282	Lesch-Nyhan syndrome, 37
DNA topoisomerases, 38	Drug dosages, 234	Duloxetine, 575	movement disorders, 519
DNA transcription	calculations, 231	Duodenal atresia, 359	nigrostriatal pathway and, 499
deacetylation, 34	lethal median, 234	Duodenal ulcer, 380	treatment of, 241
DNA viruses, <b>164</b>	liver disease, 231	Duodenum	Dystrophic calcification, 211, 227
characteristics, <b>163</b>	loading, 231	basal electric rhythm, 362	Dystrophin gene, 61
genomes, 163 Dobutamine, 242	maintenance dose, 231	biliary structures and, 368	Dysuria, 654
	median effective, 234	histology of, 362	cystitis, 181 urinary catheterization, 185
Dogs (disease vectors) 145, 149	renal disease, 231 toxic dose, 234	location, 360	UTIs causing, 600
Dogs (disease vectors), 145, 149 Dolutegravir, 203	Drug elimination, 231	secretory cells, 373 Duplex collecting system, <b>579</b>	C 1 13 Cattoring, 000
Dominant inheritance, 59	Drug-induced lupus, 250	Dural venous sinuses, <b>503</b>	E
Dominant negative mutations, 57	Drug interactions	Dura mater, 496	– Ear
Donepezil, 240, 549	additive, type, 235	Dwarfism	pharyngeal pouch derivation, 621
Do not resuscitate (DNR) order, 266	antagonistic, type, 235	achondroplasia, 462	Eardrum, 533
Dopamine, 242	permissive, type 235	D-xylose test, 381	Early complement deficiencies (C1-
basal ganglia, 500	potentiation, type, 235	Dynein	C4), 107
bupropion effect, 576	synergistic, type, 235	movement of, 48	Eating disorders
changes with disease, 495	tachyphylactic, type, 235	Dynein motors, 171	anovulation and, 645
function of, 328	Drug metabolism, 232	Dysarthria, 516	binge-eating disorder, 567
Huntington disease, 520	cytochrome P-450 dependent,	Friedreich ataxia as, 531	bulimia nervosa, 567
kidney functions and, 589	232	in botulism, 138	characteristics of, 567
L-DOPA, 548, 549	geriatric patients in, 232	osmotic demyelination syndrome,	pica, 567
MAO inhibition, 549, 575	Drug name conventions, <b>253</b> –255	524	Eaton agar
Parkinson disease, 548	Drug overdoses	Dysbetalipoproteinemia, 94	culture requirements, 126
PCT secretion of, 589	of weak acids, 233	Dysentery	Ebola virus, 167, <b>171</b>
pheochromocytoma secretion, 350	of weak bases, 233	Entamoeba histolytica, 179	Ebstein anomaly, 281, 298, 300
vitamin B <sub>6</sub> and, 67	Drug reactions	Escherichia coli, 145	lithium side effect, 574
Dopamine agonists, 330, 339, 548	cardiovascular, 248	Shigella spp, 132, 144, 179	E-cadherin, 219, 474
Dopamine receptors, 238	endocrine/reproductive, <b>249</b>	Dysfunctional uterine bleeding, 633	ECF
Dopaminergic pathways, <b>499</b>	gastrointestinal, 249	Dysgerminoma, 647	body compartments of, 231
Dornase alfa (DNAse), 60	hematologic, <b>250</b>	Dysgeusia, 71	Echinocandins, 200

FAS1\_2019\_21\_Index\_749-806.indd 765 11/21/19 12:27 PM

discase association, 161 Ego defermas, 554, 555 Ego-dystonic behavior, 563 Ego-dystonic behavior, 565, 566 Elempta, 300, 643 Elementary, 143 E	Echinococcus granulosus	EGFK gene, 684	Emancipated minors, 265	prion disease, 1/8
bekinners, 414- Eigo-dastonic behavior, 505 Echoramons, 167, 168 Echinopis, 300, 643 Echinopis, 300, 643 Echinopis, 300, 643 Echinopis, 300, 643 Echinopis, 300, 643 Echinopis, 300, 643 Echinopis, 300, 643 Echinopis, 300, 643 Echinopis, 300, 643 Echinopis, 300, 643 Echinopis, 300, 643 Echinopis, 300, 643 Echinopis, 300, 643 Echinopis, 300, 643 Echinopis, 300, 643 Echinopis, 300, 643 Echinopis, 300, 643 Echinopis, 300, 643 Echinopis, 300, 643 Echinopis, 300, 643 Echinopis, 300, 643 Echinopis, 300, 643 Echinopis, 300, 643 Echinopis, 300, 643 Echinopis, 300, 643 Echinopis, 300, 643 Echinopis, 300, 643 Echinopis, 300, 643 Echinopis, 300, 643 Echinopis, 300, 643 Echinopis, 300, 643 Echinopis, 300, 643 Echinopis, 300, 643 Echinopis, 300, 643 Echinopis, 300, 643 Echinopis, 300, 643 Echinopis, 300, 643 Echinopis, 300, 643 Echinopis, 300, 643 Echinopis, 300, 643 Echinopis, 300, 643 Echinopis, 300, 643 Echinopis, 300, 643 Echinopis, 300, 643 Echinopis, 300, 643 Echinopis, 300, 643 Echinopis, 300, 643 Echinopis, 300, 643 Echinopis, 300, 644 Echinopis, 300, 644 Echinopis, 300, 644 Echinopis, 300, 644 Echinopis, 300, 644 Echinopis, 300, 644 Echinopis, 300, 644 Echinopis, 300, 644 Echinopis, 300, 644 Echinopis, 300, 644 Echinopis, 300, 644 Echinopis, 300, 644 Echinopis, 300, 644 Echinopis, 300, 644 Echinopis, 300, 644 Echinopis, 300, 644 Echinopis, 300, 644 Echinopis, 300, 644 Echinopis, 300, 644 Echinopis, 300, 644 Echinopis, 300, 644 Echinopis, 300, 644 Echinopis, 300 Echinopis, 300, 644 Echinopis, 300, 644 Echinopis, 300, 644 Echinopis, 300, 644 Echinopis, 300, 644 Echinopis, 300, 644 Echinopis, 300, 644 Echinopis, 300, 644 Echinopis, 300, 644 Echinopis, 300, 644 Echinopis, 300, 644 Echinopis, 300, 644 Echinopis, 300, 644 Echinopis, 300, 644 Echinopis, 300, 644 Echinopis, 300, 644 Echinopis, 300, 644 Echinopis, 300, 644 Echinopis, 300, 644 Echinopis, 300, 644 Echinopis, 300, 644 Echinopis, 300, 644 Echinopis, 300, 644 Echinopis, 300, 644 Echinopis, 300, 644 Echinopis, 300, 644 Echinopis, 300, 644 Echinopis, 300, 644 Echino	cestodes, 160	"Eggshell" calcification, 677	EMB agar	renal failure, 603
Febrobinshin, 57 (20 Expostration behavior, 55, 556 Edinos Dandon so unbone febroary, 516 Edinos Sandonos app. 143 Poeudonosa spp. 143 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa spp. 145 Poeudonosa				
Eckanomia, 300, c91 Beach annual, 300, c91 Beach annual, 300, c91 Beach annual, 41 Beach annual, 41 Beach annual, 42 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach annual, 43 Beach an				
picampains, 167, 168 Cellingups, 200, 641 Cellingups, 200, 642 Cellingups, 200, 642 Cellingups, 200, 643 Cellingups, 200, 643 Cellingups, 200, 644 Cellingups, 200, 644 Cellingups, 200, 644 Cellingups, 200, 644 Cellingups, 200, 644 Cellingups, 200, 644 Cellingups, 200, 644 Cellingups, 200, 644 Cellingups, 200, 644 Cellingups, 200, 644 Cellingups, 200, 644 Cellingups, 200, 644 Cellingups, 200, 644 Cellingups, 200, 644 Cellingups, 200, 644 Cellingups, 200, 644 Cellingups, 200, 644 Cellingups, 200, 644 Cellingups, 200, 644 Cellingups, 200, 644 Cellingups, 200, 644 Cellingups, 200, 644 Cellingups, 200, 644 Cellingups, 200, 644 Cellingups, 200, 644 Cellingups, 200, 644 Cellingups, 200, 644 Cellingups, 200, 644 Cellingups, 200, 644 Cellingups, 200, 644 Cellingups, 200, 644 Cellingups, 200, 644 Cellingups, 200, 644 Cellingups, 200, 644 Cellingups, 200, 644 Cellingups, 200, 644 Cellingups, 200, 644 Cellingups, 200, 644 Cellingups, 200, 644 Cellingups, 200, 644 Cellingups, 200, 644 Cellingups, 200, 644 Cellingups, 200, 644 Cellingups, 200, 644 Cellingups, 200, 644 Cellingups, 200, 644 Cellingups, 200, 644 Cellingups, 200, 644 Cellingups, 200, 644 Cellingups, 200, 644 Cellingups, 200, 644 Cellingups, 200, 644 Cellingups, 200, 644 Cellingups, 200, 644 Cellingups, 200, 644 Cellingups, 200, 644 Cellingups, 200, 644 Cellingups, 200, 644 Cellingups, 200, 644 Cellingups, 200, 644 Cellingups, 200, 644 Cellingups, 200, 644 Cellingups, 200, 644 Cellingups, 200, 644 Cellingups, 200, 644 Cellingups, 200, 644 Cellingups, 200, 644 Cellingups, 200, 644 Cellingups, 200, 644 Cellingups, 200, 644 Cellingups, 200, 644 Cellingups, 200, 644 Cellingups, 200, 644 Cellingups, 200, 644 Cellingups, 200, 644 Cellingups, 200, 644 Cellingups, 200, 644 Cellingups, 200, 644 Cellingups, 200, 644 Cellingups, 200, 644 Cellingups, 200, 644 Cellingups, 200, 644 Cellingups, 200, 644 Cellingups, 200, 644 Cellingups, 200, 644 Cellingups, 200, 644 Cellingups, 200, 644 Cellingups, 200, 644 Cellingups, 200, 644 Cellingups, 200, 644 Cellingups, 200, 644 Cellingup				
hechampia, 300, 643 Excellentame augmentonum, 145 Excellentame augmentonum, 145 Excellentame augmentonum, 145 Excellentame augmentonum, 145 Excellentame augmentonum, 145 Excellentame augmentonum, 145 Excellentame augmentonum, 145 Excellentame, 146 Excellentame, 146 Excellentame, 146 Excellentame, 146 Excellentame, 146 Excellentame, 146 Excellentame, 146 Excellentame, 146 Excellentame, 147 Excellentame, 147 Excellentame, 147 Excellentame, 147 Excellentame, 147 Excellentame, 147 Excellentame, 147 Excellentame, 147 Excellentame, 147 Excellentame, 147 Excellentame, 147 Excellentame, 147 Excellentame, 147 Excellentame, 147 Excellentame, 147 Excellentame, 147 Excellentame, 147 Excellentame, 147 Excellentame, 147 Excellentame, 147 Excellentame, 147 Excellentame, 147 Excellentame, 147 Excellentame, 147 Excellentame, 147 Excellentame, 147 Excellentame, 147 Excellentame, 147 Excellentame, 147 Excellentame, 147 Excellentame, 147 Excellentame, 147 Excellentame, 147 Excellentame, 147 Excellentame, 147 Excellentame, 147 Excellentame, 147 Excellentame, 147 Excellentame, 147 Excellentame, 147 Excellentame, 147 Excellentame, 147 Excellentame, 147 Excellentame, 147 Excellentame, 147 Excellentame, 147 Excellentame, 147 Excellentame, 147 Excellentame, 147 Excellentame, 147 Excellentame, 147 Excellentame, 147 Excellentame, 147 Excellentame, 147 Excellentame, 147 Excellentame, 147 Excellentame, 147 Excellentame, 147 Excellentame, 147 Excellentame, 147 Excellentame, 147 Excellentame, 147 Excellentame, 147 Excellentame, 147 Excellentame, 147 Excellentame, 147 Excellentame, 147 Excellentame, 147 Excellentame, 147 Excellentame, 147 Excellentame, 147 Excellentame, 147 Excellentame, 147 Excellentame, 147 Excellentame, 147 Excellentame, 147 Excellentame, 147 Excellentame, 147 Excellentame, 147 Excellentame, 147 Excellentame, 147 Excellentame, 147 Excellentame, 147 Excellentame, 147 Excellentame, 147 Excellentame, 147 Excellentame, 147 Excellentame, 147 Excellentame, 147 Excellentame, 147 Excellentame, 147 Excellentame, 147 Excellentame, 14				
real-point gaugemenoum, 143 Debedomenous pp. 143 Debedomenous pp. 143 Debedomenous pp. 143 Debedomenous pp. 143 Debedomenous pp. 143 Debedomenous pp. 143 Debedomenous pp. 143 Debedomenous pp. 143 Debedomenous pp. 143 Debedomenous pp. 143 Debedomenous pp. 143 Debedomenous pp. 143 Debedomenous pp. 143 Debedomenous pp. 143 Debedomenous pp. 143 Debedomenous pp. 143 Debedomenous pp. 143 Debedomenous pp. 143 Debedomenous pp. 143 Debedomenous pp. 143 Debedomenous pp. 143 Debedomenous pp. 143 Debedomenous pp. 143 Debedomenous pp. 143 Debedomenous pp. 143 Debedomenous pp. 143 Debedomenous pp. 143 Debedomenous pp. 143 Debedomenous pp. 143 Debedomenous pp. 143 Debedomenous pp. 143 Debedomenous pp. 143 Debedomenous pp. 143 Debedomenous pp. 143 Debedomenous pp. 143 Debedomenous pp. 143 Debedomenous pp. 143 Debedomenous pp. 143 Debedomenous pp. 143 Debedomenous pp. 143 Debedomenous pp. 143 Debedomenous pp. 143 Debedomenous pp. 143 Debedomenous pp. 144 Debedomenous pp. 144 Debedomenous pp. 144 Debedomenous pp. 144 Debedomenous pp. 144 Debedomenous pp. 144 Debedomenous pp. 144 Debedomenous pp. 144 Debedomenous pp. 144 Debedomenous pp. 144 Debedomenous pp. 144 Debedomenous pp. 144 Debedomenous pp. 144 Debedomenous pp. 144 Debedomenous pp. 144 Debedomenous pp. 144 Debedomenous pp. 144 Debedomenous pp. 144 Debedomenous pp. 144 Debedomenous pp. 144 Debedomenous pp. 144 Debedomenous pp. 144 Debedomenous pp. 144 Debedomenous pp. 144 Debedomenous pp. 144 Debedomenous pp. 144 Debedomenous pp. 144 Debedomenous pp. 144 Debedomenous pp. 144 Debedomenous pp. 144 Debedomenous pp. 144 Debedomenous pp. 144 Debedomenous pp. 144 Debedomenous pp. 144 Debedomenous pp. 144 Debedomenous pp. 144 Debedomenous pp. 144 Debedomenous pp. 144 Debedomenous pp. 144 Debedomenous pp. 144 Debedomenous pp. 144 Debedomenous pp. 144 Debedomenous pp. 144 Debedomenous pp. 144 Debedomenous pp. 144 Debedomenous pp. 144 Debedomenous pp. 144 Debedomenous pp. 144 Debedomenous pp. 144 Debedomenous pp. 144 Debedomenous pp. 144 Debedomenous pp. 144 Debedomenous pp. 144 De				
December of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Content of the Conte				
beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachial clefs, 619 beachi	Ecthyma gangrenosum, 143		pulmonary, 310	Endocardial fibroelastosis, 308
Educine superance, 61 derionities of, 619 derionities of, 619 derionities of, 619 derionities of, 619 derionities of, 619 derionities of, 619 derionities of, 619 derionities of, 619 derionities of, 619 derionities of, 619 derionities of, 619 derionities of, 619 derionities of, 619 derionities of, 619 derionities of, 619 derionities of, 619 derionities of, 619 derionities of, 619 derionities of, 619 derionities of, 619 derionities of, 619 derionities of, 627 sperm pathway in, 626 Epiculation immeration of, 627 sperm pathway in, 626 Epiculation immeration of, 627 sperm pathway in, 626 Epiculation immeration of, 627 sperm pathway in, 626 Epiculation immeration of, 627 sperm pathway in, 626 Epiculation immeration of, 627 sperm pathway in, 626 Epiculation immeration of, 627 sperm pathway in, 626 Epiculation immeration of, 627 sperm pathway in, 626 Epiculation immeration of, 627 sperm pathway in, 626 Epiculation immeration of, 627 sperm pathway in, 626 Epiculation immeration of, 627 sperm pathway in, 626 Epiculation immeration of, 627 sperm pathway in, 626 Epiculation immeration of, 627 sperm pathway in, 626 Epiculation immeration of, 627 sperm pathway in, 626 Epiculation immeration of, 627 sperm pathway in, 626 Epiculation immeration of, 627 sperm pathway in, 626 Epiculation immeration of, 627 sperm pathway in, 626 Epiculation immeration of, 627 sperm pathway in, 626 Epiculation immeration of, 627 sperm pathway in, 626 Epiculation immeration of, 627 sperm pathway in, 626 Epiculation immeration of, 627 sperm pathway in, 626 Epiculation immeration of, 627 sperm pathway in, 626 Epiculation immeration of, 627 sperm pathway in, 626 Epiculation immeration of, 627 sperm pathway in, 626 Epiculation immeration of, 627 sperm pathway in, 626 Epiculation and immeration of, 627 sperm pathway in, 626 Epiculation and immeration of, 627 sperm pathway in, 626 Epiculation and immeration of, 627 sperm pathway in, 626 Epiculation and immeration of, 627 sperm pathway in, 626 Epiculation and immeration of, 627 sperm pathway in, 626 Epicu	Pseudomonas spp, 143			
branchial clefts, 619 derivatives of, 613 Ectopa pregnancy, 641 appendixis differential diagnosis, 162 Ectopa pregnancy, 641 appendixis differential diagnosis, 163 Ectopa pregnancy, 641 Ectopa pregnancy, 641 Ectopa pregnancy, 641 Extragence syndrome, 99 methotecate for, 440 salpingtis and, 155 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculiza	Ectocervix, 626	heart murmur with, 291	Emboliform nucleus, 499	bacterial, 311
branchial clefts, 619 derivatives of, 613 Ectopa pregnancy, 641 appendixis differential diagnosis, 162 Ectopa pregnancy, 641 appendixis differential diagnosis, 163 Ectopa pregnancy, 641 Ectopa pregnancy, 641 Ectopa pregnancy, 641 Extragence syndrome, 99 methotecate for, 440 salpingtis and, 155 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculizamab, 125 Eculiza	Ectoderm	Ehrlichia spp	Embryogenesis	Candida albicans, 153
Ectopairs personave, 641 apprendictis differential diagnosis, 283  Chilamytha truchomatis, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation, 149 personation,	branchial clefts, 619	animal transmission, 149	genes involved in, 612	coarctation of aorta, 299
Ectopair pregnancy, 641 appendictis differential diagnosis, 195 fedebase produced in debate control of 6.77 mineration of 6.77 mineration of 6.79 methotreate for, 440 applied truchomatis, 149 methotreate for, 440 applied to the control of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.77 mineration of 6.	derivatives of, 613	Ehrlichia chaffeensis, 149	intrinsic pathway and, 208	Coxiella burnetii, 150
Eketopic pregnancy, 641 agpondicitis differential diagnosis, 353 CMamydia teachomatis, 149 bCG in, 633 CMangoner syndrome, 249 Escalation of Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the Company of the		Gram stain, 125		
appendictins differential diagnosis, 383 Collamydia trachomatis, 149 Execution of 627 spern pathway in, 626 Eliculation disc, 440 salpingits and, 185 Continuon discontinuon, 187 alonjic demailitis, 477 elocitariums, 127 alonjic demailitis, 477 elocitariums, 175 type I lipherensitivity, 112 Viskota-Malcho syndrome, 175 type I lipherensitivity, 112 Collegia acute postbreptoeoccal goldinorphinitis, 596 Arthus reaction, 175 expanding fluid exchange and, 297 datanzo f, 638 diabetic ketoacidosis, 317 endotoxins, 133 fluidrocortisone, 354 heart failure and, 399 with hyperaldosteronism, 349 animunosuppressmits, 120 Exercisone and, 399 with hyperaldosteronism, 349 animunosuppressmits, 120 Exercisone and, 399 every hyperaldosteronism, 396 immunosuppressmits, 120 Exercisone and, 399 with hyperaldosteronism, 396 immunosuppressmit, 120 Exercisone and, 399 with hyperaldosteronism, 396 immunosuppressmits, 120 Exercisone and, 399 with hyperaldosteronism, 396 immunosuppressmits, 120 Exercisone and, 399 with hyperaldosteronism, 396 immunosuppressmits, 120 Exercisone and, 399 with hyperaldosteronism, 396 immunosuppressmits, 120 Exercisone and, 399 with hyperaldosteronism, 396 immunosuppressmits, 120 Exercisone and, 399 with hyperaldosteronism, 396 immunosuppressmits, 120 Exercisone and, 399 with hyperaldosteronism, 396 immunosuppressmits, 120 Exercisone and, 399 vasogenic, 496 were therefore, 66 Friedial elispides, 390 pentides and the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the second of the sec				
Signature for the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the control of the con	1 1 0 1 2			
Chilamotha trachomaths, 149 More thanks of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the composition of the comp	11			
bCG iii, 633 Kartagener syndrome, 49 methoteraste for, 440 saphinglist and, 185 Eculizumah, 122 Eczema autopic dermatitis, 477 activity in emphysema, 674 Elastic recroll (lung and chest wall), paper 1 hypersensitivity, 12 Wiskotk-lddrich syndrome, 117 Edema acute postkreptoecoccal glomerulonephrinis, 596 Arthus reaction, 113 calcium channol blockes, 318 capillary fluid exchange and, 297 danazol, 658 dabetic ketoacidosis, 347 endotoxins, 135 dabetic ketoacidosis, 347 endotoxin, 313, 354 fluidrocortisore, 359 diabetic ketoacidosis, 347 endotoxin, 319, 010 projiberal, 390, 610 politius, 309 pseudoephedrine/phenylephrine, 668 Pirchanelis spirals, 199 Electromerophalogram (EFCC) Electromerophalogram (EFCC) Electromerophalogram (EFCC) Electromerophalogram (EFCC) Electromerophalogram (EFCC) Electromerophalogram (EFCC) Electromerophalogram (EFCC) Electromerophalogram (EFCC) Electromerophalogram (EFCC) Electromerophalogram (EFCC) Electromerophalogram (EFCC) Electromerophalogram (EFCC) Electromerophalogram (EFCC) Electromerophalogram (EFCC) Electromerophalogram (EFCC) Electromerophalogram (EFCC) Electromerophalogram (EFCC) Electromerophalogram (EFCC) Electromerophalogram (EFCC) Electromerophalogram (EFCC) Electromerophalogram (EFCC) Electromerophalogram (EFCC) Electromerophalogram (EFCC) Electromerophalogram (EFCC) Electromerophalogram (EFCC) Electromerophalogram (EFCC) Electromerophalogram (EFCC) Electromerophalogram (EFCC) Electromerophalogram (EFCC) Electromerophalogram (EFCC) Electromerophalogram (EFCC) Electromerophalogram (EFCC) Electromerophalogram (EFCC) Electromerophalogram (EFCC) Electromerophalogram (EFCC) Electromerophalogram (EFCC) Electromerophalogram (EFCC) Electromerophalogram (EFCC) Electromerophalogram (EFCC) Electromerophalogram (EFCC) Electromerophalogram (EFCC) Electromerophalogram (EFCC) Electromerophalogram (EFCC) Electromerophalogram (EFCC) Electromerophalogram (EFCC) Electromerophalogram (EFCC) Electromerophalogram (EFCC) Electromerophalogram (EFCC) Electromerophalogram (EFCC) Electromerophalogra				
Existragence syndrome, 49 metholoresate for, 440 salpingitis and, 185 embryology of, 622 embryology of, 622 embryology of, 622 embryology of, 622 embryology of, 622 embryological, 490–492 pancreas and spleen, 159, 360 equation for, 225 elastase, 373 eactivity in emphysema, 674 elastic recoil (lung and chest wall), 62 elastic recoil (lung and chest wall), 62 elastic recoil (lung and chest wall), 62 elastic recoil (lung and chest wall), 62 elastic recoil (lung and chest wall), 62 elastic recoil (lung and chest wall), 62 elastic recoil (lung and chest wall), 62 elastic recoil (lung and chest wall), 63 educate, 373 eactivity in emphysema, 674 elastic recoil (lung and chest wall), 62 elastic recoil (lung and chest wall), 63 educate, 373 eactivity in emphysema, 674 elastic recoil (lung and chest wall), 64 elastic recoil (lung and chest wall), 64 elastic recoil (lung and chest wall), 64 elastic recoil (lung and chest wall), 64 elastic recoil (lung and chest wall), 64 elastic recoil (lung and chest wall), 64 elastic recoil (lung and chest wall), 64 elastic recoil (lung and chest wall), 64 elastic recoil (lung and chest wall), 64 elastic recoil (lung and chest wall), 64 elastic recoil (lung and chest wall), 64 elastic recoil (lung and chest wall), 64 elastic recoil (lung and chest wall), 64 elastic recoil (lung and chest wall), 64 elastic recoil (lung and chest wall), 64 elastic recoil (lung and chest wall), 64 elastic recoil (lung and chest wall), 64 elastic recoil (lung and chest wall), 64 elastic recoil (lung and chest wall), 64 elastic recoil (lung and chest wall), 64 elastic recoil (lung and chest wall), 65 elastic recoil (lung and chest wall), 65 elastic recoil (lung and chest wall), 65 elastic recoil (lung and chest wall), 65 elastic recoil (lung and chest wall), 65 elastic recoil (lung and chest wall), 65 elastic recoil (lung and chest wall), 65 elastic recoil (lung and chest wall), 65 elastic recoil (lung and chest wall), 65 elastic recoil (lung and chest wall), 65 elastic recoil (lung and chest wall), 65 elast			<u> </u>	
methorecate for, 440 splingitis and, 185 Excilizamab, 122 Excerna adaptic dermatitis, 477 eccematous dermatitis, 477 eccematous dermatitis, 477 eccematous dermatitis, 475 pherilytektomuria, 84 skin scales in, 147 externa adaptic dermatitis, 475 pherilytektomuria, 84 skin scales in, 147 externa adaptic dermatitis, 475 pherilytektomuria, 84 skin scales in, 147 externa adaptic dermatitis, 475 externativity in emphysema, 674 ellastic record (ling and chest wall), 665 Elastin externativity, 112 tellema cauthe poststreptococcal glomerulonephritis, 596 Arthis reaction, 113 each externation of, 187 exaltis reaction, 187 exaltis reaction, 187 exaltis reaction, 187 exaltis reaction, 187 exaltis reaction, 187 exaltis reaction, 187 exaltis reaction, 187 exaltis reaction, 187 exaltis reaction, 187 exaltis reaction, 187 exaltis reaction, 187 exaltis reaction, 187 exaltis reaction, 187 exaltis reaction, 187 exaltis reaction, 187 exaltis reaction, 187 exaltis reaction, 187 exaltis reaction, 187 exaltis reaction, 187 exaltis reaction, 187 exaltis reaction, 187 exaltis reaction, 187 exaltis reaction, 187 exaltis reaction, 187 exaltis reaction, 187 examination, 187 exaltis reaction, 187 examination, 187 exaltis reaction, 187 examination, 187 exaltis reaction, 187 exaltis reaction, 187 exaltis reaction, 187 examination, 187 exaltis reaction, 187 examination, 187 exaltis reaction, 187 examination, 187 examination, 187 exaltis reaction, 187 examination, 187 exam				A
salpingitis and, 185 Eczena daptic dermaltiis, 477 eczematous dermaltiis, 477 eczematous dermaltiis, 477 eczematous dermaltiis, 477 eczematous dermaltiis, 477 eczematous dermaltiis, 477 estikatis, 548 skin scales in, 475 by leifylersensitivity, 112 Wiskotk-Marich syndrome, 177 delema acute potherphylersecoal acute potherius, 596 damaerteristics of, 52 elastin (Ederma acute potherius, 194 damaerteristics, 195 danaerteristics, 195 demolitation, 195 electrocoreousiatic therapy (ECT) adverse effects, 562 postpartum psychosis, 502 electrocoreousiate therapy (ECT) adverse effects, 562 postpartum psychosis, 502 electrocoreousiate therapy (ECT) adverse effects, 562 postpartum psychosis, 502 electrocoreousiate therapy (ECT) adverse effects, 562 postpartum psychosis, 502 electrocoreousiate therapy (ECT) adverse effects, 562 postpartum psychosis, 502 electrocoreousiate therapy (ECT) adverse effects, 562 postpartum psychosis, 502 electrocoreousiate therapy (ECT) adverse effects, 562 postpartum psychosis, 502 electrocoreousiate therapy (ECT) adverse effects, 562 postpartum psychosis, 502 electrocoreousiate therapy (ECT) adverse effects, 562 postpartum psychosis, 502 electrocoreousiate therapy (ECT) adverse effects, 562 postpartum psychosis, 502 electrocoreousiate therapy (ECT) adverse effects, 562 postpartum psychosis, 502 electrocoreousiate therapy (ECT) adverse effects, 562 postpartum psychosis, 502 electrocoreousiate therapy (ECT) adverse effects, 562 postpartum psychosis, 502 electrocoreousiate therapy (ECT) adverse effects, 562 postpartum psychosis, 502 electrocoreousiate therapy (ECT) adverse effects, 562 postpartum psychosis, 502 electrocoreousiate therapy (ECT) adverse effects, 562 postpartum psychosis, 502 electrocoreousiate t				
Exclusivands, 122 Eczematous dermatitis, 475 pekenylketonuria, 34 skin scales in, 475 type I hypersensitivity, 112 Wiskoit-Aldrich yandrome, 1, 175 edlema acute poststreptococcal glomerulonephritis, 596 Arthus reaction, 1, 13 calcium channel blockers, 318 capillary fluid ecknage and, 297 danazol, 658 dabette ketoacdosis, 347 endotoxin, 135 calcium channel blockers, 318 capillary fluid ecknage and, 297 danazol, 658 dibette ketoacdosis, 347 endotoxin, 135 calcium channel blockers, 318 capillary fluid ecknage and, 297 danazol, 658 dibette ketoacdosis, 347 endotoxin, 135 calcium channel blockers, 318 capillary fluid ecknage and, 399 with hyperaldosteronism, 499 immunosuppressants, 120 Examisasi discense and, 314 Lewshiorkor, 71 loop directies for, 608 peripheral, 309, 610 pitting, 309 pseudocphedimerphenylephrine, 686 pulmonary hypertension, 668 ritchiculus prophysiolis, 190, 161 peripheral, 309, 610 pitting, 399 pseudocphedimerphenylephrine, 686 pulmonary hypertension, 668 ritchiculus prophysiolis, 191, 161 trichinosis, 159 Electron acceptors (universal), 75 Electron transport chain and oxidative phosphorylation, 418 Electron acceptors (universal), 75 Electron transport chain and oxidative phosphorylation, 418 Electron acceptors (universal), 75 Electron transport chain and oxidative phosphorylation, 418 Electron acceptors (universal), 75 Electron transport chain and oxidative phosphorylation, 418 Electron acceptors (universal), 75 Electron transport chain and oxidative phosphorylation, 418 Englantiasis, 159 Electron acceptors (universal), 75 Electron transport chain and oxidative phosphorylation, 418 Englantiasis, 159 Electron acceptors (universal), 75 Electron acceptors (universal), 75 Electron acceptors (universal), 75 Electron acceptors (universal), 75 Electron acceptors (universal), 75 Electron acceptors (universal), 75 Electron acceptors (universal), 75 Electron acceptors (universal), 75 Electron acceptors (universal), 75 Electron acceptors (universal), 75 Electron acceptors (universal), 75 Electron acceptors				
Eczenia atopic dermatitis, 477 eczematous dermatitis, 477 eczematous dermatitis, 477 eczematous dermatitis, 475 phenyllketounutia, 54 skin scales in, 475 tybe I hypersensitivity, 112 Wiskort-Addrich syndrome, 117 Edema acute poststreptococcal glomentonephritis, 596 Arthus reaction, 113 calcium chamel blockers, 318 capillary fluid exchange and, 297 danazol, 658 diabetic ketoacidosis, 347 endotoxius, 133 fluidrocortisone, 354 leart failure and, 309 with hyperaldosteronism, 349 immunosuppressants, 120 Kawasaki diseane and, 314 kwashinokor, 71 loop directis for, 608 periphetal, 390, 610 periphetal, 390, 610 periphetal, 390, 610 periphetal, 390, 610 periphetal, 390, 610 periphetal, 390, 610 periphetal, 590 Edicorosorosorosorosorosorosorosorosorosoro	1 0			
activity in emphysema, 674 eleastic record (lung and chest wall), 665 shir scales in, 475 bpe Ily ppesensitivity, 112 bille pythosensitivity, 112 calcium channel blockers, 318 calcium channel blockers, 318 calcium channel blockers, 318 calcium channel blockers, 318 calcium channel blockers, 318 calcium channel blockers, 318 calcium channel blockers, 318 calcium channel blockers, 318 calcium channel blockers, 318 calcium channel blockers, 318 calcium channel blockers, 318 calcium channel blockers, 318 calcium channel blockers, 318 calcium channel blockers, 318 calcium channel blockers, 318 calcium channel blockers, 318 calcium channel blockers, 318 calcium channel blockers, 318 calcium channel blockers, 318 calcium channel blockers, 318 calcium channel blockers, 318 calcium channel blockers, 318 calcium channel blockers, 318 calcium channel blockers, 318 calcium channel blockers, 318 calcium channel blockers, 318 calcium channel blockers, 318 calcium channel blockers, 318 calcium channel blockers, 318 calcium channel blockers, 318 calcium channel blockers, 318 calcium channel blockers, 318 calcium channel blockers, 318 calcium channel blockers, 318 calcium channel blockers, 318 calcium channel blockers, 318 calcium channel blockers, 318 calcium channel blockers, 318 calcium channel blockers, 318 calcium channel blockers, 318 calcium channel blockers, 318 calcium channel blockers, 318 calcium channel blockers, 318 calcium channel blockers, 318 calcium channel blockers, 318 calcium channel blockers, 318 calcium channel blockers, 318 calcium channel blockers, 318 calcium channel blockers, 318 calcium channel blockers, 318 calcium channel blockers, 318 calcium channel blockers, 318 calcium channel blockers, 318 calcium channel blockers, 318 calcium channel blockers, 318 calcium channel blockers, 318 calcium channel blockers, 318 calcium channel blockers, 318 calcium channel blockers, 318 calcium channel blockers, 318 calcium channel blockers, 318 calcium channel blockers, 318 calcium channel blockers, 318 calcium ch		*		
cezematous dermatitis, 475 phenyllektomina, 54 skin scales in, 475 type I hypersensitivity, 112 Wiskokl-Addrich syndrome, 117 Edema acute poststreptococcal glomeruloophritis, 596 Arthus reaction, 113 capillary fluid exchange and, 297 danazol, 658 diabetic ketoacidosis, 347 endotoxins, 135 fluidocortisone, 354 heart failure and, 399 with hyperaldosteronism, 349 immunosuppressants, 120 Kawasaki disease and, 314 kashisohor, 71 loop diuretics for, 608 Priechinella spratia, 159, 161 peraphenal, 399, 610 prilting, 309 pseudoephethine/phenylephrine, 668 Priechinella spratia, 159, 161 peraphenal, 399, 610 prilting, 309 pseudoephethine/phenylephrine, 668 Priechinella spratia, 159, 161 peraphenal, 390, 610 Pitting, 309 pseudoephethine/phenylephrine, 668 Priechinella spratia, 159, 161 peraphenal, 390, 610 Pitting, 309 pseudoephethine/phenylephrine, 668 Priechinella spratia, 159, 161 peraphenal, 390, 610 Pitting, 309 pseudoephethine/phenylephrine, 668 Priechinella spratia, 159, 161 peraphenal, 390, 610 Pitting, 309 pseudoephethine/phenylephrine, 668 Priechinella spratia, 159, 161 peraphenal, 390, 610 Pitting, 309 pseudoephethine/phenylephrine, 668 Priechinella spratia, 159, 161 peraphenal, 390, 610 Pitting, 309 pseudoephethine/phenylephrine, 668 Priechinella spratia, 159, 161 peraphenal, 390, 610 Pitting, 309 pseudoephethine/phenylephrine, 668 Priechinella spratia, 159, 161 peraphenal, 390, 610 Pitting, 309 pseudoephethine/phenylephrine, 668 Priechinella spratia, 159, 161 peraphenal, 390, 610 Pitting, 309 pseudoephethine/phenylephrine, 668 Priechinella spratia, 159, 161 peraphenal, 390, 610 Pitting, 309 pseudoephethine/phenylephrine, 668 Priechinella spratia, 159, 161 peraphenal, 390, 610 Pitting, 309 pseudoephethine/phenylephrine, 668 Priechinella spratia, 159, 161 peraphenal, 390, 610 Pitting, 309 pseudoephenal, 622 Pitting, 390, 610 Pitting, 390 pseudoephenal, 622 Pitting, 390, 610 Pitting, 390 Pitting, 390 Pitting, 390 Pitting, 390 Pitting, 390 Pitting, 390 Pitting, 390 Pitting, 390 Pitting, 390 Pitting, 390 Pitting, 3			* 2	
phenylketonuria, 84 skin scales in, 475 type I hypersensitivity, 112 Wiskott-Aldrich syndrome, 117 Edema acute poststreptococcal glomerulonephritis, 596 characteristics of, 52 Ellow injuries, 459, 461 Ederly cardiocordin, 115 calcium channel blockers, 318 capillary fluid exchange and, 297 chanazol, 658 diabetic ketoacidosis, 347 endotoxins, 133 dudocortisone, 554 heart failure and, 309 with hyperaldosteronism, 349 immunosuppressants, 120 Kawasaki disease and, 314 kwashiorkor, 71 bloop diuretics for, 608 periorbital, 159, 161 peripheral, 309, 610 politing, 309 pseudoephedrine/phenylephrine, 686 Trichimelia spiralis, 159, 161 richimoss, 159 acularosant politics, 596 Ederma factor bactus, 203 Ederboynosium, 240 Edwards syndrome, 65 cataracts and, 535 echromosome association, 64 Edwards syndrome, 65 cataracts and, 535 echromosome association, 64 Edwards syndrome, 65 cataracts and, 535 echromosome association, 64 Edwards syndrome, 65 cataracts and, 535 echromosome association, 64 Edwards syndrome, 65 class C autaracts and, 535 echromosome association, 64 Edwards syndrome, 65 clateract factor glaves of the complex of the complex of the complex of the complex of the complex of the complex of the complex of the complex of the complex of the complex of the complex of the complex of the complex of the complex of the complex of the complex of the complex of the complex of the complex of the complex of the complex of the complex of the complex of the complex of the complex of the complex of the complex of the complex of the complex of the complex of the complex of the complex of the complex of the complex of the complex of the complex of the complex of the complex of the complex of the complex of the complex of the complex of the complex of the complex of the complex of the complex of the complex of the complex of the complex of the complex of the complex of the complex of the complex of the complex of the complex of the complex of the complex of the complex of the complex of the complex of the complex of the complex of th				
skin scales in, 475 bye I hypersensitivity, 112 Wiskott-Aldrich syndrome, 117 Edema acute poststreptococcal glomenulonephritis, 596 Arthus reaction, 113 capillary fluid exchange and, 297 danazol, 658 diabetic ketoacidosis, 347 endotoxins, 133 fluidrocortisone, 554 leaf fulfure and, 309 with hyperaldosteronism, 349 munonespressants, 120 Kansaaki disease and, 314 washiorkor, 71 aloop dimertes for, 608 periorbial, 159, 161 principlina, 309 priorbial, 159, 161 principlina, 309 priorbial, 159, 161 principlina, 159 Edectroal acceptors (universal), 75 Edema acute posterpelograms (ECC) advite hyperaldosteronism, 349 munonauppressants, 120 Kansaaki disease and, 314 washiorkor, 71 adverse effects, 552 Electroal conversable and the conversable and the conversable and the conversable and the conversable and the conversable and the conversable and the conversable and the conversable and the conversable and the conversable and the conversable and the conversable and the conversable and the conversable and the conversable and the conversable and the conversable and the conversable and the conversable and the conversable and the conversable and the conversable and the conversable and the conversable and the conversable and the conversable and the conversable and the conversable and the conversable and the conversable and the conversable and the conversable and the conversable and the conversable and the conversable and the conversable and the conversable and the conversable and the conversable and the conversable and the conversable and the conversable and the conversable and the conversable and the conversable and the conversable and the conversable and the conversable and the conversable and the conversable and the conversable and the conversable and the conversable and the conversable and the conversable and the conversable and the conversable and the conversable and the conversable and the conversable and the conversable and the conversable and the conversable and the conversable and the conversable and the conversable and				
type I hypersensitivity, 112 Wiskott-Aldrich syndrome, 117 Edema acute poststeptococcal glomerulonephritis, 596 Arbths reaction, 113 calcium channel blockers, 318 capillan fluid exchange and, 297 darazol, 658 diabetic ketacaidosis, 347 endotosins, 133 fludrocortisone, 354 hudrocortisone, 354 hudrocortisone, 354 hudrocortisone, 354 perorbital, 159, 161 peripheral, 309, 610 peripheral, 309, 610 peripheral, 309, 610 peripheral, 309, 610 peripheral, 309, 610 peripheral, 309, 610 peripheral, 309, 610 peripheral, 309, 610 peripheral, 309, 610 peripheral, 309, 610 peripheral, 309, 610 peripheral, 309, 610 peripheral, 309, 610 peripheral, 309, 610 peripheral, 309, 610 peripheral, 309, 610 peripheral, 309, 610 peripheral, 309, 610 peripheral, 309, 610 peripheral, 309, 610 peripheral, 309, 610 peripheral, 309, 610 peripheral, 309, 610 peripheral, 309, 610 peripheral, 309, 610 peripheral, 309, 610 peripheral, 309, 610 peripheral, 309, 610 peripheral, 309, 610 peripheral, 309, 610 peripheral, 309, 610 peripheral, 309, 610 peripheral, 309, 610 peripheral, 309, 610 peripheral, 309, 610 peripheral, 309, 610 peripheral, 309, 610 peripheral, 309, 610 peripheral, 309, 610 peripheral, 309, 610 peripheral, 309, 610 peripheral, 309, 610 peripheral, 309, 610 peripheral, 309, 610 peripheral, 309, 610 peripheral, 309, 610 peripheral, 309, 610 peripheral, 309, 610 peripheral, 309, 610 peripheral, 309, 610 peripheral, 309, 610 peripheral, 309, 610 peripheral, 309, 610 peripheral, 309, 610 peripheral, 309, 610 peripheral, 309, 610 peripheral, 309, 610 peripheral, 309, 610 peripheral, 309, 610 peripheral, 309, 610 peripheral, 309, 610 peripheral, 309, 610 peripheral, 309, 610 peripheral, 309, 610 peripheral, 309, 610 peripheral, 309, 610 peripheral, 309, 610 peripheral, 309, 610 peripheral, 309, 610 peripheral, 309, 610 peripheral, 309, 610 peripheral, 309, 610 peripheral, 309, 610 peripheral, 309, 610 peripheral, 309, 610 peripheral, 309, 610 peripheral, 309, 610 peripheral, 309, 610 peripheral, 309, 610 peripheral, 309, 610 peripheral,				
Wishort-Aldrich syndrome, 117 Edema acute poststreptococcal glomenulonephritis, 596 Arthus reaction, 113 capillary fluid exchange and, 297 danazol, 658 diabetic ketoacidosis, 347 endotoxins, 133 fludrocortisone, 354 hudrocortisone, 355 hudrocortisone, 356 hudrocortisone, 357 hudrocortisone, 357 hudrocortisone, 356 hudrocortisone, 357 hudrocortisone, 357 hudrocortisone, 357 hudrocortisone, 357 hudrocortisone, 357 hudrocortisone, 357 hudrocortisone, 357 hudrocortisone, 357 hudrocortisone, 357 hudrocortisone, 357 hudrocortisone, 357 hudrocortisone, 357 hudrocortisone, 357 hudrocortisone, 358 hudrocortisone, 358 hudrocortisone, 359 hudrocortisone, 359 hudrocortisone, 359 hudrocortisone, 359 hudrocortisone, 359 hudrocortisone, 359 hudrocortisone, 359 hudrocortisone, 359 hudrocortisone, 359 hudrocortisone, 359 hudrocortisone, 359 hudrocortisone, 359 hudrocortisone, 359 hudrocortisone, 359 hudrocortisone, 359 hudrocortisone, 359 hudrocortisone, 359 hudrocortisone, 359 hudrocortisone, 359 hudrocortisone, 359 hudrocortisone, 359 hudrocortisone, 359 hudrocortisone, 359 hudrocortisone, 359 hudrocortisone, 359 hudrocortisone, 359 hudrocortisone, 359 hudrocortisone, 359 hudrocortisone, 359 hudrocortisone, 359 hudrocortisone, 359 hudrocortisone, 359 hudrocortisone, 359 hudrocortisone, 359 hudrocortisone, 359 hudrocortisone, 359 hudrocortisone, 359 hudrocortisone, 359 hudrocortisone, 359 hudrocortisone, 359 hudrocortisone, 359 hudrocortisone, 359 hudrocortisone, 359 hudrocortisone, 359 hudrocortisone, 359 hudrocortisone, 359 hudrocortisone, 359 hudrocortisone, 359 hudrocortisone, 359 hudrocortisone, 359 hudrocortisone, 359 hudrocortisone, 359 hudrocortisone, 359 hudrocortisone, 359 hudrocortisone, 359 hudrocorti				
Edlerna acute poststreptococcal glomerulonephirits, 596 acute poststreptococcal glomerulonephirits, 596 acute poststreptococcal glomerulonephirits, 596 acute poststreptococcal glomerulonephirits, 596 acute poststreptococcal glomerulonephirits, 596 acute poststreptococcal glomerulonephirits, 596 acute poststreptococcal glomerulonephirits, 596 acute posts representation, 131 calcium channel blockers, 318 acute pericarditis on, 313 cardiac tamponade on, 310 cardiac tamponade on, 310 cardiac tamponade on, 310 danazol, 658 acute posts capital devalority, 596 acute posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of the posts of th	type I hypersensitivity, 112	,		embryology, 326
acute poststreptococcal glomenulonephirits, 596 Arthus reaction, 113 capillary fluid exchange and, 297 danazol, 658 dabetic ketoacidosis, 347 endotoxins, 153 capillary fluid exchange and, 297 danazol, 658 dabetic ketoacidosis, 347 endotoxins, 153 capillary fluid exchange and, 297 danazol, 658 dabetic ketoacidosis, 347 endotoxins, 153 carliature and, 309 duffudrocortisone, 554 heart failure and, 309 viith piperaldosteronism, 349 immunosuppressants, 120 Kawasaki disease and, 314 kawashiorkor, 71 loop diuretics for, 608 periorbital, 159, 161 peripheral, 309 periorbital, 159, 161 prepipheral, 309, 610 pritting, 309 periorbital, 159, 161 richinosis, 159 diumonary hypertension, 668 Trichinella spradis, 159, 161 richinosis, 159 deforphonium, 240 Getwards syndrome, 63 Trichinella spradis, 159, 161 richinosis, 159 deforphonium, 240 Getwards syndrome, 63 Electrophoresis hemoglobin, 410 Elemen association, 64 and metyrapone, 335 Elementary bodies (chlamydiae). 148 Elephantiasis, 159 Ellish frices, 64 Elminiation constant, 231 Elementary bodies (chlamydiae). 148 Elephantiasis, 159 Elminiation of drug, 232 urince pH and, 233 Elfective refractory period Class IA antiarrhythmic effect, 322 Invocardial action potential, 292 Elficertic refractory period Class IA antiarrhythmic effect, 322 Invocardial action potential, 292 Elficertic refractory period Class IA antiarrhythmic effect, 322 Invocardial action potential, 292 Elficertic refractory period Class IA antiarrhythmic effect, 322 Invocardial action potential, 292 Elficertic refractory period Class IA antiarrhythmic effect, 322 Invocardial action potential, 292 Elficertic refractory period Class IA antiarrhythmic effect, 322 Invocardial action potential, 292 Elficertic refractory period Class IA antiarrhythmic effect, 322 Invocardial action potential, 292 Elficertic refractory period Class IA antiarrhythmic effect, 322 Invocardial action potential, 292 Elficertic refractory period Class IA antiarrhythmic effect, 322 Invocardial action potential, 292 Elficertic refractory peri	Wiskott-Aldrich syndrome, 117	Elbow injuries, 459, 461		hormones acting on kidney, 589,
glomerulonephritis, 596 Arthus reaction, 113 calcium channel blockers, 318 capillary fluid exchange and, 297 danazol, 658 diabetic ketoacidosis, 347 endotoxins, 133 diabetic ketoacidosis, 347 endotoxins, 133 fluidrocortisone, 554 fluidrocortisone, 554 meart failure and, 309 with hyperaldosteronism, 349 minumosuppressants, 120 Rawasaki disease and, 314 kwashiorkor, 71 loop diuretics for, 608 peripheral, 309, 610 priting, 309 poulmonary hypertension, 668 Trichimella spiralis, 159 tacipore disconting for the condition of, 527 letterton transport chain and oxidative phosphorylation, 78 Electron transport chain and oxidative phosphorylation, 78 Electron transport chain and oxidative phosphorylation, 240 Edewards syndrome, 63 cataracts and, 555 cataracts and, 555 Class IA antarrhythmic effect, 322 calcas IC antarrhythmic effect, 322 calcas IC antarrhythmic effect, 322 calcas IC antarrhythmic effect, 322 calcas IC antarrhythmic effect, 322 calcas IC antarrhythmic effect, 322 calcas IC antarrhythmic effect, 322 calcas IC antarrhythmic effect, 322 calcas IC antarrhythmic effect, 322 calcas IC antarrhythmic effect, 322 calcas IC antarrhythmic effect, 322 calcas IC antarrhythmic effect, 322 calcas IC antarrhythmic effect, 322 calcas IC antarrhythmic effect, 322 calcas IC antarrhythmic effect, 322 calcas IC antarrhythmic effect, 322 calcas IC antarrhythmic effect, 322 calcas IC antarrhythmic effect, 322 calcas IC antarrhythmic effect, 322 calcas IC antarrhythmic effect, 322 calcas IC antarrhythmic effect, 322 calcas IC antarrhythmic effect, 322 calcas IC antarrhythmic effect, 322 calcas IC antarrhythmic effect, 322 calcas IC antarrhythmic effect, 322 calcas IC antarrhythmic effect, 322 calcas IC antarrhythmic effect, 322 calcas IC antarrhythmic effect, 322 calcas IC antarrhythmic effect, 322 calcas IC antarrhythmic effect, 322 calcas IC antarrhythmic effect, 322 calcas IC antarrhythmic effect, 322 calcas IC antarrhythmic effect, 322 calcas IC antarrhythmic effect, 322 calcas IC antarrhythmic effect, 322 calcas IC antarrhyt	Edema	Elderly	Embryonic morphogenic errors, 613	
glomerulonephritis, 596 Arthus reaction, 113 calcium channel blockers, 318 capillary fluid exchange and, 297 danazol, 658 diabetic ketoacidosis, 347 endotoxins, 133 diabetic ketoacidosis, 347 endotoxins, 133 fluidrocortisone, 554 fluidrocortisone, 554 meart failure and, 309 with hyperaldosteronism, 349 minumosuppressants, 120 Rawasaki disease and, 314 kwashiorkor, 71 loop diuretics for, 608 peripheral, 309, 610 priting, 309 poulmonary hypertension, 668 Trichimella spiralis, 159 tacipore disconting for the condition of, 527 letterton transport chain and oxidative phosphorylation, 78 Electron transport chain and oxidative phosphorylation, 78 Electron transport chain and oxidative phosphorylation, 240 Edewards syndrome, 63 cataracts and, 555 cataracts and, 555 Class IA antarrhythmic effect, 322 calcas IC antarrhythmic effect, 322 calcas IC antarrhythmic effect, 322 calcas IC antarrhythmic effect, 322 calcas IC antarrhythmic effect, 322 calcas IC antarrhythmic effect, 322 calcas IC antarrhythmic effect, 322 calcas IC antarrhythmic effect, 322 calcas IC antarrhythmic effect, 322 calcas IC antarrhythmic effect, 322 calcas IC antarrhythmic effect, 322 calcas IC antarrhythmic effect, 322 calcas IC antarrhythmic effect, 322 calcas IC antarrhythmic effect, 322 calcas IC antarrhythmic effect, 322 calcas IC antarrhythmic effect, 322 calcas IC antarrhythmic effect, 322 calcas IC antarrhythmic effect, 322 calcas IC antarrhythmic effect, 322 calcas IC antarrhythmic effect, 322 calcas IC antarrhythmic effect, 322 calcas IC antarrhythmic effect, 322 calcas IC antarrhythmic effect, 322 calcas IC antarrhythmic effect, 322 calcas IC antarrhythmic effect, 322 calcas IC antarrhythmic effect, 322 calcas IC antarrhythmic effect, 322 calcas IC antarrhythmic effect, 322 calcas IC antarrhythmic effect, 322 calcas IC antarrhythmic effect, 322 calcas IC antarrhythmic effect, 322 calcas IC antarrhythmic effect, 322 calcas IC antarrhythmic effect, 322 calcas IC antarrhythmic effect, 322 calcas IC antarrhythmic effect, 322 calcas IC antarrhyt	acute poststreptococcal		Embryonic stage (development), 660	hormone signaling pathways, 337
calcium channel blockers, 318 capillary fluid exchange and, 297 danazol, 658 diabetic ketoacidosis, 347 endotoxins, 133 fluidrocortisone, 554 leart failure and, 599 with hyperaldosteronism, 349 minumouspressants, 120 Kawasaki disease and, 314 kwashiorkor, 71 loop diuretics for, 608 periorbital, 159, 161 peripheral, 309, 610 pitting, 309 pitting, 309 pitting, 309 pitting, 309 pitting, 309 diamazol, 588 dinibitors of, 78 Electron acceptors (universal), 75 Electron transport chain and pulmonary hypertension, 668 Trichimelia spiralis, 159 Raziilus anthracis, 152 Edinger-Westphal nuclei, 539 Edinger-Westphal nuclei, 539 Edinary for the memoglobin, 410 Electron acceptors in the memoglobin, 410 Electron acceptors (hor) Electron transport chain and pulmonary hypertension, 64 Elevier efractory period Class IA anthratythmic effect, 322 Chass IC antharrhythmic effect, 322 Chass IC antharrhyth	glomerulonephritis, 596	Electrocardiograms (ECGs), 293	Embryotoxic, 204	
calcium channel blockers, 318 capillary fluid exchange and, 297 danazol, 658 diabetic ketoacidosis, 347 endotoxins, 133 fluidrocortisone, 554 leart failure and, 599 with hyperaldosteronism, 349 minumouspressants, 120 Kawasaki disease and, 314 kwashiorkor, 71 loop diuretics for, 608 periorbital, 159, 161 peripheral, 309, 610 pitting, 309 pitting, 309 pitting, 309 pitting, 309 pitting, 309 diamazol, 588 dinibitors of, 78 Electron acceptors (universal), 75 Electron transport chain and pulmonary hypertension, 668 Trichimelia spiralis, 159 Raziilus anthracis, 152 Edinger-Westphal nuclei, 539 Edinger-Westphal nuclei, 539 Edinary for the memoglobin, 410 Electron acceptors in the memoglobin, 410 Electron acceptors (hor) Electron transport chain and pulmonary hypertension, 64 Elevier efractory period Class IA anthratythmic effect, 322 Chass IC antharrhythmic effect, 322 Chass IC antharrhyth	Arthus reaction, 113	acute pericarditis on, 313	Emergent care proxy, 269	pharmacology, 352-354
capillary fluid exchange and, 297 chanazol, 658 diabetic ketoacidosis, 347 endotoxins, 133 endotoxins, 133 endotoxins, 134 endotoxins, 135 heart failure and, 309 with hyperaldosteronism, 3+9 immunosuppressants, 120 kawashi disease and, 314 kwashiorkor, 71 loop diturctic for, 608 periorbital, 159, 161 peripheral, 309, 610 pseudoephedrine/phenylephrine, 686 pulmonary hypertension, 668 richimellar spiralis, 159, 161 richimosis, 159 vasogenic, 496 web beriberi, 66 Edlema factor Baeillus anthracis, 132 Edinger-Westphal muclei, 539 Edivorsome association, 64 Elfevierva real cuttor potential, 292 Effective refractory period Class IA antarrhythmic effect, 322 Class IC antarrhythmic effect, 322 Class IC antarrhythmic effect, 322 Class IC antarrhythmic effect, 322 Class IC antarrhythmic effect, 322 Class IC antarrhythmic effect, 322 Class IC antarrhythmic effect, 322 Class IC antarrhythmic effect, 322 Class IC antarrhythmic effect, 322 Class IC antarrhythmic effect, 322 Class IC antarrhythmic effect, 322 Class IC antarrhythmic effect, 322 Class IC antarrhythmic effect, 322 Class IC antarrhythmic effect, 322 Class IC antarrhythmic effect, 322 Class IC antarrhythmic effect, 322 Class IC antarrhythmic effect, 322 Class IC antarrhythmic effect, 322 Class IC antarrhythmic effect, 322 Class IC antarrhythmic effect, 322 Class IC antarrhythmic effect, 322 Class IC antarrhythmic effect, 322 Class IC antarrhythmic effect, 322 Class IC antarrhythmic effect, 322 Class IC antarrhythmic effect, 322 Class IC antarrhythmic effect, 322 Class IC antarrhythmic effect, 322 Class IC antarrhythmic effect, 322 Class IC antarrhythmic effect, 322 Class IC antarrhythmic effect, 322 Conynebacterium diphtheriae, 139 eltromosome association of, 353  Label and the antarrhythmic effect, 322 Conynebacterium diphtheriae, 139 eltromosome association of, 627 Emerotive real plasma flow, 585 Emerotionally distraught patients, 268 Emotionally distraught patients, 268 Emotionally distraught patients, 268 Emotionally distraught patients, 268 Emotionally distr	calcium channel blockers, 318	cardiac tamponade on, 310	Emission	physiology, 328–336
dahazol, 658 diabetic ketoacidosis, 347 endotoxins, 133 (the pulmonary embolism, 672 tracings of, 295 (tracings of, 295 (tectroconvulsive therapy (ECT) acceptorable properties for, 608 periorbital, 159, 161 pitting, 309 periorbital, 139, 161 pitting, 309 periorbital, 139, 161 pitting, 309 periorbital, 159, 161 trichinosis, 159 (Electron acceptors (universal), 75 Electron transport chain and oxidative phosphorylation, 686 Trichimella spiralis, 159, 161 trichinosis, 159 (Edema factor Bacillus anthracis, 132 Edinger-Westphal nuclei, 539 Edirophonium, 240 Edwards syndrome, 63 catarates and, 535 echomosome association, 64 Elevirenze altarates and, 535 echomosome association, 64 Effective refractory period Class I A antarhythmic effect, 322 (Class IC antiarrhythmic effect, 322 (Constriction of, 588 (Constriction of, 588 (Constriction of, 588 (Constriction of, 588 (Constriction of, 588 (Constriction of, 588 (Constriction of, 588 (Constriction of, 588 (Constriction of, 588 (Constriction of, 588 (Constriction of, 588 (Constriction of, 588 (Constriction of, 588 (Constriction of, 588 (Constriction of, 588 (Constriction of, 588 (Constriction of, 588 (Constriction of, 588 (Constriction of, 588 (Constriction of, 588 (Constriction of, 588 (Constriction of, 588 (Constriction of, 588 (Constriction of, 588 (Constriction of, 588 (Constriction of, 588 (Constriction of, 588 (Constriction of, 588 (Constriction of, 588 (Constriction of, 588 (Constriction of, 588 (Constriction of, 588 (Constriction of, 588 (Constriction of, 588 (Constriction of, 588 (Constriction of, 588 (Constriction of, 588 (Constriction of, 588 (Constriction of, 588 (Constriction of, 588 (Constriction of, 588 (Constriction of, 588 (Constriction of, 588 (Constriction of, 588 (Constriction of, 588 (Constriction of, 588 (Constriction of, 588 (Constriction of, 588 (Constriction of, 588 (	capillary fluid exchange and, 297		innervation of, 627	
diabetic ketoacidosis, 347 endotoxins, 133 fludrocortisone, 354 heart failure and, 309 with hypertallosteronism, 349 immunosuppressants, 120 Kawasaki disease and, 314 kwashiorkor, 71 loop diurctics for, 608 periorbital, 159, 161 peripheral, 309, 610 pitting, 309 pseudoephedrine/phenylephrine, 666 pulmonary hypertension, 668 Trichinella spiralis, 159, 161 trichinosis, 159 vasogenic, 496 wet bernberi, 66 Edema factor Bacillus anthracis, 132 Edinger-Westphal muclei, 539 Edirept-Westphal muclei, 539 eltromboraga cataracts and, 355 ehromosome association, 64 Efferent zaffetor werfactory period Class IA antarrhythmic effect, 322 Class IC antarrhythmic effect, 322 Class IC antarrhythmic effect, 322 Class IC antarrhythmic effect, 322 Class IC antarrhythmic effect, 322 Class IC antarrhythmic effect, 322 Class IC antarrhythmic effect, 322 Class IC antarrhythmic effect, 322 Class IC antarrhythmic effect, 322 Class IC antarrhythmic effect, 322 Class IC antarrhythmic effect, 322 Class IC antarrhythmic effect, 322 Class IC antarrhythmic effect, 322 Class IC antarrhythmic effect, 322 Class IC antarrhythmic effect, 322 Class IC antarrhythmic effect, 322 Class IC antarrhythmic effect, 322 Class IC antarrhythmic effect, 322 Class IC antarrhythmic effect, 322 Class IC antarrhythmic effect, 322 Class IC antarrhythmic effect, 322 Class IC antarrhythmic effect, 322 Class IC antarrhythmic effect, 322 Class IC antarrhythmic effect, 322 Class IC antarrhythmic effect, 322 Class IC antarrhythmic effect, 322 Class IC antarrhythmic effect, 322 Class IC antarrhythmic effect, 322 Class IC antarrhythmic effect, 322 Class IC antarrhythmic effect, 322 Class IC antarrhythmic effect, 322 Conymehacterium diphtheriae, and an antarrhythmic effect, 322 Conymehacterium diphtheriae, and an antarrhythmic effect, 322 Conymehacterium diphtheriae, and an antarrhythmic effect, 322 Conymehacterium diphtheriae, and an antarrhythmic effect, 322 Conymehacterium diphtheriae, and an antarrhythmic effect, 322 Conymehacterium diphtheriae, and an antarrhythmic effec				
endotoxins, 133 fludrocotrisons, 354 heart failure and, 309 with hyperaldosteronism, 349 mimmunosuppressants, 120 Kawasaki disease and, 314 kwashiorkor, 71 loop diuretics for, 608 periorbital, 159, 161 petiting, 309 petimorbital, 159, 161 pitting, 309 petimorbital, 159, 161 pitting, 309 petimorbital, 159, 161 pitting, 309 pulmonary hypertension, 668 Trichinella spiralis, 159, 161 trichinosis, 159 wet beriberi, 66 Electron acceptors (universal), 75 Electron acceptors (universal), 75 Electron berostor (universal), 75 Electron acceptors (universal), 75 Electron acceptors (universal), 75 Electron acceptors (universal), 75 Electron acceptors (universal), 75 Electron acceptors (universal), 75 Electron acceptors (universal), 75 Electron acceptors (universal), 75 Electron acceptors (universal), 75 Electron acceptors (universal), 75 Electron acceptors (universal), 75 Electron acceptors (universal), 75 Electron acceptors (universal), 75 Electron acceptors (universal), 75 Electron acceptors (universal), 75 Electron acceptors (universal), 75 Electron acceptors (universal), 75 Electron acceptors (universal), 75 Electron acceptors (universal), 75 Electron acceptors (universal), 75 Electron acceptors (universal), 75 Electron acceptors (universal), 75 Electron acceptors (universal), 75 Electron acceptors (universal), 75 Electron acceptors (universal), 75 Electron acceptors (universal), 75 Electron acceptors (universal), 75 Electron acceptors (universal), 75 Electron acceptors (universal), 75 Electron acceptors (universal), 75 Electron acceptors (universal), 75 Electron acceptors (universal), 75 Electron acceptors (universal), 75 Electron acceptors (universal), 75 Electron acceptors (universal), 75 Electron acceptors (universal), 75 Electron acceptors (universal), 75 Electron acceptors (universal), 75 Electron acceptors (universal), 75 Electron acceptors (universal), 75 Electron acceptors (universal), 75 Electron acceptors (universal), 75 Electron acceptors (universal), 75 Electron acceptors (universal), 75 Electron acceptors (				
Fludrocortisone, 554 heart failure and, 309 with hyperaldosteronism, 349 immunosuppressants, 120 Electrocenephalogram (EEG) Kawasaki disease and, 314 kwashiorkor, 71 loop diureties for, 608 periorbital, 159, 161 peripheral, 309, 610 pitting, 309 pseudoephedrine/phenylephrine, 686 Trichinella spiralis, 159, 161 ved berriberi, 66 Frichinella spiralis, 159, 161 peripheral, 309, 610 pitting, 309 pseudoephedrine/phenylephrine, 686 Trichinella spiralis, 159, 161 peripheral, 309, 610 pitting, 309 pseudoephedrine/phenylephrine, 686 Trichinella spiralis, 159, 161 peripheral, 309, 610 pitting, 309 pseudoephedrine/phenylephrine, 686 Trichinella spiralis, 159, 161 peripheral, 309, 610 pitting, 309 pseudoephedrine/phenylephrine, 686 Trichinella spiralis, 159, 161 peripheral, 309, 610 pitting, 309 pseudoephedrine/phenylephrine, 686 Trichinella spiralis, 159, 161 peripheral, 309, 610 pitting, 309 pseudoephedrine/phenylephrine, 686 Trichinella spiralis, 159, 161 peripheral, 309, 610 pitting, 309 pseudoephedrine/phenylephrine, 686 Electrolytes disturbances in, 591 Electron transport chain and embergation of feets, 552 Electrolytes disturbances in, 591 panacinar, 392 Electron transport chain and embergation of feets, 552 Endometrial attroportial acracinoma, 648 elastin in, 52 panacinar, 392 Embry/full can test, 446 Empty/full can test, 446 Em		tracings of 295		
heart failure and, 309 with hyperaldosteronism, 349 immunosuppressants, 120 Kawasaki disease and, 314 kwashiorkor, 71 loop diureties for, 608 periorbital, 159, 161 peripheral, 309, 610 pitting, 309 pulmonary hypertension, 668 Trichinella spiralis, 159, 161 trichinosis, 159 wasogenic, 496 wet beriberi, 66 Edinger-Westphal nuclei, 539 Edirophonium, 240 Edinger-Westphal nuclei, 539 Edirophonium, 240 Edinger-Westphal nuclei, 539 Ediretive refractory period Class IA antiarrhythmic effect, 322 Class IC antiarrhythmic effect, 322 Class IC antiarrhythmic effect, 322 Class IC antiarrhythmic effect, 322 Class IC antiarrhythmic effect, 322 Class IC antiarrhythmic effect, 322 Class IC antiarrhythmic effect, 322 Class IC antiarrhythmic effect, 322 Class IC antiarrhythmic effect, 322 Class IC antiarrhythmic effect, 322 Class IC antiarrhythmic effect, 322 Class IC antiarrhythmic effect, 322 Class IC antiarrhythmic effect, 322 Class IC antiarrhythmic effect, 322 Class IC antiarrhythmic effect, 322 Class IC antiarrhythmic effect, 322 Class IC antiarrhythmic effect, 322 Class IC antiarrhythmic effect, 322 Class IC antiarrhythmic effect, 322 Class IC antiarrhythmic effect, 322 Class IC antiarrhythmic effect, 322 Class IC antiarrhythmic effect, 322 Class IC antiarrhythmic effect, 322 Class IC antiarrhythmic effect, 322 Class IC antiarrhythmic effect, 322 Class IC antiarrhythmic effect, 322 Class IC antiarrhythmic effect, 322 Class IC antiarrhythmic effect, 322 Class IC antiarrhythmic effect, 322 Class IC antiarrhythmic effect, 322 Class IC antiarrhythmic effect, 322 Class IC antiarrhythmic effect, 322 Class IC antiarrhythmic effect, 322 Class IC antiarrhythmic effect, 322 Class IC antiarrhythmic effect, 322 Class IC antiarrhythmic effect, 322 Class IC antiarrhythmic effect, 322 Class IC antiarrhythmic effect, 322 Class IC antiarrhythmic effect, 322 Class IC antiarrhythmic effect, 322 Class IC antiarrhythmic effect, 322 Class IC antiarrhythmic effect, 322 Class IC antiarrhythmic effect, 322 Class IC antiarrhythmic effect, 322 Class				
with hyperaldosteronism, 349 immunosuppressants, 120 Electroencephalogram (EEG) Creutzfelds-Jakob disease, 521 in delirium, 558 electroencephalogram (EEG) Creutzfelds-Jakob disease, 521 in delirium, 558 shorters for, 608 periorbital, 159, 161 peripheral, 309, 610 pitting, 309 pseudoephedrine/phenylephrine, 686 pulmonary hypertension, 668 ruchienionsis, 159 vasogenic, 496 web beriberi, 66 Edema factor Bacillus anthracis, 132 Elementary bodies (chlamydiae), Edwards syndrome, 63 cataracts and, 535 chromosome association, 64 Elewards syndrome, 63 cataracts and, 535 chromosome association, 64 Elementary bodies (chlamydiae) Effective rerale plasma flow, 582 Efferent Mafrectory period Class IC antiarrhythmic effect, 322 myocardial action potential, 292 Efferent arteriole, 580 ANP/BNP, 588 ANP/BNP, 588 ANP/BNP, 588 Constriction of, 583 Endogram psychosis, 562 Electroon transpositions, 520 in delirium, 52 lectrooneephalogram (EEG) Creutzfelds-Jakob disease, 521 in delirium, 558 sheep, sages, 497 electrooneephalogram (EEG) Creutzfelds-Jakob disease, 521 in delirium, 558 sheep, sages, 497 electrooneephalogram (EEG) Creutzfelds-Jakob disease, 521 in delirium, 558 sheep, sages, 497 electrooneephalogram (EEG) Creutzfelds-Jakob disease, 521 in delirium, 558 sheep, sages, 497 electrooneephalogram (EEG) Creutzfelds-Jakob disease, 521 in delirium, 558 sheep, sages, 497 electrooneephalogram (EEG) Creutzfelds-Jakob disease, 521 in delirium, 558 sheep, sages, 497 electrooneephalogram (EEG) Creutzfelds-Jakob disease, 521 in delirium, 558 sheep sages, 497 electrooneephalogram (EEG) Creutzfelds-Jakob disease, 521 in delirium, 558 sheep sages, 497 electrooneephalogram (EEG) Creutzfelds-Jakob disease, 521 in delirium, 558 electrooneephalogram (EEG) Creutzfelds-Jakob disease, 521 in delirium, 558 sheep sages, 496 electroon ransport chain and oxidative phosphorylation, 78 lectroon acceptors (universal), 75 electroon acceptors (universal), 75 electroon acceptors (not previous for particular data provided diffusion-limited gas exchange, ele		adverse effects 562		
immunosuppressants, 120 Kawasaki disease and, 314 kwashiorkor, 71 loop diuretics for, 608 periorbital, 159, 161 peripheral, 309, 610 pitting, 309 pulmonary hypertension, 668 Trichinella spiralis, 159, 161 trichinosis, 159 asogenic, 496 wet beriberi, 66 Edema factor Bacillus anthracis, 132 Edimper-Westphal nuclei, 539 Ediophonium, 240 Edwards syndrome, 63 cataracts and, 535 chromosome association, 64 Eleviterize HIV-positive adults, 203 Elfective real plasma flow, 582 Efferentival Ferent nerves, 296 Efferent arteriole, 580 ANP/BNP, 588 ANP/BNP, 588 ANP/BNP, 588 Constriction of, 583  Electronecphalogram (EEG) Creutzfeldt-Jakob disease, 521 in delirium, 558 sleep stages, 497 diffusion in, 668 Emphyslema, 674 diffusion in, 668 ed fifusion-inmitted gas exchange, diffusion-inmitted gas exchange, eastor in, 668 Emphyful can test, 446 Emphysema, 592 Emptyful can test, 446 Emphysema, 592 Emptyful can test, 446 Emphysema, 392 Emphysema, 674 diffusion-inmitted gas exchange, diffusion-in				
Kawasaki disease and, 314 kwashiorkor, 71 loop diuretics for, 608 periorbital, 159, 161 peripheral, 309, 610 pitting, 309 gene disturbances in, 591 diuretic effects on, 609 pulmonary hypertension, 668 pulmonary hypertension, 668 richinosis, 159 vasogenic, 496 wet beriberi, 66 Edema factor Bacillus anthracis, 132 Elementary bodies (chlamydiae), Ediager-Westphal nuclei, 539 elaranets and, 535 chromosome association, 64 Efferitur effects or, 69 Efferent arteriole, 580 ANP/BNP, 588 constriction of, 583  ANP/BNP, 588 Constriction of, 583  Electrop fores in delirium, 558 sleep stages, 497 diffusion in, 668 diffusion in, 668 diffusion in, 668 diffusion-limited gas exchange, 674 diffusion in, 668 diffusion-limited gas exchange, 668 elastin in, 52 panacinar, 392 Electron transport chain and oxidative phosphorylation, 78 lelectron transport chain and oxidative phosphorylation, 78 linhibitors of, 78 inhibitors of, 78 lelectrophoresis hemoglobin, 410 Elek test, 139 lelectrophoresis hemoglobin, 410 Elementary bodies (chlamydiae), 118-hydroxylase, 335 l-l-deoxycortisol and metyrapone, 335 l-l-deoxycortisol and metyrapone, 335 l-l-deoxycortisol and metyrapone, 335 l-l-deoxycortisol constant, 231 Elimination of drugs, 232 myocardial action potential, 292 Effective renal plasma flow, 582 Efferent Merter ten verse, 296 Efferent arteriole, 580 ANP/BNP, 588 constriction of, 583  Emphysema, 674 diffusion-limited gas exchange, 668 elastin in, 52 panacinar, 392 Emphyfull can test, 446 Empty sells syndrome, 339 Electrophoresis hemoglobin, 410 Enchortrial carcinoma, 648 eriophorial (affusion-limited gas exchange, 674 diffusion-limited gas exchange, 674 diffusion-limited gas exchange, 678 diffusion-limited gas exchange, 678 diffusion-limited gas exchange, 678 diffusion-limited gas exchange, 678 diffusion-limited gas exchange, 678 diffusion-limited gas exchange, 678 diffusion-limited gas exchange, 678 diffusion-limited gas exchange, 678 diffusion-limited gas exchange, 678 diffusion-limited gas exchange, 678 diffusion-limited gas exchange		Fleetroepeephalogram (FEC)		
kwashiorkor, 71 loop diuretics for, 608 periorbital, 159, 161 peripheral, 309, 610 pitting, 309 pseudoephedrine/phenylephrine, 686 Trichinella spiralis, 159, 161 trichinosis, 159 web beriberi, 66 Edema factor Bacillus anthracis, 132 Edimagr-Westphal nuclei, 539 Ediorphonium, 240 Edwards syndrome, 63 cataracts and, 535 Ederom cases and, 535 Electron range of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the properties of the propert				
loop diuretics for, 608 periorbital, 159, 161 peripheral, 309, 610 pitting, 309 pseudoephedrine/phenylephrine, 686 pulmonary hypertension, 668 pulmonary hypertension, 668 pulmonary hypertension, 668 pulmonary hypertension, 668 pulmonary hypertension, 668 pulmonary hypertension, 668 pulmonary hypertension, 668 pulmonary hypertension, 668 pulmonary hypertension, 668 pulmonary hypertension, 668 pulmonary hypertension, 668 pulmonary hypertension, 668 pulmonary hypertension, 668 pulmonary hypertension, 668 pulmonary hypertension, 668 pulmonary hypertension, 668 pulmonary hypertension, 668 pulmonary hypertension, 668 pulmonary hypertension, 668 pulmonary hypertension, 668 pulmonary hypertension, 668 pulmonary hypertension, 668 pulmonary hypertension, 668 pulmonary hypertension, 668 pulmonary hypertension, 668 pulmonary hypertension, 668 pulmonary hypertension, 668 pulmonary hypertension, 668 pulmonary hypertension, 668 pulmonary hypertension, 668 pulmonary hypertension, 668 pulmonary hypertension, 668 pulmonary hypertension, 668 pulmonary hypertension, 668 pulmonary hypertension, 668 pulmonary hypertension, 668 pulmonary hypertension, 668 pulmonary hypertension, 668 pulmonary hypertension, 668 pulmonary hypertension, 668 pulmonary hypertension, 668 pulmonary hypertension, 668 pulmonary hypertension, 668 pulmonary hypertension, 668 pulmonary hypertension, 668 pulmonary hypertension, 668 pulmonary hypertension, 668 pulmonary hypertension, 668 pulmonary hypertension, 668 pulmonary hypertension, 668 pulmonary hypertension of 68 pulmonary hypertension, 668 pulmonary hypertension, 67 pulmonary hypertension, 68 pulmonary hypertension, 68 pulmonary hypertension, 68 pulmolary hypertension, 68 pulmolary hyperplasion, 78 panacinar, 392 panacinar, 392 panacinar, 392 panacinar, 392 panacinar, 392 panacinar, 392 panacinar, 392 panacinar, 392 panacinar, 392 panacinar, 392 panacinar, 392 panacinar, 392 panacinar, 392 panacinar, 392 panacinar, 392 panacinar, 392 panacinar, 392 panacinar, 392 panacinar, 392 panacinar, 392 panacinar, 3				
periorbital, 159, 161 peripheral, 309, 610 pitting, 309 pseudoephedrine/phenylephrine, 686 Trichinella spiralis, 159, 161 trichinosis, 159 wet beriberi, 66 Edera factor Beacillus anthracis, 132 Edinger-Westphal nuclei, 539 Edrophonium, 240 Edwards syndrome, 63 cataracts and, 535 chromosome association, 64 Effevire refractory period Class IA antiarrhythmic effect, 322 myocardial action potential, 292 Effective refractory period Class IA antiarrhythmic effect, 322 myocardial action potential, 292 Effective refractory period Class IA antiarrhythmic effect, 322 myocardial action potential, 292 Effective refractory period Class IA antiarrhythmic effect, 322 myocardial action potential, 292 Effective refractory period Class IA antiarrhythmic effect, 322 myocardial action potential, 292 Effective refractory period Class IA antiarrhythmic effect, 322 myocardial action potential, 292 Effective refractory period Class IA antiarrhythmic effect, 322 myocardial action potential, 292 Effective refractory period Class IA antiarrhythmic effect, 322 myocardial action potential, 292 Effective refractory period Class IA antiarrhythmic effect, 322 myocardial action potential, 292 Effective refractory period Class IA antiarrhythmic effect, 322 myocardial action potential, 292 Effective refractory period Class IA antiarrhythmic effect, 322 myocardial action potential, 292 Effective refractory period Class IA antiarrhythmic effect, 322 myocardial action potential, 292 Effective refractory period Class IA antiarrhythmic effect, 322 myocardial action potential, 292 Effective refractory period Class IA antiarrhythmic effect, 322 myocardial action potential, 292 Effective refractory period Class IA antiarrhythmic effect, 322 myocardial action potential, 292 Effective refractory period Class IA antiarrhythmic effect, 322 myocardial action potential, 292 Effective refractory period Class IA antiarrhythmic effect, 322 myocardial action potential, 292 Effective refractory period Class IA antiarrhythmic effect, 322 myocardial action potential				
peripheral, 309, 610 pitting, 309 pseudoephedrine/phenylephrine, 686 pulmonary hypertension, 668 Trichinella spiralis, 159, 161 trichinosis, 159 vasogenic, 496 wet beriberi, 66 Edema factor Bacillus anthracis, 132 Edinger-Westphal nuclei, 539 Edrophonium, 240 Edwards syndrome, 63 cataracts and, 535 chromosome association, 64 EEdivirenz HIV-positive adults, 203 Electron succeptors (chlamydiae), 11-deoxycortisol and metyrapone, 335 Effective refractory period Class IA antiarrhythmic effect, 322 myocardial action potential, 292 Efferctive renal plasma flow, 582 Effective renal plasma flow,	*			
pitting, 309 pseudoephedrine/phenylephrine, 686 pulmonary hypertension, 668 Trichinella spiralis, 159, 161 trichinosis, 159 vasogenic, 496 wet beriberi, 66 Edema factor Bacillus anthracis, 132 Edionger-Westphal nuclei, 539 Edwards syndrome, 63 cataracts and, 555 chromosome association, 64 Effective refractory period Class IA antiarrhythmic effect, 322 myocardial action potential, 292 Effective refractory period Effective refractory period Effective renal plasma flow, 582 Efferent arteriole, 580 ANP/BNP, 588 constriction of, 583  diuretic effects on, 609 Electron suniversal), 75 Electron transport chain and oxidative phosphorylation, 77 Electron transport chain and oxidative phosphorylation, 77 Trichinella spiralis, 159, 161 Trichinella spiralis, 159, 161 Trichinella spiralis, 159, 161 Trichinella spiralis, 159, 161 Trichinella spiralis, 159, 161 Trichinella spiralis, 159, 161 Trichinella spiralis, 159, 161 Trichinella spiralis, 159, 161 Trichinella spiralis, 159, 161 Trichinella spiralis, 159, 161 Trichinella spiralis, 159, 161 Trichinella spiralis, 159, 161 Trichinella spiralis, 159, 161 Trichinella spiralis, 159, 161 Trichinella spiralis, 159, 161 Trichinella spiralis, 159, 161 Trichinella spiralis, 159 Leletron transport chain and oxidative phosphorylation, 78 Eletron transport chain and Emptyfull can test, 446 Empty sella syndrome, 339 Endraril, 203 Endapril, 610 Emcapsulated bacteria, 127 infections with immunodeficiency, 18 Encephalitis Encephalitis Encephalitis Encephalitis Inhibitors of, 78 Ill-deoxycorticosterone, 335 Ill-deoxycorticosterone, 335 Ill-deoxycorticosterone, 335 Ill-deoxycorticosterone, 335 Ill-deoxycorticosterone, 335 Ill-deoxycorticosterone, 335 Ill-deoxycorticosterone, 335 Ill-deoxycorticosterone, 335 Ill-deoxycorticosterone, 335 Ill-deoxycorticosterone, 335 Ill-deoxycorticosterone, 335 Ill-deoxycorticosterone, 335 Ill-deoxycorticosterone, 335 Ill-deoxycorticosterone, 335 Ill-deoxycorticosterone, 335 Ill-deoxycorticosterone, 335 Ill-deoxycorticosterone, 335 Ill-deoxycorticosterone, 335				
pseudoephedrine/phenylephrine, 686 Electron acceptors (universal), 75 Electron transport chain and oxidative phosphorylation, principles application oxidative phosphorylation, principles application oxidative phosphorylation, principles application oxidative phosphorylation, principles application oxidative phosphorylation, principles application oxidative phosphorylation, oxidative phosphorylation, principles application oxidative phosphorylation, oxidative phosphorylation, principles application oxidative phosphorylation, oxidative phosphorylation, principles application oxidative phosphorylation, oxidative phosphorylation, principles application oxidative phosphorylation, oxidative phosphorylation, principles application oxidative phosphorylation, principles application oxidative phosphorylation, principles application, oxidative phosphorylation, principles application, oxidative phosphorylation, principles application, oxidative phosphorylation, principles application, oxidative phosphorylation, principles application, oxidative phosphorylation, principles application, oxidative phosphorylation, principles application, oxidative phosphorylation, principles application, oxidative phosphorylation, principles application, oxidative phosphorylation, principles application, oxidative phosphorylation, principles application, oxidative phosphorylation, principles application, oxidative phosphorylation, principles application, oxidative phosphorylation, principles application, oxidative phosphorylation, principles application, oxidative phosphorylation, principles application, oxidative phosphorylation, principles application, oxidative phosphorylation, principles application, oxidative phosphorylation, principles application, oxidative phosphorylation, principles application, oxidation, oxidative phosphorylation, principles application, oxidation, oxidative phosphorylation, principles application, oxidation, oxidativ				
Electron transport chain and pulmonary hypertension, 668 principal spiralis, 159, 161 trichinosis, 159 vasogenic, 496 properties (and the properties of Electrophoresis hemoglobin, 410 elek test, 139 leltronbonium, 240 elek test, 139 leltronborose association, 64 effective refractory period Class IA antiarrhythmic effect, 322 myocardial action potential, 292 effective renal plasma flow, 582 constriction of, 583 electrophoresis (and referent arteriole, 580 constriction of, 583 electrophoresis (and the properties) (arminum oxidative phosphorylation, oxidative phosphorylation, oxidative phosphorylation, oxidative phosphorylation, oxidative phosphorylation, oxidative phosphorylation, oxidative phosphorylation, oxidative phosphorylation, oxidative phosphorylation, oxidative phosphorylation, oxidative phosphorylation, oxidative phosphorylation, oxidative phosphorylation, oxidative phosphorylation, oxidative phosphorylation, oxidative phosphorylation, oxidative phosphorylation, oxidative phosphorylation, oxidative phosphorylation, oxidative phosphorylation, oxidative phosphorylation, oxidative phosphorylation, oxidative phosphorylation, oxidative phosphorylation, oxidative phosphorylation, oxidative phosphorylation, oxidative phosphorylation, oxidative phosphorylation, oxidative phosphorylation, oxidative phosphorylation, oxidative phosphorylation, oxidative phosphorylation, oxidative phosphorylation, oxidative phosphorylation, oxidative phosphorylation, oxidative phosphorylation, oxidative phosphorylation, oxidative phosphorylation, oxidative phosphorylation, oxidative phosphorylation, oxidative phosphorylation, oxidative phosphorylation, oxidative phosphorylation, oxidative phosphorylation, oxidative phosphorylation, oxidative phosphorylation, oxidative phosphorylation, oxidative phosphorylation, oxidative phosphorylation, oxidative phosphorylation, oxidative phosphorylation, oxidative phosphorylation, oxidative phosphorylation, oxidative phosphorylation, oxidative phosphorylation, oxidative phosphorylation, oxida	pitting, 309			
pulmonary hypertension, 668 Trichinella spiralis, 159, 161 Trichinosis, 159 vasogenic, 496 wet beriberi, 66 Edema factor Bacillus anthracis, 132 Edinger-Westphal nuclei, 539 Edwards syndrome, 63 cataracts and, 535 chromosome association, 64 Effective refractory period Class IA antiarrhythmic effect, 322 myocardial action potential, 292 Effective renal plasma flow, 582 cmstriction of, 583  minibitors of, 78 Electrophoresis hemoglobin, 410 Elek test, 139 Elementary bodies (chlamydiae), 118 Encephalitis anti-NMDA receptor, 228 Endometrial hyperplasia follicular cysts, 646 Endometrial polyps uterine bleeding with, 633 Endometrial polyps uterine bleeding with, 633 Endometrial polyps uterine bleeding with, 633 Endometrial polyps uterine bleeding with, 633 Endometrial polyps uterine bleeding with, 633 Endometrial polyps uterine bleeding with, 633 Endometrial polyps uterine bleeding with, 633 Endometrial polyps uterine bleeding with, 633 Endometrial polyps uterine bleeding with, 633 Endometrial polyps uterine bleeding with, 633 Endometrial polyps uterine bleeding with, 633 Endometrial polyps uterine bleeding with, 633 Endometrial polyps uterine bleeding with, 633 Endometrial polyps uterine bleeding with, 633 Endometrial polyps uterine bleeding with, 633 Endometrial polyps uterine bleeding with, 633 Endometrial polyps uterine bleeding with, 633 Endometrial polyps uterine bleeding with, 633 Endometrial polyps uterine bleeding with, 633 Endometrial polyps uterine bleeding with, 633 Endometrial polyps uterine bleeding with, 633 Endometrial polyps uterine bleeding with, 633 Endometrial polyps uterine bleeding with, 633 Endometrial polyps uterine bleeding with, 633 Endometrial polyps uterine bleeding with, 633 Endometrial polyps uterine bleeding with, 633 Endometrial polyps uterine bleeding with, 633 Endometrial polyps uterine bleeding with, 633 Endometrial polyps uterine bleeding with 632 Endometrial polyps uterine bleeding with 632 Endometrial polyps uterine bleeding with 632 Endometrial polyps uterine bleeding with 632 En				
Trichinella spiralis, 159, 161 trichinosis, 159 inhibitors of, 78 inhibitors of, 78 inhibitors of, 78 electrophoresis wet beriberi, 66 bedema factor Bacillus anthracis, 132 Elementary bodies (chlamydiae), Edinger-Westphal nuclei, 539 Ediophonium, 240 Elementary bodies (chlamydiae), Edwards syndrome, 63 cataracts and, 535 chromosome association, 64 Effeverite adults, 203 EHIV-positive adults, 203 EHIV-positive adults, 203 EHIP-positive adults, 203 Elementary bodies (chlamydiae), 11-deoxycortisol and metyrapone, 335 Elephantiasis, 159 11-deoxycorticosterone, 335 Elfin facies, 64 Elimination constant, 231 Elimination of drugs, 232 myocardial action potential, 292 Effective renal plasma flow, 582 Efferent arteriole, 580 ANP/BNP, 588 constriction of, 583  Emtricitabine, 203 HIV-positive adults, 203 Enalapril, 610 Encapsulated bacteria, 127 infections with immunodeficiency, infections with immunodeficiency, infections with immunodeficiency, infections with immunodeficiency, infections with immunodeficiency, infections with immunodeficiency, infections with immunodeficiency, infections with immunodeficiency, infections with immunodeficiency, infections with immunodeficiency, infections with immunodeficiency, infections with immunodeficiency, infections with immunodeficiency, infections with immunodeficiency, infections with immunodeficiency, infections with immunodeficiency, infections with immunodeficiency, infections with immunodeficiency, infections with immunodeficiency, infections with immunodeficiency, infections with immunodeficiency, infections with immunodeficiency, infections with immunodeficiency, infections with immunodeficiency, infections with immunodeficiency, infections with immunodeficiency, infections with immunodeficiency, infections with immunodeficiency, infections with immunodeficiency, infections with immunodeficiency, infections with immunodeficiency, infections with immunodeficiency, infections with immunodeficiency, infections with immunodeficiency, infections with immunodeficiency, infectio				
trichinosis, 159 vasogenic, 496 wet beriberi, 66 Edema factor Bacillus anthracis, 132 Edinger-Westphal nuclei, 539 Edwards syndrome, 63 cataracts and, 535 chromosome association, 64 Effevirenz HIV-positive adults, 203 Elementary bodies (chlamydiae), 118 Encephalltis Encephalltis Encephalltis Encephalltis anti-NMDA receptor, 228 Cryptococcus neoformans, 153 guanosine analogs, 201 herpesviruses, 165, 180 HIV-positive adults, 203 Endometrial polyps utterine bleeding with, 633 Endometrial vein, 617 infections with immunodeficiency, infections with immunodeficiency, 118 Encephalltis Characteristics and treatment, 648 danazol for, 658 Endometriial polyps utterine bleeding with, 633 Endometrial polyps uterine bleeding with, 633 Endometrial vein, 617 infections with immunodeficiency, 118 Encephalltis Encephalltis Ananzol for, 658 Endometrial vein, 617 infections with immunodeficiency, 118 Encephalltis Endometrial polyps uterine bleeding with, 633 Endometrial vein, 617 infections with immunodeficiency, 118 Encephalltis Endometrial vein, 617 Endometrial vein, 617 infections with immunodeficiency, 118 Endometrial vein, 617 Endometrial vein, 617 Endometrial vein, 617 Endometrial vein, 617 Endometrial vein, 617 Endometrial vein, 617 Endometrial vein, 617 Endometrial vein, 617 Endometrial vein, 617 Endometrial vein, 617 Endometrial vein, 617 Endometrial vein, 617 Endometrial vein, 617 Endometrial vein, 617 Endometrial vein, 617 Endometrial vein, 617 Endometrial vein, 617 Endometrial vein, 617 Endometrial vein, 617 Endometrial vein, 617 Endometrial vein, 617 Endometrial vein, 617 Endometrial vein, 617 Endometrial polyps uterine bleeding with, 633 Endometrial po			* *	
vasogenic, 496 wet beriberi, 66 hemoglobin, 410 Edema factor Bacillus anthracis, 132 Edinger-Westphal nuclei, 539 Edrophonium, 240 Edwards syndrome, 63 cataracts and, 535 chromosome association, 64 Effevienz HIV-positive adults, 203 Effective refractory period Class IA antiarrhythmic effect, 322 myocardial action potential, 292 Efferent arteriole, 580 ANP/BNP, 588 constriction of, 583  Electrophoresis hemoglobin, 410 Encapsulated bacteria, 127 infections with immunodeficiency, infections with immunodeficiency, infections with immunodeficiency, infections with immunodeficiency, infections with immunodeficiency, 118 Encephalitis anti-NMDA receptor, 228 Cryptococcus neoformans, 153 guanosine analogs, 201 herpesviruses, 165, 180 hemoglobin, 410 Encapsulated bacteria, 127 Endometrial vein, 617 Endometriosis characteristics and treatment, 648 danazol for, 658 Endometritis, 648 Endometritis, 648 Endometriitis, 648 Endometriitis, 648 Endometriitis, 648 Endometriitis, 648 Endometriitis, 648 Endometrial vein, 617 Endometrial vein, 617 Endometriosis characteristics and treatment, 648 danazol for, 658 Endometriitis, 648 Endometriitis, 648 Endometriitis, 648 Endometriitis, 648 Endometriitis, 648 Endometriitis, 648 Endometriitis, 648 Endometriitis, 648 Endometriitis, 648 Endometriitis, 648 Endometriitis, 648 Endometriitis, 648 Endometriitis, 648 Endometriitis, 648 Endometriitis, 648 Endometriitis, 648 Endometriitis, 648 Endometriitis, 648 Endometriitis, 648 Endometriitis, 648 Endometriitis, 648 Endometriitis, 648 Endometriitis, 648 Endometriitis, 648 Endometriitis, 648 Endometriitis, 648 Endometriitis, 648 Endometriitis, 648 Endometriitis, 648 Endometriitis, 648 Endometriitis, 648 Endometriitis, 648 Endometriitis, 648 Endometriitis, 648 Endometriitis, 648 Endometriitis, 648 Endometriitis, 648 Endometriitis, 648 Endometriitis, 648 Endometriitis, 648 Endometriitis, 648 Endometriitis, 648 Endometriitis, 648 Endometriitis, 648 Endometriitis, 648 Endometriitis, 648 Endometriitis, 648 Endometriitis, 648 Endometriitis, 648 Endometr				
wet beriberi, 66 Edema factor Edem factor Bacillus anthracis, 132 Edinger-Westphal nuclei, 539 Edrophonium, 240 Edwards syndrome, 63 cataracts and, 535 chromosome association, 64 Effective refractory period Class IA antiarrhythmic effect, 322 myocardial action potential, 292 Efferent arteriole, 580 ANP/BNP, 588 constriction of, 583  hemoglobin, 410 Elek test, 139 Elek test, 139 Elek test, 139 Elek test, 139 Elek test, 139 Elek test, 139 Elek test, 139 Elek test, 139 Elek test, 139 Elek test, 139 Elek test, 139 Elek test, 139 Elek test, 139 Elek test, 139 Elek test, 139 Elek test, 139 Elek test, 139 Elek test, 139 Elek test, 139 Elek test, 139 Elek test, 139 Elek test, 139 I148 Encephalitis anti-NMDA receptor, 228 Cryptococcus neoformans, 153 guanosine analogs, 201 herpesviruses, 165, 180 herpesviruses, 165, 180 HKV identification, 166 Lassa fever, 167 neonatal, 182 Encephalomyelitis paraneoplastic, 228 paraneoplastic, 228 paraneoplastic syndrome, 228 Encephalopathy hepatic, 365, 391 hypertensive emergency, 300 Parametrial vein, 617 Endometriosis characteristics and treatment, 648 danazol for, 658 Endometritis, 648 Encapsulated bacteria, 127 Endometriosis characteristics and treatment, 648 danazol for, 658 Endometriosis characteristics and treatment, 648 danazol for, 658 Endometriosis characteristics and treatment, 648 danazol for, 658 Endometriosis characteristics and treatment, 648 danazol for, 658 Endometriosis characteristics and treatment, 648 danazol for, 658 Endometriosis characteristics and treatment, 648 danazol for, 658 Endometriosis characteristics and treatment, 648 danazol for, 658 Endometriosis characteristics and treatment, 648 danazol for, 658 Endometriosis characteristics and treatment, 648 danazol for, 658 Endometriosis characteristics and teatment, 648 danazol for, 658 Endometriosis characteristics and teatment, 648 danazol for, 658 Endometriosis characteristics and teatment, 648 danazol for, 658 Endometrium hyperplasia, 648–649 maintenance of, 632 Endometrium hyperplasia, 648–649 maintenance	trichinosis, 159	inhibitors of, 78		
Edema factor Bacillus anthracis, 132 Edinger-Westphal nuclei, 539 Edrophonium, 240 Edwards syndrome, 63 cataracts and, 535 chromosome association, 64 Effective refractory period Class IC antiarrhythmic effect, 322 myocardial action potential, 292 Efferent arteriole, 580 ANP/BNP, 588 constriction of, 583  Elek test, 139 Elek test, 139 Elementary bodies (chlamydiae), 118 Encephallitis anti-NMDA receptor, 228 Endometritis, 648 Encophalitis anti-NMDA receptor, 228 Endometritis, 648 Endometrium hyperplasia, 648–649 maintenance of, 632 Endometrium hyperplasia, 648–649 maintenance of, 632 Endometrium hyperplasia, 648 Endometrium hyperplasia, 648–649 maintenance of, 632 Endometrium hyperplasia, 648 Endometrium hyperplasia, 648 Endometrium hyperplasia, 648 Endometrium hyperplasia, 648 Endometrium hyperplasia, 648 Endometrium hyperplasia, 648 Endometrium hyperplasia, 648 Endometrium hyperplasia, 648 Endometrium hyperplasia, 648 Endometrium hyperplasia, 648 Endometrium hyperplasia, 648 Endometrium hyperplasia, 648 Endometrium hyperplasia, 648 Endometrium hyperplasia, 648 Endometrium hyperplasia, 648 Endometrium hyperplasia, 648 Endometrium hyperplasia, 648 Endometrium hyperplasia, 648 Endometrium hyperplasia, 648 Endometrium hyperplasia, 648 Endometrium hyperplasia, 648 Endometrium hyperplasia, 648 Endometrium hyperplasia, 648 Endometrium hyperplasia, 648 Endometrium hyperplasia, 648 Endometrium hyperplasia, 648 Endometrium hyperplasia, 648 Endometrium hyperplasia, 648 Endometrium hyperplasia, 648 Endometrium hyperplasia, 648 Endometrium hyperplasia, 648 Endometrium hyperplasia, 648 Endometrium hyperplasia, 648 Endometrium hyperplasia, 648 Endometrium hyperplasia, 648 Endometrium hyperplasia, 648 Endometrium hyperplasia, 648 Endometrium hyperplasia, 648 Endometrium hyperplasia, 648 Endometrium hyperplasia, 648 Endometrium hyperplasia, 648 Endometrium hyperplasia, 648 Endometrium hyperplasia, 648 Endometrium hyperplasia, 648 Endometrium hyperplasia, 648 Endometrium hyperplasia, 648 Endometrium hyperplasia, 648 Endometrium	vasogenic, 496	Electrophoresis	Enalapril, 610	uterine bleeding with, 633
Bacillus anthracis, 132 Edinger-Westphal nuclei, 539 Edrophonium, 240 Edwards syndrome, 63 cataracts and, 535 chromosome association, 64 Effavirenz HIV-positive adults, 203 Effective refractory period Class IA antiarrhythmic effect, 322 myocardial action potential, 292 Efferent/afferent nerves, 296 Efferent/afferent nerves, 296 ANP/BNP, 588 constriction of, 583  Elementary bodies (chlamydiae), 148 Encephalitis anti-NMDA receptor, 228 Cryptococcus neoformans, 153 guanosine analogs, 201 herpesviruses, 165, 180 HSV identification, 166 Lassa fever, 167 neonatal, 182 West Nile virus, 180 Endometritis, 648 Endometritis, 648 Endometrium hyperplasia, 648–649 maintenance of, 632 Endoneurium, 495 Endoplasmic reticulum, 46, 47 rough, 46 smooth, 46 Encephalomyelitis paraneoplastic, 228 paraneoplastic syndrome, 228 Encephalopathy hepatic, 365, 391 hypertensive emergency, 300 paraneoplastic semergency, 300 hypertensive emergency, 300 naming conventions for, 254 Endothelium-derived relaxing factor	wet beriberi, 66	hemoglobin, 410	Encapsulated bacteria, <b>127</b>	Endometrial vein, 617
Edinger-Westphal nuclei, 539 Edrophonium, 240 Edwards syndrome, 63 cataracts and, 535 chromosome association, 64 Effevirenz HIV-positive adults, 203 Effective refractory period Class IA antiarrhythmic effect, 322 Class IC antiarrhythmic effect, 322 myocardial action potential, 292 Effective renal plasma flow, 582 Effective renal plasma flow, 582 Effective renal plasma flow, 582 ANP/BNP, 588 constriction of, 583  I 48 Elephantiasis, 159 Elephantiasis, 159 Cryptococcus neoformans, 153 guanosine analogs, 201 herpesviruses, 165, 180 HSV identification, 166 Lassa fever, 167 neonatal, 182 West Nile virus, 180 Encephalomyelitis paraneoplastic, 228 paraneoplastic, 228 paraneoplastic syndrome, 228 Encephalopathy hyperplasia, 648–649 maintenance of, 632 Endoneurium, 495 Endoneurium, 495 Endoneurium, 495 Endoneurium, 495 Endoneurium, 495 Endoneurium, 495 Endoneurium, 495 Endoneurium, 495 Endoplasmic reticulum, 46, 47 rough, 46 smooth, 46 Encephalomyelitis paraneoplastic, 228 paraneoplastic syndrome, 228 Encephalopathy hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365,	Edema factor	Elek test, 139	infections with immunodeficiency,	Endometriosis
Edrophonium, 240 Edwards syndrome, 63 cataracts and, 535 chromosome association, 64 Efavirenz HIV-positive adults, 203 Effective refractory period Class IA antiarrhythmic effect, 322 myocardial action potential, 292 Effective renal plasma flow, 582 Effective renal plasma flow, 582 Efferent/afferent nerves, 296 Efferent arteriole, 580 ANP/BNP, 588 constriction of, 583  Elephantiasis, 159 anti-NMDA receptor, 228 Cryptococcus neoformans, 153 guanosine analogs, 201 hyperplasia, 648 Endometrium hyperplasia, 648 Endometrium hyperplasia, 649 maintenance of, 632 Endometrium hyperplasia, 648 Endometrium hyperplasia, 648 Endometrium hyperplasia, 648 Endometrium hyperplasia, 648 Endometrium hyperplasia, 648 Endometrium hyperplasia, 648 Encophalomys, 153 Elimination constant, 231 Elimination constant, 231 Elimination of drugs, 232 myocardial action potential, 292 Effective renal plasma flow, 582 Encephalomyelitis paraneoplastic syndrome, 228 Encephalopathy hyperplasia, 648 Endometrium hyperplasia, 648 Endometrium hyperplasia, 648 Endometrium hyperplasia, 648 Endometrium hyperplasia, 648 Endometrium hyperplasia, 648 Endometrium hyperplasia, 648 Endometrium hyperplasia, 648 Endometrium hyperplasia, 648 Endometrium hyperplasia, 648 Endometrium hyperplasia, 648 Endometrium hyperplasia, 648 Endometrium hyperplasia, 648 Endometrium hyperplasia, 648 Endometrium hyperplasia, 648 Endometrium hyperplasia, 648 Endometrium hyperplasia, 648 Endometrium hyperplasia, 648 Endometrium hyperplasia, 648 Endometrium hyperplasia, 648 Endometrium hyperplasia, 648 Endometrium hyperplasia, 648 Endometrium hyperplasia, 648 Endometrium hyperplasia, 648 Endometrium hyperplasia, 648 Endometrium hyperplasia, 648 Endometrium hyperplasia, 648 Endometrium hyperplasia, 648 Endometrium hyperplasia, 648 Endometrium hyperplasia, 648 Endometrium hyperplasia, 648 Endometrium hyperplasia, 648 Endometrium hyperplasia, 648 Endometrium hyperplasia, 648 Endometrium hyperplasia, 648 Endometrium hyperplasia, 648 Endometrium hyperplasia, 648 Endometrium hyperplasia,	Bacillus anthracis, 132	Elementary bodies (chlamydiae),	118	characteristics and treatment, 648
Edwards syndrome, 63 cataracts and, 535 chromosome association, 64 Efavirenz HIV-positive adults, 203 Effective refractory period Class IC antiarrhythmic effect, 322 myocardial action potential, 292 Effective renal plasma flow, 582 Effective renal plasma flow, 582 Effective renal plasma flow, 582 Efferent arteriole, 580 ANP/BNP, 588 constriction of, 583  I1-deoxycortisol and metyrapone, 335 I1-deoxycorticosterone, 335 HSV identification, 166 Lassa fever, 167 neonatal, 182 west Nile virus, 180 Endometrium hyperplasia, 648–649 maintenance of, 632 Endoneurium, 495 Endoplasmic reticulum, 46, 47 rough, 46 smooth, 46 Encephalomyelitis paraneoplastic, 228 paraneoplastic syndrome, 228 Encephalopathy hepatic, 365, 391 Endometrium hyperplasia, 648–649 maintenance of, 632 Endoneurium, 495 Endoplasmic reticulum, 46, 47 rough, 46 smooth, 46 Encephalomyelitis paraneoplastic syndrome, 228 Encephalopathy hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365 hepatic, 365 hepatic, 365 hepatic, 365 hepatic, 365 hepatic, 365 hepatic, 365 hepatic, 365 hepatic, 365 hepatic, 365 hepatic, 365 hepatic, 365 hepatic, 365 hepatic, 365 hepatic, 365 hepatic, 365 hepatic, 365 hepatic, 365 hepatic, 365 hepatic, 365 hepatic, 365 hepatic, 365 hepatic, 365 hepatic, 365 hepatic, 365 hepatic, 365 hepatic, 365 hepatic, 365 hepatic, 365 hepatic, 365 hepatic, 365 hepatic, 365 hepatic, 365 hepatic, 365 hepatic, 365 hepat	Edinger-Westphal nuclei, 539	148	Encephalitis	danazol for, 658
Edwards syndrome, 63 cataracts and, 535 chromosome association, 64 Efavirenz HIV-positive adults, 203 Effective refractory period Class IC antiarrhythmic effect, 322 myocardial action potential, 292 Effective renal plasma flow, 582 Effective renal plasma flow, 582 Effective renal plasma flow, 582 Efferent arteriole, 580 ANP/BNP, 588 constriction of, 583  I1-deoxycortisol and metyrapone, 335 I1-deoxycorticosterone, 335 HSV identification, 166 Lassa fever, 167 neonatal, 182 west Nile virus, 180 Endometrium hyperplasia, 648–649 maintenance of, 632 Endoneurium, 495 Endoplasmic reticulum, 46, 47 rough, 46 smooth, 46 Encephalomyelitis paraneoplastic, 228 paraneoplastic syndrome, 228 Encephalopathy hepatic, 365, 391 Endometrium hyperplasia, 648–649 maintenance of, 632 Endoneurium, 495 Endoplasmic reticulum, 46, 47 rough, 46 smooth, 46 Encephalomyelitis paraneoplastic syndrome, 228 Encephalopathy hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365, 391 hepatic, 365 hepatic, 365 hepatic, 365 hepatic, 365 hepatic, 365 hepatic, 365 hepatic, 365 hepatic, 365 hepatic, 365 hepatic, 365 hepatic, 365 hepatic, 365 hepatic, 365 hepatic, 365 hepatic, 365 hepatic, 365 hepatic, 365 hepatic, 365 hepatic, 365 hepatic, 365 hepatic, 365 hepatic, 365 hepatic, 365 hepatic, 365 hepatic, 365 hepatic, 365 hepatic, 365 hepatic, 365 hepatic, 365 hepatic, 365 hepatic, 365 hepatic, 365 hepatic, 365 hepatic, 365 hepatic, 365 hepat	Edrophonium, 240	Elephantiasis, 159	anti-NMDA receptor, 228	Endometritis, 648
cataracts and, 535 chromosome association, 64 Efavirenz HIV-positive adults, 203 Effective refractory period Class IA antiarrhythmic effect, 322 myocardial action potential, 292 Effective renal plasma flow, 582 Effective renal plasma flow, 582 Effective renal plasma flow, 582 Effective retractorely for ion of ANP/BNP, 588 constriction of, 583  11-deoxycortisol and metyrapone, 335 HSV identification, 166 Lassa fever, 167 neonatal, 182 west Nile virus, 180 Encephalomyelitis paraneoplastic syndrome, 228 Encephalopathy hpperplasia, 648–649 maintenance of, 632 Endoneurium, 495 Endoplasmic reticulum, 46, 47 rough, 46 smooth, 46 Endosomes, 47 Endosomes, 47 Endosomes, 47 Endothelial cells in munosorbent assay), 54 Encephalopathy hpyertensive emergency, 300 naming conventions for, 254 Endothelium-derived relaxing factor				,
chromosome association, 64 Efavirenz HIV-positive adults, 203 Effective refractory period Class IA antiarrhythmic effect, 322 Class IC antiarrhythmic effect, 322 myocardial action potential, 292 Effective renal plasma flow, 582 Effective renal plasma flow, 582 Effective renal plasma flow, 582 Effective renal plasma flow, 580 ANP/BNP, 588 constriction of, 583  ANP/BNP, 588 constriction of, 583  And metyrapone, 335 Il-deoxycorticosterone, 325 Il-deoxycorticosterone, 325 Il-deoxycorticosterone, 325 Il-deoxycorticosterone, 325 Il-deoxycorticosterone, 325 Il-deoxycorticosterone, 325 Il-deoxycorticosterone, 325 Il-deoxycorticosterone, 325 Il-deoxycorticosterone, 326 Il-deoxycorticosterone, 325 Il-deoxycorticosterone, 326 Il-deoxycorticosterone, 326 Il-deoxycorticosterone, 166 Il-deoxycorticosterone, 166 Il-deoxycorticosterone, 167 Il-deoxycorticosterone, 189 Il-deoxycorticosterone, 189 Il-deoxycorticosterone, 189 Il-deoxycorticosterone, 189 Il-deoxycorticosterone, 189 Il-deoxycorticosterone, 189 Il-deoxycorticosterone, 189 Il-de				
Efavirenz HIV-positive adults, 203 Effective refractory period Class IA antiarrhythmic effect, 322 myocardial action potential, 292 Effective renal plasma flow, <b>582</b> Effective renal plasma flow, <b>582</b> Effective renal plasma flow, <b>582</b> Effective renal plasma flow, <b>582</b> Effective renal plasma flow, <b>582</b> Efferent arteriole, 580 ANP/BNP, 588 constriction of, 583  Il-deoxycorticosterone, 335 Ellin facies, 64 Lassa fever, 167 neonatal, 182 west Nile virus, 180 Encephalomyelitis paraneoplastic, 228 paraneoplastic syndrome, 228 Encephalopathy hepatic, 365, 391 hypertensive emergency, 300 naming conventions for, 254 Endothelium-derived relaxing factor		*		
HIV-positive adults, 203 Effective refractory period Class IA antiarrhythmic effect, 322 Class IC antiarrhythmic effect, 322 myocardial action potential, 292 Effective renal plasma flow, 582 Effective renal plasma flow, 582 Efferent/afferent nerves, 296 Efferent arteriole, 580 ANP/BNP, 588 constriction of, 583  Ellin facies, 64 Elimination constant, 231 Elimination of drugs, 232 urine pH and, 233 Ellimination of drugs, 232 urine pH and, 233 EllisA (enzyme-linked paraneoplastic, 228 Encephalomyelitis paraneoplastic, 228 Encephalopathy hepatic, 365, 391 Endothelial cells Endothelia cells in wound healing, 216 Endothelia receptor antagonist, 686 naming conventions for, 254 Endothelium-derived relaxing factor				
Effective refractory period Class IA antiarrhythmic effect, 322 Class IC antiarrhythmic effect, 322 myocardial action potential, 292 Effective renal plasma flow, 582 Effective renal plasma flow, 582 Effective renal plasma flow, 582 Corynebacterium diphtheriae, 139 ANP/BNP, 588 constriction of, 583 Elimination constant, 231 neonatal, 182 rough, 46 smooth, 46 Encephalomyelitis Encosomes, 47 Encophalomyelitis paraneoplastic, 228 Endothelial cells Encophalopathy hepatic, 365, 391 Endothelia, 216 Endothelia receptor antagonist, 686 hypertensive emergency, 300 naming conventions for, 254 Endothelium-derived relaxing factor				
Class IA antiarrhythmic effect, 322 Class IC antiarrhythmic effect, 322 myocardial action potential, 292 Effective renal plasma flow, <b>582</b> Efferent/afferent nerves, 296 Efferent arteriole, 580 ANP/BNP, 588 constriction of, 583  Elimination of drugs, <b>232</b> urine pH and, 233 ELISA (enzyme-linked immunosorbent assay), <b>54</b> Encephalomyelitis paraneoplastic, 228 Encephalomyelitis paraneoplastic, 228 Encephalomyelitis paraneoplastic syndrome, 228 Encephalopathy Encephalopathy Encephalopathy In wound healing, 216 Endothelin receptor antagonist, 686 hypertensive emergency, 300 naming conventions for, 254 Endothelium-derived relaxing factor				
Class IC antiarrhythmic effect, 322 myocardial action potential, 292 myocardial action potential, 292 Effective renal plasma flow, <b>582</b> immunosorbent assay), <b>54</b> Efferent/afferent nerves, 296 Efferent arteriole, 580				
myocardial action potential, 292 Effective renal plasma flow, <b>582</b> Efferent/afferent nerves, 296 Efferent arteriole, 580 ANP/BNP, 588 constriction of, 583  ELISA (enzyme-linked immunosorbent assay), <b>54</b> Ellongation Factor 2 Corynebacterium diphtheriae, 139 eltrombopag (TPO receptor agonist), and paraneoplastic, 228 Encephalopathy hepatic, 365, 391 Endothelial cells leukocyte extravasation and, 215 in wound healing, 216 Endothelin receptor antagonist, 686 hypertensive emergency, 300 naming conventions for, 254 Endothelial cells leukocyte extravasation and, 215 in wound healing, 216 Endothelial cells leukocyte extravasation and, 215 in wound healing, 216 Endothelial cells leukocyte extravasation and, 215 in wound healing, 216 Endothelial cells leukocyte extravasation and, 215 in wound healing, 216 Endothelial cells leukocyte extravasation and, 215 in wound healing, 216 Endothelial cells				
Effective renal plasma flow, <b>582</b> Efferent/afferent nerves, 296  Efferent arteriole, 580  ANP/BNP, 588  constriction of, 583  immunosorbent assay), <b>54</b> Elongation Factor 2  Corynebacterium diphtheriae, 139 eltrombopag (TPO receptor agonist), 121  immunosorbent assay), <b>54</b> Encephalopathy hepatic, 365, 391 hypertensive emergency, 300 lead poisoning, 419  leukocyte extravasation and, 215 in wound healing, 216 Endothelin receptor antagonist, 686 naming conventions for, 254 Endothelium-derived relaxing factor				*
Efferent/afferent nerves, 296 Efferent arteriole, 580 ANP/BNP, 588 constriction of, 583  Elongation Factor 2 Corynebacterium diphtheriae, 139 eltrombopag (TPO receptor agonist), 121  Encephalopathy hepatic, 365, 391 hypertensive emergency, 300 lead poisoning, 419  in wound healing, 216 Endothelin receptor antagonist, 686 naming conventions for, 254 Endothelium-derived relaxing factor				
Efferent arteriole, 580			Encophalopathy	
ANP/BNP, 588 eltrombopag (TPO receptor agonist), hypertensive emergency, 300 naming conventions for, 254 constriction of, 583 121 lead poisoning, 419 Endothelium-derived relaxing factor				
constriction of, 583 121 lead poisoning, 419 Endothelium-derived relaxing factor				
Entracty vs potency of drugs, 255 Entriegravit, 205 Lyme disease, 146 (EDRF), 33/				
	Emcacy vs potency of drugs, 233	Eivitegravir, 205	Lyme disease, 140	(EDKF), 55/

FAS1\_2019\_21\_Index\_749-806.indd 766 11/21/19 12:27 PM

P 1
Endotoxins
effects of, 133
features of, 131
Enflurane, 550
seizures with, 251
Enfuvirtide, 203
HIV-positive adults, 203
Enhancers (gene expression), 41
Enoxacin, 195
Entacapone, 548
Entamoeba histolytica
amebiasis, 155
bloody diarrhea, 179
metronidazole, 195
Enteric gram ⊝ bacteria
facultative anaerobic metabolism,
127
Enteric nerves, 362, 401
Enteritis
vitamin B <sub>12</sub> deficiency, 69
vitamin B <sub>5</sub> deficiency, 67
vitamin B <sub>7</sub> deficiency, 68
Entered rates are garden 190
Enterobacter aerogenes, 189
Enterobacter spp
nosocomial infection, 185
Enterobius spp
diseases association, 161
infection routes, 158
Enterobius vermicularis, 159
Enterochromaffin-like (ECL) cells,
350, 373
Enterococci, <b>137</b>
penicillins for, 188
vancomycin 100
vancomycin, 190
vancomycin-resistant (VRE), 137
Enterococcus spp
UTIs, 181
Enterococcus faecalis, 137
Enterococcus faecium, 137
Enterocolitis
vitamin E excess, 70
Enterocolitis (necrotizing), 386
Enterocolitis (necrotizing), 386 Enterohemorrhagic Escherichia coli
Enterocolitis (necrotizing), 386 Enterohemorrhagic Escherichia coli
Enterocolitis (necrotizing), 386 Enterohemorrhagic <i>Escherichia coli</i> (EHEC), 132, 145, 178, 179
Enterocolitis (necrotizing), 386 Enterohemorrhagic Escherichia coli (EHEC), 132, 145, 178, 179 Enteroinvasive Escherichia coli
Enterocolitis (necrotizing), 386 Enterohemorrhagic Escherichia coli (EHEC), 132, 145, 178, 179 Enteroinvasive Escherichia coli (EIEC), 145, 179
Enterocolitis (necrotizing), 386 Enterohemorrhagic Escherichia coli (EHEC), 132, 145, 178, 179 Enteroinvasive Escherichia coli (EIEC), 145, 179 Enterokinase/enteropeptidase, 373
Enterocolitis (necrotizing), 386 Enterohemorrhagic Escherichia coli (EHEC), 132, 145, 178, 179 Enteroinvasive Escherichia coli (EIEC), 145, 179 Enterokinase/enteropeptidase, 373 Enteropathogenic Escherichia coli
Enterocolitis (necrotizing), 386 Enterohemorrhagic Escherichia coli (EHEC), 132, 145, 178, 179 Enteroinvasive Escherichia coli (EIEC), 145, 179 Enterokinase/enteropeptidase, 373 Enteropathogenic Escherichia coli (EPEC), 145
Enterocolitis (necrotizing), 386 Enterohemorrhagic Escherichia coli (EHEC), 132, 145, 178, 179 Enteroinvasive Escherichia coli (EIEC), 145, 179 Enterokinase/enteropeptidase, 373 Enteropathogenic Escherichia coli (EPEC), 145 Enterotoxigenic Escherichia coli
Enterocolitis (necrotizing), 386 Enterohemorrhagic Escherichia coli (EHEC), 132, 145, 178, 179 Enteroinvasive Escherichia coli (EIEC), 145, 179 Enterokinase/enteropeptidase, 373 Enteropathogenic Escherichia coli (EPEC), 145 Enterotoxigenic Escherichia coli (ETEC), 132, 179
Enterocolitis (necrotizing), 386 Enterohemorrhagic Escherichia coli (EHEC), 132, 145, 178, 179 Enteroinvasive Escherichia coli (EIEC), 145, 179 Enterokinase/enteropeptidase, 373 Enteropathogenic Escherichia coli (EPEC), 145 Enterotoxigenic Escherichia coli (ETEC), 132, 179 Enterovirus meningitis, 179, 180
Enterocolitis (necrotizing), 386 Enterohemorrhagic Escherichia coli (EHEC), 132, 145, 178, 179 Enteroinvasive Escherichia coli (EIEC), 145, 179 Enterokinase/enteropeptidase, 373 Enteropathogenic Escherichia coli (EPEC), 145 Enterotoxigenic Escherichia coli (ETEC), 132, 179 Enterovirus meningitis, 179, 180 Entorhinal cortex, 499
Enterocolitis (necrotizing), 386 Enterohemorrhagic Escherichia coli (EHEC), 132, 145, 178, 179 Enteroinvasive Escherichia coli (EIEC), 145, 179 Enterokinase/enteropeptidase, 373 Enteropathogenic Escherichia coli (EPEC), 145 Enterotoxigenic Escherichia coli (ETEC), 132, 179 Enterovirus meningitis, 179, 180
Enterocolitis (necrotizing), 386 Enterohemorrhagic Escherichia coli (EHEC), 132, 145, 178, 179 Enteroinvasive Escherichia coli (EIEC), 145, 179 Enterokinase/enteropeptidase, 373 Enteropathogenic Escherichia coli (EPEC), 145 Enterotoxigenic Escherichia coli (ETEC), 132, 179 Enterovirus meningitis, 179, 180 Entorhinal cortex, 499
Enterocolitis (necrotizing), 386 Enterohemorrhagic Escherichia coli (EHEC), 132, 145, 178, 179 Enteroinvasive Escherichia coli (EIEC), 145, 179 Enterokinase/enteropeptidase, 373 Enteropathogenic Escherichia coli (EPEC), 145 Enterotoxigenic Escherichia coli (ETEC), 132, 179 Enterovirus meningitis, 179, 180 Entorhinal cortex, 499 Enuresis
Enterocolitis (necrotizing), 386 Enterohemorrhagic Escherichia coli (EHEC), 132, 145, 178, 179 Enteroinvasive Escherichia coli (EIEC), 145, 179 Enterokinase/enteropeptidase, 373 Enteropathogenic Escherichia coli (EPEC), 145 Enterotoxigenic Escherichia coli (ETEC), 132, 179 Enterovirus meningitis, 179, 180 Entorhinal cortex, 499 Enuresis characteristics/treatment, 568 sleep stages and, 497
Enterocolitis (necrotizing), 386 Enterohemorrhagic Escherichia coli (EHEC), 132, 145, 178, 179 Enteroinvasive Escherichia coli (EIEC), 145, 179 Enterokinase/enteropeptidase, 373 Enteropathogenic Escherichia coli (EPEC), 145 Enterotoxigenic Escherichia coli (ETEC), 132, 179 Enterovirus meningitis, 179, 180 Entorhinal cortex, 499 Enuresis characteristics/treatment, 568 sleep stages and, 497 TCA use for, 575
Enterocolitis (necrotizing), 386 Enterohemorrhagic Escherichia coli (EHEC), 132, 145, 178, 179 Enteroinvasive Escherichia coli (EIEC), 145, 179 Enterokinase/enteropeptidase, 373 Enteropathogenic Escherichia coli (EPEC), 145 Enterotoxigenic Escherichia coli (ETEC), 132, 179 Enterovirus meningitis, 179, 180 Entorhinal cortex, 499 Enuresis characteristics/treatment, 568 sleep stages and, 497 TCA use for, 575 Envelopes (viral), 163
Enterocolitis (necrotizing), 386 Enterohemorrhagic Escherichia coli (EHEC), 132, 145, 178, 179 Enteroinvasive Escherichia coli (EIEC), 145, 179 Enterokinase/enteropeptidase, 373 Enteropathogenic Escherichia coli (EPEC), 145 Enterotoxigenic Escherichia coli (ETEC), 132, 179 Enterovirus meningitis, 179, 180 Entorhinal cortex, 499 Enuresis characteristics/treatment, 568 sleep stages and, 497 TCA use for, 575 Envelopes (viral), 163 env gene, 175
Enterocolitis (necrotizing), 386 Enterohemorrhagic Escherichia coli (EHEC), 132, 145, 178, 179 Enteroinvasive Escherichia coli (EIEC), 145, 179 Enterokinase/enteropeptidase, 373 Enteropathogenic Escherichia coli (EPEC), 145 Enterotoxigenic Escherichia coli (ETEC), 132, 179 Enterovirus meningitis, 179, 180 Entorhinal cortex, 499 Enuresis characteristics/treatment, 568 sleep stages and, 497 TCA use for, 575 Envelopes (viral), 163 env gene, 175 Enzalutamide, 658
Enterocolitis (necrotizing), 386 Enterohemorrhagic Escherichia coli (EHEC), 132, 145, 178, 179 Enteroinvasive Escherichia coli (EIEC), 145, 179 Enterokinase/enteropeptidase, 373 Enteropathogenic Escherichia coli (EPEC), 145 Enterotoxigenic Escherichia coli (ETEC), 132, 179 Enterovirus meningitis, 179, 180 Entorhinal cortex, 499 Enuresis characteristics/treatment, 568 sleep stages and, 497 TCA use for, 575 Envelopes (viral), 163 env gene, 175 Enzalutamide, 658 Enzyme kinetics, 230
Enterocolitis (necrotizing), 386 Enterohemorrhagic Escherichia coli (EHEC), 132, 145, 178, 179 Enteroinvasive Escherichia coli (EIEC), 145, 179 Enterokinase/enteropeptidase, 373 Enteropathogenic Escherichia coli (EPEC), 145 Enterotoxigenic Escherichia coli (ETEC), 132, 179 Enterovirus meningitis, 179, 180 Entorhinal cortex, 499 Enuresis characteristics/treatment, 568 sleep stages and, 497 TCA use for, 575 Envelopes (viral), 163 env gene, 175 Enzalutamide, 658 Enzyme kinetics, 230 antagonists, 234
Enterocolitis (necrotizing), 386 Enterohemorrhagic Escherichia coli (EHEC), 132, 145, 178, 179 Enteroinvasive Escherichia coli (EIEC), 145, 179 Enterokinase/enteropeptidase, 373 Enteropathogenic Escherichia coli (EPEC), 145 Enterotoxigenic Escherichia coli (ETEC), 132, 179 Enterovirus meningitis, 179, 180 Entorhinal cortex, 499 Enuresis characteristics/treatment, 568 sleep stages and, 497 TCA use for, 575 Envelopes (viral), 163 env gene, 175 Enzalutamide, 658 Enzyme kinetics, 230 antagonists, 234 partial agonists, 234
Enterocolitis (necrotizing), 386 Enterohemorrhagic Escherichia coli (EHEC), 132, 145, 178, 179 Enteroinvasive Escherichia coli (EIEC), 145, 179 Enterokinase/enteropeptidase, 373 Enteropathogenic Escherichia coli (EPEC), 145 Enterotoxigenic Escherichia coli (ETEC), 132, 179 Enterovirus meningitis, 179, 180 Entorhinal cortex, 499 Enuresis characteristics/treatment, 568 sleep stages and, 497 TCA use for, 575 Envelopes (viral), 163 env gene, 175 Enzalutamide, 658 Enzyme kinetics, 230 antagonists, 234 partial agonists, 234 Enzymes
Enterocolitis (necrotizing), 386 Enterohemorrhagic Escherichia coli (EHEC), 132, 145, 178, 179 Enteroinvasive Escherichia coli (EIEC), 145, 179 Enterokinase/enteropeptidase, 373 Enteropathogenic Escherichia coli (EPEC), 145 Enterotoxigenic Escherichia coli (ETEC), 132, 179 Enterovirus meningitis, 179, 180 Entorhinal cortex, 499 Enuresis characteristics/treatment, 568 sleep stages and, 497 TCA use for, 575 Envelopes (viral), 163 env gene, 175 Enzalutamide, 658 Enzyme kinetics, 230 antagonists, 234 partial agonists, 234 Enzymes glycolysis regulation, 76
Enterocolitis (necrotizing), 386 Enterohemorrhagic Escherichia coli (EHEC), 132, 145, 178, 179 Enteroinvasive Escherichia coli (EIEC), 145, 179 Enterokinase/enteropeptidase, 373 Enteropathogenic Escherichia coli (EPEC), 145 Enterotoxigenic Escherichia coli (ETEC), 132, 179 Enterovirus meningitis, 179, 180 Entorhinal cortex, 499 Enuresis characteristics/treatment, 568 sleep stages and, 497 TCA use for, 575 Envelopes (viral), 163 env gene, 175 Enzalutamide, 658 Enzyme kinetics, 230 antagonists, 234 partial agonists, 234 Enzymes glycolysis regulation, 76 lipid transport and, 91, 92
Enterocolitis (necrotizing), 386 Enterohemorrhagic Escherichia coli (EHEC), 132, 145, 178, 179 Enteroinvasive Escherichia coli (EIEC), 145, 179 Enterokinase/enteropeptidase, 373 Enteropathogenic Escherichia coli (EPEC), 145 Enterotoxigenic Escherichia coli (ETEC), 132, 179 Enterovirus meningitis, 179, 180 Entorhinal cortex, 499 Enuresis characteristics/treatment, 568 sleep stages and, 497 TCA use for, 575 Envelopes (viral), 163 env gene, 175 Enzalutamide, 658 Enzyme kinetics, 230 antagonists, 234 partial agonists, 234 Enzymes glycolysis regulation, 76 lipid transport and, 91, 92 rate-determining, 73
Enterocolitis (necrotizing), 386 Enterohemorrhagic Escherichia coli (EHEC), 132, 145, 178, 179 Enteroinvasive Escherichia coli (EIC), 145, 179 Enterokinase/enteropeptidase, 373 Enteropathogenic Escherichia coli (EPEC), 145 Enterotoxigenic Escherichia coli (ETEC), 132, 179 Enterovirus meningitis, 179, 180 Entorhinal cortex, 499 Enuresis characteristics/treatment, 568 sleep stages and, 497 TCA use for, 575 Envelopes (viral), 163 env gene, 175 Enzalutamide, 658 Enzyme kinetics, 230 antagonists, 234 partial agonists, 234 Enzymes glycolysis regulation, 76 lipid transport and, 91, 92 rate-determining, 73 terminology for, 73
Enterocolitis (necrotizing), 386 Enterohemorrhagic Escherichia coli (EHEC), 132, 145, 178, 179 Enteroinvasive Escherichia coli (EIC), 145, 179 Enterokinase/enteropeptidase, 373 Enteropathogenic Escherichia coli (EPEC), 145 Enterotoxigenic Escherichia coli (ETEC), 132, 179 Enterovirus meningitis, 179, 180 Entorhinal cortex, 499 Enuresis characteristics/treatment, 568 sleep stages and, 497 TCA use for, 575 Envelopes (viral), 163 env gene, 175 Enzalutamide, 658 Enzyme kinetics, 230 antagonists, 234 partial agonists, 234 Enzymes glycolysis regulation, 76 lipid transport and, 91, 92 rate-determining, 73 terminology for, 73 Eosin-methylene blue (EMB) agar
Enterocolitis (necrotizing), 386 Enterohemorrhagic Escherichia coli (EHEC), 132, 145, 178, 179 Enteroinvasive Escherichia coli (EIC), 145, 179 Enterokinase/enteropeptidase, 373 Enteropathogenic Escherichia coli (EPEC), 145 Enterotoxigenic Escherichia coli (ETEC), 132, 179 Enterovirus meningitis, 179, 180 Entorhinal cortex, 499 Enuresis characteristics/treatment, 568 sleep stages and, 497 TCA use for, 575 Envelopes (viral), 163 env gene, 175 Enzalutamide, 658 Enzyme kinetics, 230 antagonists, 234 partial agonists, 234 Enzymes glycolysis regulation, 76 lipid transport and, 91, 92 rate-determining, 73 terminology for, 73
Enterocolitis (necrotizing), 386 Enterohemorrhagic Escherichia coli (EHEC), 132, 145, 178, 179 Enteroinvasive Escherichia coli (EIC), 145, 179 Enterokinase/enteropeptidase, 373 Enteropathogenic Escherichia coli (EPEC), 145 Enterotoxigenic Escherichia coli (ETEC), 132, 179 Enterovirus meningitis, 179, 180 Entorhinal cortex, 499 Enuresis characteristics/treatment, 568 sleep stages and, 497 TCA use for, 575 Envelopes (viral), 163 env gene, 175 Enzalutamide, 658 Enzyme kinetics, 230 antagonists, 234 partial agonists, 234 Enzymes glycolysis regulation, 76 lipid transport and, 91, 92 rate-determining, 73 terminology for, 73 Eosin-methylene blue (EMB) agar
Enterocolitis (necrotizing), 386 Enterohemorrhagic Escherichia coli (EHEC), 132, 145, 178, 179 Enteroinvasive Escherichia coli (EIEC), 145, 179 Enterokinase/enteropeptidase, 373 Enteropathogenic Escherichia coli (EPEC), 145 Enterotoxigenic Escherichia coli (ETEC), 132, 179 Enterovirus meningitis, 179, 180 Entorhinal cortex, 499 Enuresis characteristics/treatment, 568 sleep stages and, 497 TCA use for, 575 Envelopes (viral), 163 env gene, 175 Enzalutamide, 658 Enzyme kinetics, 230 antagonists, 234 partial agonists, 234 Enzymes glycolysis regulation, 76 lipid transport and, 91, 92 rate-determining, 73 terminology for, 73 Eosin-methylene blue (EMB) agar special culture, 126
Enterocolitis (necrotizing), 386 Enterohemorrhagic Escherichia coli (EHEC), 132, 145, 178, 179 Enteroinvasive Escherichia coli (EIEC), 145, 179 Enterokinase/enteropeptidase, 373 Enteropathogenic Escherichia coli (EPEC), 145 Enterotoxigenic Escherichia coli (ETEC), 132, 179 Enterovirus meningitis, 179, 180 Entorhinal cortex, 499 Enuresis characteristics/treatment, 568 sleep stages and, 497 TCA use for, 575 Envelopes (viral), 163 env gene, 175 Enzalutamide, 658 Enzyme kinetics, 230 antagonists, 234 partial agonists, 234 Enzymes glycolysis regulation, 76 lipid transport and, 91, 92 rate-determining, 73 terminology for, 73 Eosin-methylene blue (EMB) agar special culture, 126 Eosinopenia, 424 Eosinophilia
Enterocolitis (necrotizing), 386 Enterohemorrhagic Escherichia coli (EHEC), 132, 145, 178, 179 Enteroinvasive Escherichia coli (EIEC), 145, 179 Enterokinase/enteropeptidase, 373 Enteropathogenic Escherichia coli (EPEC), 145 Enterotoxigenic Escherichia coli (ETEC), 132, 179 Enterovirus meningitis, 179, 180 Entorhinal cortex, 499 Enuresis characteristics/treatment, 568 sleep stages and, 497 TCA use for, 575 Envelopes (viral), 163 env gene, 175 Enzalutamide, 658 Enzyme kinetics, 230 antagonists, 234 partial agonists, 234 Enzymes glycolysis regulation, 76 lipid transport and, 91, 92 rate-determining, 73 terminology for, 73 Eosin-methylene blue (EMB) agar special culture, 126 Eosinopenia, 424 Eosinophilia Aspergillus fumigatus, 153
Enterocolitis (necrotizing), 386 Enterohemorrhagic Escherichia coli (EHEC), 132, 145, 178, 179 Enteroinvasive Escherichia coli (EIEC), 145, 179 Enterokinase/enteropeptidase, 373 Enteropathogenic Escherichia coli (EPEC), 145 Enterotoxigenic Escherichia coli (ETEC), 132, 179 Enterovirus meningitis, 179, 180 Entorhinal cortex, 499 Enuresis characteristics/treatment, 568 sleep stages and, 497 TCA use for, 575 Envelopes (viral), 163 env gene, 175 Enzalutamide, 658 Enzyme kinetics, 230 antagonists, 234 partial agonists, 234 Enzymes glycolysis regulation, 76 lipid transport and, 91, 92 rate-determining, 73 terminology for, 73 Eosin-methylene blue (EMB) agar special culture, 126 Eosinopenia, 424 Eosinophilia Aspergillus fumigatus, 153 Chlamydia trachomatis, 149
Enterocolitis (necrotizing), 386 Enterohemorrhagic Escherichia coli (EHEC), 132, 145, 178, 179 Enteroinvasive Escherichia coli (EIEC), 145, 179 Enterokinase/enteropeptidase, 373 Enteropathogenic Escherichia coli (EPEC), 145 Enterotoxigenic Escherichia coli (ETEC), 132, 179 Enterovirus meningitis, 179, 180 Entorhinal cortex, 499 Enuresis characteristics/treatment, 568 sleep stages and, 497 TCA use for, 575 Envelopes (viral), 163 env gene, 175 Enzalutamide, 658 Enzyme kinetics, 230 antagonists, 234 partial agonists, 234 Enzymes glycolysis regulation, 76 lipid transport and, 91, 92 rate-determining, 73 terminology for, 73 Eosin-methylene blue (EMB) agar special culture, 126 Eosinopenia, 424 Eosinophilia Aspergillus fumigatus, 153

Eosinophilic casts (urine), 600
Eosinophilic esophagitis, 377
Eosinophilic granuloma, 675
Eosinophilic granulomatosis
autoantibody, 115 Eosinophilic granulomatosis with
polyangiitis, 315
Eosinophils, 408
corticosteroid effects, 424
in esophagus, 377
Ependymal cells, <b>493</b> Ependymoma, 528
Ephedrine, 242
Epicanthal folds
cri-du-chat syndrome, 64
Down syndrome, 63
Epidemic typhus, 149 Epidemiology/biostatistics, 256–262
Epidermal growth factor (EGF)
signaling pathways for, 337
in wound healing, 216
Epidermis, 473
embryologic derivatives, 613 Epidermophyton, 152
Epididymis, 626
embryology of, 622
Epididymitis, 184, 654
Epidural hematomas, 513
Epidural space, 496
Epigastric pain chronic mesenteric ischemia, 386
Ménétrier disease, 379
pancreatitis, 397
Epigastric veins, 365
Epiglottitis
Haemophilus influenzae, 142 unvaccinated children, 186
Epilepsy
confidentiality exceptions for
patients with, 267
gustatory hallucinations in, 559
hallucinations in, 559 seizures, 517
Epinephrine, 242
adrenal medulla secretion, 327
glaucoma treatment, 552
glycogen regulation by, 85 pheochromocytoma secretion,
350
unopposed secretion of, 346
vitamin B <sub>6</sub> and, 67
Epineurium, 495
Epiphysis estrogen effects on, 459
slipped capital femoral, 461, 463
tumors in, 464
widening of, 463
Episcleritis
inflammatory bowel disease, 382 Epispadias, 624
Epistaxis, <b>671</b>
hereditary hemorrhagic
telangiectasia, 316
Epithelial cell junctions, <b>474</b>
Epithelial cells tumor nomenclature of, 220
Epithelial histology (female), <b>626</b>
Epithelial hyperplasia, 649
Eplerenone, 609
Epley maneuver, 534

Epoetin alfa (EPO analog), 121

Epstein-Barr virus (EBV)

aplastic anemia, 421

Burkitt lymphoma, 430

false-positive VDRL, 148

hairy leukoplakia and, 479

```
head and neck cancer, 671
  HIV-positive adults, 17
  Hodgkin lymphoma, 429
  in immunodeficient patients, 118
  nasopharyngeal carcinomas, 165
  oncogenesis of, 226
  paracortical hyperplasia in, 96
  receptors for, 166
Eptifibatide, 438
  thrombogenesis and, 411
Equations
  half-life of, 231
Erb palsy, 448
Erectile dysfunction, 567
β-blockers and, 245, 323
  cimetidine, 399
  Lambert-Eaton myasthenic
         syndrome, 472
  Peyronie disease, 651 sildenafil, 686
Erection
  autonomic innervation, 627
  ischemic priapism, 651
Ergocalciferol, 70
Ergosterol synthesis inhibitors, 253
Ergot alkaloids
  coronary vasospasm, 248
Erlotinib, 442
Erosions (gastrointestinal), 362, 379
Errors (medical), 274
Erysipelas, 479
  Streptococcus pyogenes, 136
Erythema
  complicated hernias, 370
  Kawasaki disease, 314
Erythema marginatum, 312
Erythema migrans
  in Lyme disease, 146
Erythema multiforme, 481
  Coccidioidomycosis, 151
Erythema nodosum, 151, 482
  inflammatory bowel disease, 382
Erythroblastosis fetalis, 405
Erythrocytes, 407
  blood types, 405
  casts in urine, 594
  Coombs test, 423
  DAF deficiency and, 107
  erythropoietin and, 589
  glucose usage by, 334
  hereditary spherocytosis, 422
  myeloproliferative disorders, 433
  transfusion of, 429
Erythrocyte sedimentation rate
         (ESR), 214
  subacute granulomatous thyroiditis,
Erythrocytosis, 407
  oxygen-hemoglobin dissociation
         curve, 666
Erythrogenic toxin, 136
Erythromelalgia, 433
Erythromycin
  macrolides, 193
  prophylaxis, 198
  protein synthesis inhibition, 191
  reactions to, 249
erythroplasia of Queyrat, 651
Erythropoiesis, 679
  fetal, 404
Erythropoietin (EPO), 121
  anemia of chronic disease, 421
  aplastic anemia, 421
  high altitude, 670
  with pheochromocytoma, 350
  polycythemia and, 228
```

release of, 589 in renal failure, 603 signaling pathways for, 337 Eschar, 132 in cutaneous anthrax, 137 with mucormycosis, 153 Escherichia coli, 145 cephalosporins, 189 culture requirements, 126 encapsulation, 127 galactosemia, 80 lac operon, 40 lactose fermentation, 144 meningitis, 180 neonatal illness, 182 nosocomial infection, 185 O157-H7, 132, 145, 178, 179 penicillins for, 188 pneumonia, 179 prostatitis, 654 urinary tract infections, 181, 600 Escitalopram, 575 E-selectin, 215 Esmolol, 245, 323 Esomeprazole, 399 Esophageal adenocarcinoma, 378 Esophageal atresia, 359 Esophageal cancer, **378** achalasia and, 376 Esophageal dysmotility CREST syndrome, 473 Esophageal perforation, 377 Esophageal strictures, 37 Esophageal varices, 365, 377 Esophageal webs, 418 Esophagitis, 377 bisphosphonates, 486 drug reaction and, 249 HIV-positive adults, 177 Esophagus blood supply and innervation, 364 diaphragm, 663 histology of, 362 pathologies of, 377 portosystemic anastomosis, 365 Essential amino acids, 81 Essential fructosuria, 80 Essential hypertension, 316 Essential mixed cryoglobulinemia, Essential thrombocythemia, 433 Essential tremor, 519 Esters (local anesthetics), 550 Estrogen, 656 androgen insensitivity syndrome, androgen conversion to, 636 benign breast tumors, 649 bone formation, 459 epiphyseal plate closure, 636 gynecomastia, 649 menopause, 636 menstrual cycle, 632 osteoporosis, 462 ovulation, 631 premature ovarian failure, 636, 645 prolactin suppression of, 330 signaling pathways for, 337 source and function of, 630 Turner syndrome, 638 Estrogen receptor modulators (selective), 656 Eszopiclone, 546 Etanercept, 487 Ethacrynic acid, 608

Ethambutol, 196, 197

FAS1\_2019\_21\_Index\_749-806.indd 767 11/21/19 12:27 PM

Ethanol	External oblique muscle	Fallopian tubes
as carcinogen, 225	inguinal canal and, 369	anatomy, 625
gluconeogenesis and, 72	External rotation	epithelial histology, 626
lactic acidosis and, 72	arm (rotator cuff), 446	fertilization, 633
metabolism, <b>72</b> , 232 NADPH (nicotinamide adenine	hip, 451 External enermatic fascia, 360	False-negative rate, 257
dinucleotide phosphate), 72	External spermatic fascia, 369 Extinction (conditioning), 554	False-positive rate, 257 Famciclovir, <b>201</b>
zero-order elimination, 232	Extracellular fluid (ECF)	Familial adenomatous polyposis, 387
Ethics, <b>265–268</b>	volume measurement, 581	APC gene and, 389
confidentiality, 267	volume regulation, 588	chromosome association, 64
consent, 265	Extragonadal germ cell tumors, <b>652</b>	Familial amyloid cardiomyopathy,
core principles of, <b>265</b> –267	Extramammary Paget disease, 644	212
directives, 268	Extraperitoneal tissue, 369	Familial amyloid polyneuropathies,
religious beliefs and, 269 situations in, 268–269, 269–270	Extravascular hemolysis, <b>421</b> Extrinsic hemolytic anemia, <b>423</b>	212
Ethinyl estradiol, 656, 657	Extrinsic pathway, 208	Familial dyslipidemias, <b>94</b>
Ethosuximide	warfarin and, 436, 437	Familial hypercholesterolemia, 60, 94 Familial hypocalciuric
absence seizures, 544	Exudate	hypercalcemia, <b>345</b>
Ethylenediaminetetraacetic (EDTA),	"anchovy paste," 155	Family discussions, 268
419	Ex vacuo ventriculomegaly, 522	Family therapy
Ethylene glycol	Eye movements, 540	separation anxiety, 557
toxicity treatment, 248 Ethylene oxide, 204	bilateral, 543 cranial nerve palsies, 541	Famotidine, 399
Etonogestrel, 657	with stroke, 515	Fanconi anemia, 421
Etoposide/teniposide, <b>442</b>	Eyes	DNA repair in, 40
targets of, 438	anatomy of, 534	nonhomologous end joining and, 40 Fanconi syndrome, 586
teniposide, 38	aqueous humor pathway, 535	drug reaction and, 251
Euchromatin, 34	Ezetimibe, 320	renal tubular acidosis, 593
Eukaryotes	diarrhea, 249	Fascia
DNA replication, 38	F	collagen in, 50
functional gene organization, 41 mRNA start codons, 44	Fab region of antibodies, 104	Fascia of Buck, 627
ribosomes in, 45	Fabry disease, 61	Fasciculations, 529
RNA polymerase in, 42	Facial nerve (Bell) palsy, 146, 186	Fastigial nucleus, 499
RNA processing, 41	Facial nerve (CN VII), 146, 186	Fasting plasma glucose test, 346 Fasting state, 76, 91
Eukaryotic initiation factors, 45	functions of, 506	Fat emboli, 672
Eukaryotic release factors, 45	inflammatory demyelinating	Fatigue
Eustachian tubes	polyradiculopathy, 524	adrenal insufficiency, 349
embryonic derivation, 621	lesions of, <b>532</b>	heart failure and, 309
Eversion, 453 Evolucumab, 320	pharyngeal arch derivation, 620 tongue, 493	MI signs, 305
Ewing sarcoma, 465	Facies	Fatigue, medical errors and, <b>274</b>
dactinomycin for, 439	congenital syphilis, 147	Fat necrosis, 209, 649
Exanthem subitum, 165	elfin, 64	Fat redistribution, 250 Fat-soluble vitamins, 65
"Excision" event, 130	epicanthal folds, 63, 64	Fatty acids
Excitatory pathway, 500	"facial plethora," 685	gluconeogenesis, 78
Exclusive provider organization plan, 271	in fetal alcohol syndrome, 615 flat, 63	metabolism of, 72, <b>89</b> , 90
Executioner caspases, 208	leonine (lion-like), 141	oxidation of, 72, 73
Exemestane, 656	long face with a large jaw, 62	synthesis, 73
Exenatide, 353	risus sardonicus, 138	Fatty acid synthase, 67
Exercise	twisted face, 578	Fatty casts, 594
blood flow autoregulation, 297	Factitious disorder	Fatty liver disease hepatocellular carcinoma and, 392
peripheral resistance, 286	characteristics of, <b>566</b>	nonalcoholic, 391
respiratory response, 670 syncope with, 308	on another, 566 on self, 566	Fc region of antibodies, 104
Tetralogy of Fallot, 298	Factor IX concentrate, 426	Fear
Exercise-induced amenorrhea, 645	Factor VIII concentrate, 426	anxiety disorder and, 562
Exocrine glands, 236	Factor V Leiden, 413, 428	panic disorder and, 563
Exocytosis, 50	venous sinus thrombosis and, 503	Febrile nonhemolytic transfusion
Exogenous corticosteroids, 336	Factor Xa	reaction, 114
Exons	direct inhibitors of, 437	Febrile spizures 517
deletions in muscular dystrophies, 61	heparin effect on, 436	Febrile seizures, 517 Febuxostat
vs introns, 43	inhibitors of, 413 Factor XI concentrate, 426	gout, 487
Exotoxins	Facultative anaerobes	Lesch-Nyhan syndrome, 37
features of, 131	culture requirements, 127	Fecal elastase, 381
organisms with, 132-133	Facultative intracellular organisms, 127	Fecal immunochemical testing (FIT),
Pseudomonas aeruginosa, 132	FADH (flavin adenine dinucleotide),	388
Streptococcus pyogenes, 133	77	Fecalith obstruction, 383
Expectorants, 686	Failure mode and effects analysis, 274	Fecal microbiota transplant, 138
Expiratory reserve volume (ERV), 664 Extension	Failure to thrive, 556	Fecal occult blood testing (FOBT), 388
hip, 451, 453	galactosemia, 80 orotic aciduria, 420	Fecal retention, 558
External hemorrhoids, 366	SCID, 117	Feces
External iliac lymph nodes, 624	Falciform ligament, 361	explosive expulsion of, 384

Federation of State Medical Boards (FSMB), 2 Fed state, 76, 91 Fee for service, 271 Felty syndrome, 466 Female genital embryology, 622 Female/male genital homologs, 623 Female reproductive anatomy, **625** Female reproductive epithelial histology, 626 Femoral artery, 368 Femoral head osteonecrosis, 463 Femoral hernia, 370 Femoral nerve, 452 Femoral region, 368 Femoral sheath, 368 Femoral triangle, 368 Femoral vein, 368 Fenestrated capillaries, 496, 581 Fenofibrate, 320 Fenoldopam, 242, 318 Fentanyl, 551 Ferritin, 213 anemia of chronic disease, 421 iron deficiency anemia, 418 lab values in anemia, 419 sideroblastic anemia, 419 Ferrochelatase, 425 Fertility double Y males, 638 GnRH and, 328 menstrual cycle, 632 Fertilization, 631, 633 Fetal alcohol syndrome, 300, 614, 615 holoprosencephaly in, 491 Fetal circulation, 282 Fetal development early, 612 placental component, 617 Fetal erythropoiesis, 404 Fetal hypothyroidism, 341 Fetal lung maturity, 661 Fetal movement, 612 Fetal-postnatal derivatives, 282 Fetal respiration, 660 Fetal tissue collagen in, 50 Fever amphotericin B, 199 childhood rashes, 183 clindamycin, 192 complicated hernias, 370 endotoxins, 131 epiglottitis, 186 exotoxins, 133 genital herpes, 184 vs heat stroke, 517 high fever, 165, 168, 171, 183 with inflammation, 213 Jarisch-Herxheimer reaction, 148 Legionnaires' disease, 143 low-grade, 143, 171 malaria, 157 with meningococci, 142 mononucleosis, 165 neuroleptic malignant syndrome, 569 pulmonary anthrax, 137 recurring, 156 Rickettsia rickettsii, 150 Salmonella spp, 149 Salmonella typhi, 144 seizures with, 165 spiking, 158

FAS1\_2019\_21\_Index\_749-806.indd 768 11/21/19 12:27 PM

Tetralogy of Fallot, 298
thyroid storm causing, 342
toxic shock syndrome, 135
Trichinella spiralis, 159
tuberculosis, 140
undulant, 143 vasculitides, 314
Waterhouse-Friderichsen
syndrome, 142
Weil disease, 147
Fexofenadine, 686
Fibrates, 320
hepatitis and, 249
myopathy and, 250
Fibrinogen, 213 in cryoprecipitate, 429
ESR and, 214
receptor for, 407
thrombocytes, 407
Fibrinoid necrosis, 209
Fibrinous pericarditis, 305
Fibroblest growth factor (ECF)
Fibroblast growth factor (FGF)
signaling pathways for, 337
in wound healing, 216
Fibroblast growth factor receptor
(FGFR3), 462
Fibroblasts
cortisol and, 336
in wound healing, 216
Fibrocystic breast disease, 649
Fibro fog, 471
Fibroid (leiomyoma)
leuprolide for, 656
Fibromas, 647
nomenclature for, 220
Fibromuscular dysplasia, 300, 604
Fibromyalgia, 470, <b>471</b> , 575
Fibronectin
in cryoprecipitate, 429
thrombocytes, 407
Fibrosarcomas, 220
Fibrosis
diffusion-limited gas exchange, 668
silicosis, 677
Fibrous plaque in atherosclerosis, 302
Fick principle, 285
Fidaxomicin
Clostridium difficile, 138
Fifth disease
rash, 183
50S inhibitors, 191
Filgrastim (G-CSF), 121
Filoviruses
characteristics of, 167
negative-stranded, 168
Filtration fraction
glomerular dynamics, <b>583</b>
Fimbria, 124
Financial considerations in treatment,
269
Finasteride, 658
gynecomastia with, 649
reproductive hormones and, 636
Finger agnosia, 511
Finger drop, 447
Finger movements, 450
upper extremity nerve injury, 447
Fingernails, 478
Finkelstein test, 461
First-degree AV block, 295
First-order elimination, 231, <b>232</b>
Fish oil, 320
Fishy smell, 148
Fitz-Hugh-Curtis syndrome, 142, 185
5-aminosalicylic drugs, 382, 400

5α-reductase
deficiency, 622, <b>639</b> inhibitors for BPH, 654
testosterone conversion, 636
5-fluorouracil (5-FU) antimetabolites, 440
photosensitivity, 250 pyrimidine synthesis and, 36
targets of, 438
thymidylate synthase, 36 5-HT <sub>1B/ID</sub> agonists, 253 5-HT agonists, 547
5-HT agonists, 547 5-HT
opioid effects, 551
MAO inhibitor effect on, 575 trazodone effects, 576
vilazodone effects, 576 vortioxetine effects, 576
Fixation, 555
Fixed splitting, 289 Flaccid paralysis
botulinum toxin, 138 LMN lesion, 531
motor neuron signs, 529
Flagellin, 99 Flagellum, 124
Flask-shaped ulcers, 155 Flat affect, 499
Flavin nucleotides, 75
Flaviviruses, 163, 167 Fleas (disease vectors), 149, 150
Flecainide, 322 Flexion
foot, 453
hand, 450 hip, 451
Flexor digiti minimi muscle, 450 Flexor pollicis brevis muscle, 450
Flies (disease vectors), 144, 159
Floppy baby syndrome Clostridium botulinum, 138
spinal cord lesions, 530 Flow volume loops, <b>673</b>
Fluconazole, 151
Cryptococcus neoformans, 153 mechanism and use, 199
opportunistic fungal infections, 153
Flucytosine, <b>199</b> <i>Cryptococcus neoformans</i> , 153
Fludrocortisone, <b>354</b>
Fluid compartments, <b>581</b> Flumazenil
benzodiazepine overdose, 248, 546, 570
nonbenzodiazepine hypnotics, 546
Fluorescence in situ hybridization, <b>55</b> Fluorescent antibody stain
bacteria, 125 Fluoroquinolones, 38
mechanism and use, 195
Mycoplasma pneumoniae, 150 pregnancy contraindication, 204
Pseudomonas aeruginosa, 143 tendon/cartilage damage with, 250
TOP II (DNA gyrase) and TOP IV
inhibition in prokaryotes, 38
typhoid fever, 144 Fluoxetine, 575
Fluphenazine, 573
Tourette syndrome, 572 Flutamide, 658
Fluticasone, 687 Fluvoxamine, 575
FMR1 gene, 62

Foam cells
in atherosclerosis, 302
Niemann-Pick disease, 88
Focal glomerular disorders, 594
Focal hepatic necrosis, 249
Focal necrotizing vasculitis, 315
Focal neurological deficits
pituitary apoplexy, 339 Focal segmental glomerulosclerosis,
597
Focal seizures, 517
Folate antagonist
teratogenicity, 614
Folate synthesis
inhibition/block, 194
Folic acid antimicrobials and, 187
folate, 68
in pregnancy, 68
neural tube defects and, 491
Follicles (lymph), 96
Follicle-stimulating hormone (FSH)
clomiphene effect, 656
hCG and, 633
PCOS, 645
premature ovarian failure, 636 secretion of, 327
signaling pathways of, 337
Follicular conjunctivitis, 148
Follicular cysts, 646
Follicular lymphomas, <b>430</b> , 434
Follicular phase (menstrual cycle), 6
Follicular thyroid carcinomas, 343
Fomepizole
ethanol metabolism and, 72
toxicity treatment with, 248
Food-borne illness, 178 Food poisoning
Bacillus cereus, 138, 178
causes of, 178
Staphylococcus aureus, 135, 178
toxic shock syndrome toxin, 133
Food toxins, 247
Foot drop, 453 lead poisoning, 419
Foramen cecum, 326
Foramen of Magendie, 504
Foramen of Monro, 504
Foramen ovale
atrial septal defect, 299
embryology, 280
fetal circulation, 282
retained patency of, 298 Foramen primum, 280
Foramen secundum, 280
Foramina of Luschka, 504
Forced expiratory volume (FEV)
obstructive lung disease, 674
restrictive lung disease, 675
Forebrain, 490
Foregut
blood supply/innervation of, 364 development of, 358
Foreign body inhalation, 663
Formoterol, 687
Fornix (uterus), 625
45,XO, 638
47,XXY, 638
46,XX/46,XY DSD, 639
Fosamprenavir
HIV-positive adults, 203 Foscarnet, <b>202</b>
Fosphenytoin, 544
Fossa ovalis, 282
Fovea
cherry-red spot, 538

	FOXP3 protein, 102
	Fractures
	bone diseases and, 51
	chalk-stick, 463
	common pediatric, 462
	compartment syndrome with, 461
	humerus, 447
	in child abuse, 556
	pathologic, 465
	scaphoid, 449
	vertebral compression, 462
	Fragile X syndrome, <b>62</b>
	chromosome association, 64
	Frameshift mutations
	deletions, 61
	muscular dystrophy and, 61
	Francisella spp
	intracellular organism, <b>127</b>
	Francisella tularensis
	animal transmission, 149
	Frataxin, 531
	Free fatty acids
	fast/starvation states, 91
	lipid transport and, 92
	Free light chain (FLC) assay
	plasma cell dyscrasias, 431
	Free nerve endings, 494
	Free radical injury, <b>210</b>
	Fremitus (tactile), 680, 682
	Fresh frozen plasma, 429
	"Fried egg" cells, 494, 526
32	
0.4	Friedreich ataxia, <b>531</b>
	chromosome association, 64
	hypertrophic cardiomyopathy, 308
	inheritance of, 60
	mechanism of, 62
	Frontal bossing, 339
	Frontal eye fields
	cortical functions, 501
	lesions in, 511
	Frontal lobe
	lesions in, 511
	stroke effects, 514
	Frontotemporal dementia, 520
	Fructokinase, 80
	Fructose-1,6-bisphosphatase, 73
	gluconeogenesis, 78
	in matabalia pathwaya 74
	in metabolic pathways, 74
	Fructose-2,6-bisphosphate, 76
	Fructose intolerance, 80
	Fructose metabolism
	disorders, 80
	pathways, 74
	Fructosuria, 80
	FTA-ABS, 125, 147
	Fumarate, 82
	Functional hypothalamic
	amenorrhea, <b>645</b>
	Functional neurologic symptom
	disorder, 566
	Functional residual capacity (FRC),
	664
	Fungal infections
	II 12 recentor deficiency 116
	IL-12 receptor deficiency, 116
	infections with
	immunodeficiencies, 118
	Fungi
	culture requirements, 126
	immunocompromised patients,
	179
	necrosis and, 209
	opportunistic infections, 153
	silver stain, 125
	topical infections, 199
	Funny current, 292
	"funny" sodium channels, 324

FAS1\_2019\_21\_Index\_749-806.indd 769 11/21/19 12:27 PM

INDEX

Furosemide, 252, 608	Gangrenous necrosis, 209	Gastroschisis, 358	Germ cell tumors
gout with, 250	Gap junctions, 474	Gastrosplenic ligament, 361	cryptorchidism risk for, 651
pancreatitis, 249	Gardener's pupil, 241	Gastrulation, 612	hormone levels in, 653
Fusion inhibitors, 203	Gardnerella vaginalis, 148	Gaucher disease, 88	testicular, 652
Fusion protein EWS-FLI1, 465	Gardner syndrome, 387	osteonecrosis, 463	Germinal centers of lymph nodes, 96
Fusobacterium spp	Gargoylism, 88	osteonecrosis in, 463	Germinal center (spleen), 98
alcoholism, 179	Gas gangrene	Gaussian distribution, 262	Gerstmann syndrome, 511
anaerobic metabolism of, 127	alpha toxin, 133	G cells, 371	Gestational age calculation, 633
6	Clostridium perfringens, 138, 179	Gemfibrozil, 320	Gestational diabetes, 634
G	Gastrectomy, 420	Gemifloxacin, 195	Gestational hypertension, 643
G6PD	Gastric acid, 372	Gender dysphoria, <b>567</b>	GFAP (glial fibrillary acid proteins),
deficiency, 61, <b>79</b>	histamine receptors and, 238	Gender identity, 635	48, 227
HMP shunt and, 73	regulatory substances and, 371	Gene expression	astrocyte marker, 493
in respiratory burst, 109	Gastric arteries	modifications, <b>56</b>	cytoskeletal elements, 48
G6PD deficiency, <b>422</b> GABA	celiac trunk, 364 intraligmental, 361	regulation, 41 Generalized anxiety disorder (GAD),	stain, 227 Ghrelin, 336, 371
anesthesia effects, 550	Gastric bypass surgery	563	Giant cells
barbiturate effects, 546	ghrelin and, 371	buspirone, 574	with Aschoff bodies, 312
basal ganglia and, 500	vitamin B <sub>12</sub> deficiency, 69	drug therapy for, 572	astrocytomas, 525
benzodiazepine effects, 546	Gastric cancer, <b>379</b>	Selective serotonin reuptake	Warthin-Finkeldey, 170
changes with disease, 495	carcinogens causing, 225	inhibitors (SSRIs) for, 575	Giant cell (temporal) arteritis, 314,
epilepsy drugs, 544	Helicobacter pylori, 146	serotonin-norepinephrine reuptake	518
Huntington disease, 520	oncogenes and, 224	inhibitors (SNRIs) for, 575	polymyalgia rheumatica, 470
vitamin B <sub>6</sub> and, 67	oncogenic microbes and, 226	Generalized seizures, 517	Giant cell tumor, 464
Gabapentin, 544	sign of Leser-Trélat and, 228	Genes	Giardia spp
GABA <sub>B</sub> receptor agonists, 523, 551	trastuzumab for, 443	introns vs exons, 42, 43	fluorescent antibody stain, 125
gag gene, 175	types of, 379	Genetics, 56–65	watery diarrhea, 179
Gag reflex, 507	Gastric inhibitory peptide (GIP),	anticipation, 62	Giardia lamblia, <b>155</b>
Gait disorders	351	autosomal dominant diseases, 60	Giardiasis, 155
"steppage," 453	Gastric outlet obstruction, 359,	autosomal recessive diseases, 60	Giemsa stain, 125
Trendelenburg sign/gait, 453	380	autosomal trisomies, 63	Borrelia, 146
Gait disturbance	Gastric sclerosis, 473	bacterial, 130–204, 131	chlamydiae, 148
cerebellar lesions and, 499	Gastric ulcers, 380	chromosome disorders, <b>64</b>	Gigantism, 329, 339
Friedreich ataxia, 531	NSAID toxicity, 486	code features, <b>37</b>	Gilbert syndrome, 393, 394 Gingival hyperplasia
Parkinson disease, 520	Gastric vessels, 361 Gastrin, 371, 373	inheritance modes, 59 muscular dystrophies, 61	calcium channel blockers, 318
vitamin B <sub>12</sub> deficiency, 530 waddling, 61	signaling pathways for, 337	terms, <b>56</b> –57	cyclosporine, 120
Galactocerebrosidase, 88	somatostatinomas and, 351	trinucleotide repeat expansion	drug reaction and, 250
Galactocerebroside, 88	Gastrinomas, 354, 371	diseases, 62	Gingivostomatitis, 164
Galactokinase deficiency, 80	Gastrin-releasing peptide (GRP), 371	viral, 162–163	Gitelman syndrome, 586
cataracts and, 535	Gastritis, 146, <b>379</b>	X-linked recessive disorders, 61	markers in, 591
Galactorrhea	gastrin in, 371	Geniculate nuclei (thalamus), 498	Glans penis
antipsychotic drugs and, 328	H <sub>2</sub> blockers for, 399	Genital herpes, 184	lymphatic drainage of, 624
pituitary prolactinomas, 328	proton pump inhibitors for, 399	Genitalia	Glanzmann thrombasthenia, 427
tuberoinfundibular pathway,	stomach cancer and, 379	ambiguous, 622, 638, 639	Glaucoma, 242
499	Gastrocolic ligament, 361	embryology of, 612, <b>622</b>	atropine, 241
Galactose-1-phosphate	Gastroenteritis	estrogen and, 630	β-blockers for, 245
uridyltransferase, 80	caliciviruses, 167	male/female homologs, 623	carbachol for, 240
Galactose metabolism	Listeria monocytogenes, 139	Genital tubercles, 624	closed-angle, 240
disorders of, 80	rotavirus, 168	Genital ulcers, 184	diabetes mellitus and, 346
Galactosemia, 80 cataracts and, 535	Salmonella spp, <b>144</b> Gastroepiploic arteries, 361, 364	Genital warts, 184 Genitofemoral nerve, 452	diagnosis of, 240
Galantamine, 240, 549	Gastroesophageal reflux disease	Genitourinary/renal drug reactions,	epinephrine for, 242 open-angle, 240, 242
Galant reflex, 510	(GERD)	251	pilocarpine for, 240
Gallbladder	Barrett esophagus, 378	Genome editing	types of, <b>536</b>
biliary structures, 368	esophageal cancer and, 378	reverse transcriptase polymerase	Glioblastoma multiforme, 526
blood supply and innervation of,	presentation, 377	chain reaction, 52	nitrosoureas for, 441
364	Gastrohepatic ligament, 361	Genotyping microarrays, 54	Glipizide, 353
regulatory substances, 371	Gastrointestinal bleeding	Gentamicin, 191	Glitazones/thiazolidinediones, 353
Gallbladder cancer	hereditary hemorrhagic	Genu varum (bow legs), 463	Global aphasia, 516
porcelain gallbladder and, 397	telangiectasia, 316	Geriatric patients	Global payment, 271
sclerosing cholangitis and, 395	Gastrointestinal drug reactions, 249	atropine in, 241	Globoid cells
Gallstone ileus, 396	Gastrointestinal stromal tumors	Beers criteria in, 247	Krabbe disease, 88
γ-glutamyltransferase (GGT)	(GISTs), 224	changes in, 270	Globose nucleus, 499
alcohol use, 570	Gastrointestinal system	colonic ischemia and, 386	Globus pallidus externus, 500
γ-glutamyl transpeptidase (GGT), 390	anatomy, 360–369 blood supply to, 363	colorectal cancer, 388 common cause of death, 272	Glomerular disorders/disease
γ-interferon, 407	embryology, 358–359	drug-related delirium in, 558, 575	etiology and presentation, 594
Ganciclovir, <b>202</b>	innervation of, <b>364</b>	lipofuscin in, 211	nomenclature, 594 types of, <b>595</b>
agranulocytosis, 250	ligaments, 361	Medicare for, 272	Glomerular filtration barrier, <b>581</b>
Ganglion cyst, 461	pathology, 376–397	nosocomial infections, 185	Glomerular filtration parameters,
Ganglioneuromatosis	pharmacology, 398–400	osteoporosis, 462	583
oral/intestinal, 351	physiology, 371–375	PPI adverse effects, 399	Glomerular filtration rate (GFR), <b>582</b>
Gangrene	regulatory substances, <b>371</b>	respiratory system changes in, 665	ACE inhibitor effects, 610
Buerger disease, 314	secretory cells, 373	vascular skin tumors, 478	glomerular dynamics in, 583
diabetes mellitus, 346	secretory products, 372	Zenker diverticulum, 384	juxtaglomerular apparatus, 589

FAS1\_2019\_21\_Index\_749-806.indd 770 11/21/19 12:27 PM

Glomerulonephritis	Glucosuria	Gonorrhea	hyperthyroidism, 342
azathioprine for, 120	glucose clearance, 584	ceftriaxone, 189	ophthalmopathy, 340
		for the second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second s	
bacterial endocarditis, 311	threshold for, 584	gonococci, 142	thyroid cellular action in, 331
RBC casts in, 594	Glucuronidation	STI, 184	type II hypersensitivity, 112
Streptococcus pyogenes, 133, 136	drug metabolism, 232	Goodpasture syndrome, 50, 596	Gray baby syndrome, <b>192</b> , 204, 250
Wegener granulomatosis, 315	Glulisine, 352	autoantibody, 115	Gray hepatization, 683
Glomerulus	Glutamic acid	HLA-DR2, 100	Grazoprevir, 204
dynamics of, 583	ammonia transport, 82	restrictive lung disease, 675	Greater omental sac, 361
Glomus tumors, 478	classification of, 81	type II hypersensitivity reactions, 112	Great vein of Galen, 503
Glossitis	opioid analgesics and, 551	Good syndrome	Green twig (greenstick) fracture,
B-complex deficiency, 65	Glutathione	paraneoplastic syndrome, <b>228</b>	462
megaloblastic anemia, 420	acetaminophen and, 485	thymoma and, 98	Grief, <b>562</b>
vitamin B <sub>3</sub> deficiency, 67	in G6PD deficiency, 422	Goserelin, <b>656</b>	Griseofulvin, <b>200</b>
vitamin B <sub>9</sub> deficiency, 68	Glutathione peroxidase, 109	Gottron papules, 228, 471	cytochrome P-450 interaction,
Glossopharyngeal nerve (CN IX), 506	free radical elimination by, 210	Gout, <b>467</b>	252
blood flow regulation, 296	Glutathione reductase, 109	drug reaction and, 250	microtubules and, 48
pharyngeal arch derivative, 620	NADPH and, 75	drug therapy for, <b>487</b>	pregnancy contraindication, 204
tongue, 493	Gluten-sensitive enteropathy, 381	kidney stones and, 598	"Ground-glass" appearance (X-ray),
Glossoptosis, 620	Gluteus maximus muscle, 453		
Glossopiosis, 020		Lesch-Nyhan syndrome, 37	177, 661
Glove and stocking neuropathy, 346	Gluteus minimus muscle, 451	loop diuretics and, 608	Pneumocystis jirovecii, <b>154</b>
GLP-1 analogs, 353	GLUT transporters, 334	Von Gierke disease, 87	Growth factors
Glucagon, <b>333</b>	Glyburide, 353	Gower maneuver/sign, 61	tumor suppressor gene mutations
for β-blocker toxicity, 323	Glycerol	gp41, 203	and, 46
fructose bisphosphatase-2, 76	starvation days and, 91	G-protein-coupled receptors, 236	Growth hormone (GH), 354
glucagonomas and, 351	Glycogen	G-protein-linked 2nd messengers, <b>238</b>	diabetes mellitus, 346
glycogen regulation, 85	metabolism and storage, 73, <b>86</b>	Gracilis, 452	ghrelin and, 336
insulin and, 333, 334			for hypopituitarism, 339
	Glycogenesis, 73	Graft-versus-host disease, 119	ior hypopituitarism, 559
production of, 331	Glycogenolysis	type IV hypersensitivity, 113	insulin resistance and, <b>329</b>
somatostatin and, 371	rate-determining enzyme for, 73	Gram-negative organisms	secretion of, 327
somatostatinomas and, 351	thyroid hormone and, 331	cell wall structure, <b>124</b>	signaling pathways for, 337
Glucagonomas	Glycogen storage diseases, 87	cephalosporins, 189	somatostatin, 339
MEN 1 syndrome, 351	Glycogen synthase, 73, 86	lab algorithm, <b>141</b>	Growth-hormone-releasing hormone
pancreatic cell tumor, 351	Glycolysis	Gram-positive organisms	(GHRH)
somatostatin for, 354	arsenic and, 74	antibiotic tests, <b>134</b>	function of, 328
Glucocerebrosidase		cell wall structure, <b>124</b>	Growth media properties, 126
	hexokinase/glucokinase in, 75		
Gaucher disease, 88	metabolic site, 72	cephalosporins, 189	Growth retardation
Glucocerebroside	pyruvate metabolism and, 77	lab algorithm, <b>134</b>	with renal failure, 603
in sphingolipidoses, 88	rate-determining enzyme for, 73	vancomycin, 190	GTPase, 224
Glucocorticoids	regulation of, <b>76</b>	Gram stain	GTP (guanosine triphosphate), 77
adrenal insufficiency, 349	Glycoprotein IIb/IIIa inhibitors,	peptidoglycan layer and, 125	Guaifenesin, <b>686</b>
calcium pyrophosphate deposition	438	Granular casts	Guanfacine, 240, 243
disease, 467	Glycoproteins	acute tubular necrosis, 602	Guanosine analogs
diabetes mellitus, 346	bacterial pilus/fimbria, 124	"muddy brown" in urine, 594	mechanism and use, 201
		Cranulacita coloni stimulating factor	
fat redistribution with, 250	HIV, 175	Granulocyte-colony stimulating factor	Gubernaculum, 624, 625
gout, 467, 487	Glycopyrrolate, 241	(G-CSF), 337	Guessing during USMLE Step 1
immunosuppression, 120	Glycosylation	Granulocytes	exam, 23
myopathy, 250	collagen synthesis, 50	morulae, 150	Guillain-Barré syndrome
rheumatoid arthritis, 466	protein synthesis, 45	Granulocytopenia	acute inflammatory demyelinating
Glucokinase	GNAQ gene, 525	trimethoprim, 194	polyradiculopathy, 524
hexokinase vs, 75	Goblet cells, 362, 662	Granuloma inguinale, 184	Campylobacter jejuni, 145
metabolic pathways, 74	Goiter	Granulomas, 147	restrictive lung disease, 675
Gluconeogenesis	maternal hypothyroidism from,	macrophages and, 407	Schwann cell injury, 494
cortisol and, 336	341		Schwann cells, 524
ethanol metabolism and, 72	maternal iodine deficiency, 614	in systemic mycoses, 151 TNF-α and, 110	Gummas
	inatemai fodine deficiency, 017		
irreversible enzymes, <b>78</b>	in Riedel thyroiditis, 341	in tuberculosis, 140	syphilis, 147, 184
metabolic site, 72	types and causes of, 342	Granulomatosis infantiseptica	Gustatory hallucinations, 559
pyruvate metabolism and, 77	Golfer's elbow, 459	Listeria monocytogenes, 139	Gustatory pathway
rate-determining enzyme for, 73	Golgi apparatus	Granulomatosis with polyangiitis	cranial nerves in, 532
thyroid hormone and, 331	in plasma cells, 409	(Wegener)	thalamic relay for, 498
Glucose	Golgi tendon organ, 458	restrictive lung disease and, 675	Guyon canal syndrome, 459
ATP production, 74	Golimumab, 487	Granulomatous disease	Gynecologic procedures
blood-brain barrier and, 496	Gonadal drainage, <b>624</b>	catalase + organism infections	ureteric damage in, 581
clearance, <b>584</b>	Gonadal mosaicism, 57	with, 128	Gynecologic tumor epidemiology,
		·	643
glycogen metabolism, 86	Gonadotropin, 646	excess vitamin D in, 70	
insulin and, 334	Gonadotropin-releasing hormone	hypervitaminosis D with, 464	Gynecomastia, 649
metabolism of, 40	(GnRH)	Granulomatous inflammation, 217	antiandrogens for, 658
for porphyria, 425	function of, 328	Granulosa cells	azoles, 199
transporters, 334	neurons producing, 498	tumors of, 647	cimetidine, 399
Glucose-6-phosphatase	ovulation, 631	Granzyme B	SHBG and, 337
dehydrogenase deficiency, <b>79</b>	prolactin and, 330	cytotoxic T cells, 101, <b>102</b>	spironolactone, 658
gluconeogenesis, 78	signaling pathways for, 337	extrinsic pathway and, 208	tuberoinfundibular pathway, 499
HMP shunt, 79			
	spermatogenesis, 628	Grapefruit juice and cytochrome	н
Von Gierke disease, 87	Gonads	P-450, 252	
Glucose-dependent insulinotropic	dysgenesis of, 606	Graves disease	H <sub>1</sub> blockers, 251, <b>686</b>
peptide (GIP), 351, <b>371</b> , 372	Gonococcal arthritis, 468	autoantibody, 115	$H_2$
			<u> </u>
polypeptide (GIP), 334	Gonococci, vs meningococci, 142	HLA subtype associations, 100	production in tissues, 127

FAS1\_2019\_21\_Index\_749-806.indd 771 11/21/19 12:27 PM

H <sub>2</sub> blockers, <b>399</b>	Hashimoto thyroiditis, 341	Heart failure, <b>309</b>	Hemangioblastomas, 526
H <sub>2</sub> O <sub>2</sub> degradation	autoantibody, 115	ACE inhibitors for, 610	Hemangiomas, 220
catalase and, 128 H <sub>2</sub> -antagonist	HLA subtype association, 100 Hassall corpuscles, 98	acromegaly, 339 amiodarone, 323	cavernous (liver), 392 pyogenic granuloma, 478
naming conventions for, 254	Hay fever	angiotensin II receptor blockers, 610	strawberry, 478
Haemophilus ducreyi	association, 100	aortic regurgitation as precursor,	Hemarthroses
sexual transmission, 184	HbA <sub>1c</sub> test, 346	291	hemophilias, 426
Haemophilus influenzae, 142	HBcAg (hepatitis B core antigen), 174	atrial septal defect, 299	Vitamin C deficiency, 69
biofilm production, 128	HbC disease, 422	β-blockers for, 245	Hematemesis, 377
cephalosporins, 189	target cells in, 415	B-type natriuretic peptide in, 296	Hematin, 126, 142
chloramphenicol, 192	HBsAg (hepatitis B surface antigen),	calcium channel blockers, 324	Hematochezia
culture requirements, 126	174	cardiac glycosides for, 321	diverticulosis, 383
encapsulation, 127	HDL (high-density lipoprotein), 94	chronic ischemic heart disease, 304	intestinal disorders, 386
IgA protease, 129	Headaches, <b>518</b>	contractility in, 284	Meckel diverticulum, 384, 618
influenza, 169 meningitis, 179, 180	adverse effects with drugs, 195, 199, 200	diabetic ketoacidosis, 347 disopyramide, 322	Hematocrit polycythemia vera, 433
penicillins for, 188	α-blockers, 244	dobutamine for, 242	Hematologic abnormalities
pneumonia, 179	bupropion toxicity, 576	dopamine for, 242	laboratory techniques for, 54
postviral infection, 179	caffeine withdrawal, 570	Ebstein anomaly, 298	Hematologic disorders
rifamycins, 196	Chiari I malformation, 492	ESR in, 214	paraneoplastic syndromes, 228
transformation, 130	cimetidine, 399	fludrocortisone and, 354	Hematologic drug reactions, 250
type b conjugate vaccine, 127	drug adverse effects, 546	hypertension, 300, 316	Hematology/oncology
unvaccinated children, 186	electroconvulsive therapy, 562	in sleep apnea, 679	anatomy, 406–409
vaccine, 142, 180	genital herpes, 184	jugular venous pulse in, 287	pathology, 414–434
Hair	giant cell (temporal) arteritis, 518	left heart, 309	pharmacology, 435–443
"kinky," 51 Menkes disease, 51	glaucoma, 536 hydralazine, 318	Paget disease of bone, 463 potassium-sparing diuretics, 609	physiology, 410–413 Hematopoiesis, <b>406</b> , 432
vitamin C deficiency, 69	increased intracranial pressure, 521	readmissions with, 272	Hematopoietic stem cells, 110
Hairy cell leukemia, 227, <b>432</b>	Jarisch-Herxheimer reaction, 148	right heart, 309	Hematuria, 595
cladribine for, 440	lead poisoning, 425	shock caused by, 310	bladder cancer, 606
Hairy leukoplakia, 479	malaria, 157	thiazides for, 609	hereditary hemorrhagic
HÍV-positive adults, 177	Mucor spp and Rhizopus spp, 153	ventricular septal defect, 299	telangiectasia, 316
Half-life equation, 231	nitrates, 318	Heart murmurs, <b>291</b>	interstitial nephritis, 601
Halitosis	ondansetron, 400	cardiomyopathies, 308	kidney stones, 598
fetor hepaticus, 389	pituitary apoplexy, 339	patent ductus arteriosus, 299	protease inhibitors, 203
Zenker diverticulum, 384 Hallucinations, 559	ranolazine, 319	Heart rate, 243 Heart sounds, 287	renal cyst disorders, 604
cocaine, 571	Rocky Mountain spotted fever, 150 sodium-channel blockers, 322	cardiac cycle, 287	renal oncocytoma and, 605 renal papillary necrosis, 602–610
delirium, 558	subarachnoid hemorrhage, <b>513</b> ,	cardiac tamponade, 310	Schistosoma haematobium, 161
mesolimbic pathway, 499	516	splitting in, <b>289</b>	transitional cell carcinoma, 606
pellagra, 67	triptans for, 547	Heart transplant	UTIs, 181
postpartum psychosis, 562	vasculitides, 314	dilated cardiomyopathy, 308	Wegener granulomatosis, 315
tricyclic antidepressants, 575	venous sinus thrombosis and, 503	Heart valve development, 281	Wilms tumor, 606
Hallucinogen intoxication and	Head and neck cancer, <b>671</b>	Heat-labile toxin (LT)	Heme
withdrawal, 571 Haloperidol, 573	cetuximab for, 442 Head size	Clostridium botulinum, 138 Clostridium perfringens, 138	bilirubin and, 375 chloroquine, 200
torsades de pointes, <b>294</b>	Paget disease of bone, 463	Cl <sup>-</sup> secretion in gut, 132	porphyria and, <b>425</b>
Halothane, 550	Healing, wound, 216	Heat shock proteins, 45	synthesis of, <b>425</b>
hepatic necrosis, <b>249</b>	Healthcare delivery, 270–273	Heat-stable toxin (ST)	vitamin B <sub>6</sub> and, 67
Hamartin protein, 224, 525	Healthcare payment models, <b>271</b>	resorption of NaCl and H <sub>2</sub> 0 in	Hemianopia, 515, 542
Hamartomas, <b>220</b> , 525	Healthcare proxy, 269	gut, 132	Hemiballismus, 519
Hamartomatous colonic polyps, <b>387</b>	Health maintenance organization	Heat stroke, 517	brain lesions and, 511
Hamate bone, 449	plan, 271	Heavy menstrual bleeding (AUB/	Hemidesmosome, 474, 480
fracture of hook, 447	Hearing loss, 533	HMB), 633	Hemineglect, 514
Hamman sign crepitus, 672 Hammer toes, 531	conductive, 49 cytomegalovirus, 182	Heel pain, 461 Heinz bodies, 79, 414, <b>416</b> , 422	Hemiparesis saccular aneurysms, 516
Hand	osteogenesis imperfecta, 51	Helicase, 38	Hemochromatosis, <b>395</b>
distortions of, 451	Paget disease of bone, 463	Helicobacter pylori, <b>146</b>	calcium pyrophosphate deposition
injuries of, 459	sensorineural deafness, 596	as oncogenic microbe, 226	disease, 467
muscles of, 450	Heart	disease association, 379	cardiomyopathy with, 308
squamous cell carcinoma, 484	autoregulation of, 297	metronidazole, 195	chromosome association, 64
Hand-foot-mouth disease, 183	electrocardiograms, 293	penicillins for, 188	chronic, 426
Hansen disease, 141	embryology, <b>281</b>	silver stain, 125	free radical injury, 210
animal transmission, 149	fetal development, 612	urease-positive, 127	hepatocellular carcinoma and, 392
dapsone, 194 erythema nodosum, 482	ischemia in, 210 morphogenesis of, <b>280</b> –281	Heliotrope rash, 228 HELLP syndrome, 643	HLA-A3 and, 100 Hemoglobin, <b>665</b>
Hantavirus, 167	myocardial action potential, 292	"Helmet cells," 423	carbon dioxide transport, 670
Haptens	normal pressures in, 297	Helminthic infections	development of, 404
acute interstitial nephritis, 601	sclerosis of, 473	eosinophils and, 408	kinetics of, 230
amiodarone as, 323	Heartburn, 377	Helper T cells	Hemoglobin electrophoresis, 410
Haptoglobin, 421	Heart disease	cell surface proteins, 110	Hemoglobinuria
Hardy-Weinberg population genetics,	congenital, 63, <b>298–299</b>	cytokine secretion, 108	acute tubular necrosis and, 602
57	death, common causes by age, 272	Hemagglutinin	G6PD deficiency, 422
Hartnup disease, 67 vitamin B <sub>3</sub> deficiency, 67	Fabry disease, 88 ischemic, <b>304</b>	influenza viruses, 169 parainfluenza viruses, 170	intravascular hemolysis, 421 paroxysmal nocturnal, 122
vitalilli D3 delicitiey, 07	iselicinie, Joa	Parammuenza viruses, 170	Paroxysinai noctumai, 122

FAS1\_2019\_21\_Index\_749-806.indd 772 11/21/19 12:27 PM

Hemolysis	osteoporosis, 250	leishmaniasis, 158	Hexokinase
alpha toxin, 133	thrombocytopenia, 250	lysosomal storage diseases, 88	glucokinase vs, <b>75</b>
Clostridium perfringens, 138	toxicity treatment, 248	mononucleosis, 165	metabolic pathways, 74
G6PD deficiency, 250	warfarin vs, <b>436</b> , <b>437</b>	TORCH infections, 182	"HF" cells (lungs), 309
HELLP syndrome, 643 sulfonamides, 194	Heparin-induced thrombocytopenia (HIT), 436	Hepatosteatosis, 72 Hepatotoxicity	HFE gene hemochromatosis and, 395
Hemolytic anemia, 421	Hepatic adenomas, 392	amiodarone, 323	HGPRT (hypoxanthine guanine
autoimmune, 189	Hepatic arteries, 364, 367	bosentan, 686	phosphoribosyltransferase),
babesiosis, 157	Hepatic ascites, 609	danazol, 658	37, 440
cephalosporins, 189	Hepatic ducts, 368 Hepatic encephalopathy, <b>391</b>	inhaled anesthetics, 550	Hiatal hernias, 370 Hiccups, 519
direct Coombs-positive, 250 extrinsic, 421, <b>423</b>	Hepatic fibrosis, 367	isoniazid, 197 leflunomide, 486	High altitude respiratory response, 670
folate deficiency and, 420	Hepatic lipase, 93	methotrexate, 440	High-frequency recombination (Hfr)
G6PD deficiency, 79	Hepatic necrosis, 249, 485	pyrazinamide, 197	cells, 130
intrinsic, 421, <b>422</b>	Hepatic steatosis, 391	rifamycins, 196	Highly active antiretroviral therapy
penicillin G, V, 187 pyruvate kinase deficiency and, 422	Hepatitis alcoholic, 391, 571	terbinafine, 199 thionamides, 354	(HAART), 203 High-riding prostate, 627
spherocytes in, 415	drug reaction and, 249	valproic acid, 544	Hilar lymph nodes
sulfa drug allergies, 252	heroin addiction and, 576	zileuton, 687	calcification of, 677
Wilson disease, 395	hyperbilirubinemia, 393	Hepcidin, 213	Hilar mass, 684
Hemolytic disease of the newborn,	Hepatitis A (HAV)	in anemia of chronic disease, 421	Hilum (lung), 663 lymphadenopathy, 675
112, <b>405</b> Hemolytic reactions and blood types	characteristics of, 172 picornavirus, 167, <b>168</b>	Hepeviruses characteristics, 167	Hindbrain, 490
newborns, 405	serologic markers, 174	genomes, 163	Hindgut
Hemolytic-uremic syndrome (HUS)	Hepatitis antigens, 174	naked viruses, 163	blood supply/innervation of, 364
Escherichia coli, <b>145</b> , 179	Hepatitis B (HBV)	HER2/neu (c-erbB2), 224	development of, 358
exotoxins, 132 platelet disorders, 427	characteristics of, 172 extrahepatic manifestations, 173	"Herald patch" (pityriasis rosea), 482 Herceptin (trastuzumab), 443	Hip dislocation nerve injury with, 453
Hemophagocytic lymphohistiocytosis,	hepatocellular carcinomas and, 392	Hereditary amyloidosis, 212	Hip injuries/conditions
<b>435</b> , 544	medical importance, 164	Hereditary angioedema, 658	common, <b>460</b>
Hemophilia, 426	nosocomial infection, 185	complement disorder and, 107	developmental dysplasia, 461
X-linked recessive disorder, 61	as oncogenic microbe, 226	Hereditary elliptocytosis, 414	Hip muscles, <b>451</b>
Hemoptysis Aspergillus fumigatus, 177	passive antibodies for, 110 polyarteritis nodosa and, 314	Hereditary hemorrhagic telangiectasia, <b>316</b>	Hippocampus lesions in, 511
bronchiectasis, 675	serologic markers, 174	autosomal dominance of, 60	limbic system, 499
choriocarcinomas, 642	sexually transmitted infection, 184	Hereditary hyperbilirubinemias, 394	pyramidal cells, 210
lung cancer, 684	Hepatitis C (HCV)	Hereditary motor and sensory	Hippurate test, for Streptococcus
tuberculosis, 140 Wegener granulomatosis, 315	characteristics of, 172 extrahepatic manifestations, 173	neuropathy, 524 Hereditary spherocytosis, 422	agalactiae, 137 Hirschsprung disease, <b>384</b>
Hemorrhage	flaviviruses, 167	spherocytes in, 415	Hirsutism
acute pancreatitis, 397	hepatocellular carcinoma and, 392	Hereditary thrombosis syndromes,	cyclosporine, 120
AIDS retinitis, 165	lichen planus, 482	428	danazol, 658
baroreceptors and, 296	as oncogenic microbe, 226 therapy for, <b>204</b>	Hermaphrodites, 639	menopause, 636
bevacizumab, 442 delirium caused by, 558	Hepatitis D (HDV), 172	Hernias, <b>370</b> Herniation syndromes, <b>529</b>	SHBG and, 337 Histaminase, 408
Ebola virus, 171	Hepatitis E (HEV), 172	Heroin, 551	Histamine blockers, 398, <b>399</b>
intracranial, 513	hepevirus, 167	detoxification medications, 576	Histamine receptors, 238
intraventricular, 512	Hepatitis viruses, 172	intoxication and withdrawal, 570	Histamines
pulmonary, 137 shock from, 310	aplastic anemia, 421 serologic markers for, <b>174</b>	opioids for withdrawal, 551 Herpes genitalis, 164	in basophils, 408 cortisol effect on, 336
subarachnoid hemorrhage, <b>513</b> ,	Hepatocellular carcinomas, <b>392</b>	Herpes labialis, 164	location of, 373
516	Åspergillus fumigatus, 153	Herpes simplex virus (HSV), <b>164–166</b>	mast cells and, 408
ulcers, 380	Budd-Chiari syndrome and, 392	HSV-1/HSV-2, 164, 184	seafood toxins, 247
Weil disease, 147	carcinogens causing, 225 cirrhosis and, 389	cidofovir, 202 clinical significance, 164	signaling pathways for, 337
Hemorrhagic cystitis adenovirus, 164	hemochromatosis, 395	envelope, 163	vitamin B <sub>6</sub> and, 67 Histidine, 81
drug reaction, 251	non-alcoholic fatty liver disease,	foscarnet for, 202	Histiocytosis (Langerhans cell), 434
Hemorrhagic fever	391	guanosine analogs, 201	Histocompatibility complex I and
bunyavirus, 167	oncogenic microbes, 226	identification, 166	II, 100
filovirus, 167 Hemorrhagic stroke, 513	Hepatocytes, 86 Hepatoduodenal ligament, 361	meningitis caused by, 180 skin infections, 479	Histones acetylation, 34
Hemorrhoids, 366	Hepatomas, <b>392</b>	STI, 184	amino acids in, 81
Hemosiderinuria, 421	Hepatomegaly	TORCH infection, 182	deacetylation, 34
Hemostasis, 407	Budd-Chiari syndrome, 392	Herpes zoster	methylation, 34
platelet plug formation, <b>411</b> Henderson-Hasselbalch equation, 592	galactosemia, 80 hepatocellular carcinoma, 392	dorsal root latency, 165 famciclovir, 201	Histoplasma spp treatment, 199
Henoch-Schönlein purpura, 315	pulmonary hypertension, 668	reactivation, 443	Histoplasma capsulatum
Hepadnaviruses	right heart failure, 309	Herpetic whitlow, 164	HIV-positive adults, 177
characteristics of, 164	Von Gierke disease, 87	Heterochromatin, 34	necrosis and, 209
genome, 163 Heparin, <b>436</b>	Zellweger syndrome, 47 Hepatosplenomegaly	Heterodimer, 48 Heterodisomy, 57	Histoplasmosis, 151
acute coronary syndromes, 307	β-thalassemia and, 418	Heterogeneous nuclear RNA	erythema nodosum, 482 Histrionic personality disorder, 565
in basophils, 408	biliary tract disease, 395	(hnRNA), 41	HIV (human immunodeficiency
in coagulation cascade, 413	graft-versus-host disease, 119	Heteroplasmy, 57	virus), <b>175</b>
mast cells and, 408	hyperchylomicronemia, 94	Heterozygosity loss, 56	aplastic anemia in, 421

FAS1\_2019\_21\_Index\_749-806.indd 773 11/21/19 12:27 PM

INDEX

HIV (continued) common disease associations, <b>177</b>
diagnosis, <b>175</b>
flow cytometry diagnosis, 54
hairy leukoplakia, 479 heroin addiction and, 576
Kaposi sarcoma, 165, 478
lymphopenia, 424
meningitis, 180
non-Hodgkin lymphoma and, 429 Pneumocystis jirovecii, 154
primary central nervous system
lymphoma and, 430
prophylaxis for HIV patients, 198 pulmonary arterial hypertension,
679
retrovirus, 167
rifamycins in, 196
STI, 184 T cells and, 409
therapy for, <b>203</b>
TORCH infection, 182
untreated time course, 176 viral receptor, 166
HLA-B8
graves disease and, 342
HLA-DR3
graves disease and, 342 HLA-DR4, 466
HLA genes
celiac disease and, 381
disease associations, <b>100</b> , 341 DM type 1 association, 347
seronegative spondyloarthritis, 469
HMG-CoA reductase
cholesterol synthesis, 73
metabolic pathways, 74 HMG-CoA synthase, 73
HMP shunt
metabolic site, 72
NADPH production, 75, <b>79</b> rate-determining enzyme, 73
vitamin B <sub>1</sub> deficiency, 66
Hoarseness
gastroesophageal reflux disease, 377
lung cancer, 684 Ortner syndrome, 283
Pancoast tumor, 685
thyroid cancer, 343
Hodgkin lymphoma, <b>429</b> bleomycin for, 439
non-Hodgkin vs, <b>429</b>
oncogenic microbes and, 226
paraneoplastic cerebellar degeneration and, 228
vinca alkaloids for, 441
Holistic medical therapy, 269
Holoprosencephaly, <b>491</b>
Patau syndrome, 63 Homatropine, 241
Homer-Wright rosettes, 528
Homicide, 272
Homocysteine folate deficiency, 420
vitamin B <sub>9</sub> deficiency, 68
vitamin B <sub>12</sub> deficiency, 69, 420
Homocysteine methyltransferase
deficiency in, 84 vitamin B <sub>12</sub> and, 69
Homocystinuria
causes of, <b>84</b>
Homologous recombination repair, 40
Homovanillic acid (HVA)
in neuroblastomas, 350
Homunculus, 502

Hookworms, 159 Hormone effects on kidney, <b>590</b> Hormone replacement therapy, <b>657</b>
estrogens for, 656 for hypopituitarism, 339 thrombotic complications, 250 Hormone-sensitive lipase, 93
Hormones (reproductive), 655 Horn cysts, 477 Horner syndrome, 514, 518, <b>540</b> cavernous sinus, 542
lung cancer, 684 Pancoast tumor, 685 Horse flies (disease vector), 159 Horseshoe kidney, <b>579</b>
Hospice care, <b>272</b> Hospital readmission causes, <b>272</b> Hot flashes
drug reaction and, 249 "Hourglass stomach," 370 Howell-Jolly bodies postsplenectomy, 98 Hu antigens, 228
Human chorionic gonadotropin (hCG) as tumor marker, 226
choriocarcinomas, 642 ectopic pregnancy, 641 hydatidiform moles, 642 secretion of, 612, <b>633</b>
signaling pathways, 337 source and functions of, <b>633</b> Human factors design, <b>273</b> Human herpesvirus 4 (HHV-4), 165 Human herpesvirus 6 (HHV-6), 165,
Human herpesvirus 7 (HHV-7), 165 Human herpesvirus 8 (HHV-8), 165, 177
Kaposi sarcoma, 478 as oncogenic microbe, 226 Humanized monoclonal antibodies, 110
Human papillomavirus 6 (HPV-6), 184 Human papillomavirus 11 (HPV-11),
184 Human papillomavirus 16 (HPV-16), 671 Human papillomavirus (HPV)
cervical pathology, 645 HIV-positive adults, 177 as oncogenic microbe, 226 penile cancer, 651
tumor epidemiology, 643 verrucae, 477 warts, 164 Human placental lactogen, <b>634</b>
Humerus fracture axillary nerve and, 447 radial nerve with, 447 Humoral immune response, 409
Hunger/satiety regulation, 498 Hunter syndrome, 60, 61, <b>88</b> Huntington disease drug therapy for, 549
movement disorders, 519 neurodegenerative disorder, 520 neurotransmitters for, 495 trinucleotide repeat expansion
diseases, 62 Hurler syndrome, 88 Hürthle cells, 341 Hutchinson teeth, 147
Hyaline arteriolosclerosis, 301 Hyaline casts (urine), 594

Hydatid cysts, 161
Hydatidiform mole, <b>642</b> hCG in, 633
theca-lutein cysts and, 646 Hydralazine
gestational hypertension, 316 heart failure, 309
mechanism and clinical use, <b>318</b> Hydrocele (scrotal)
acquired, 652 congenital, 652
Hydrocephalus, 522
childhood tumors, 528 headaches with, 518
posterior fossa malformations, 492 risk for developing, 513
Toxoplasma gondii, 182 Hydrochlorothiazide (HCTZ), 609
for diabetes insipidus, 338 hyperglycemia, 249
pancreatitis, 249
Hydrogen peroxide, 204 Hydronephrosis, <b>599</b>
BPH, 654 horseshoe kidney, 579
kidney stones, 598 posterior urethral valves, 579
Hydrophobia, 171 Hydrops fetalis
parvovirus B19, 182, 183 syphilis, 182
Hydroxychloroquine myopathy, 250
Hydroxylases, 73
Hydroxylation collagen synthesis, 50
in protein synthesis, 45 Vitamin C and, 50
Hydroxyurea, <b>442</b> polycythemia vera, 433
purine synthesis, 36 sickle cell anemia, 422
targets of, 438 Hyoid artery, 619
Hyoscyamine, 241 Hyperacute transplant rejection, 119
Hyperaldosteronism, 349
hypertension with, 300 potassium-sparing diuretics for, 609
Hyperammonemia, <b>82</b> , 85 fatty acid metabolism and, 89
Hyperbilirubinemia conjugated (direct), 393
hereditary, 394 jaundice with, 393
unconjugated (indirect), 393 Hypercalcemia
acute pancreatitis and, 397 adult T-cell lymphoma, 430
bisphosphonates for, 486
calcium carbonate antacid effects,
diabetes insipidus, 338 hyperparathyroidism, 345
loop diuretics for, 608 lung cancer, 684
paraneoplastic syndrome, 228 succinylcholine, 551
teriparatide, 487 thiazides, 609
Williams syndrome, 64
Hypercalciuria hyperparathyroidism, 345
thiazides for, 609 Hypercapnia
contractility in, 284

Hypercholesterolemia, 94
familial, 60
Hyperchylomicronemia, 94
Hypercoagulability, 671 hereditary syndromes, 428
in pregnancy, 633
marantic endocarditis in, 311
venous sinus thrombosis with, 503 warfarin adverse effect, 436
Hyperemesis gravidarum, 642
Hyperemia pseudoephedrine/phenylephrine,
686
Hypereosinophilic syndrome, 308
Hyperestrogenism, 646 Hyperglycemia
Cushing syndrome, 348
diabetic ketoacidosis, 347
diabetic retinopathy, 537 drug reaction and, 249
glucagon and, 333
hyperkalemia, 590
immunosuppressants, 120 pancreatic cell tumors, 351
protease inhibitors, 203
thiazides, 609
vitamin B <sub>3</sub> toxicity, 67 Hypergonadotropic hypogonadism,
639
Hypergranulosis, <b>475</b> , 482
Hyper-IgM syndrome, 117 Hyperinsulinemia, 645
Hyperkalemia
aldosterone in, 588 aliskiren, 610
angiotensin II receptor blockers, 610
cardiac glycosides, 321
causes of, 590 depolarizing neuromuscular
blocking drugs, 551
diabetic ketoacidosis, 347
potassium-sparing diuretics, 609 primary adrenal insufficiency, 349
Hyperkalemic tubular acidosis (type
4, 593 Hyperkeratosis, <b>475</b> , 477
Hyperlipidemia, <b>301</b>
atherosclerosis and, 302
immunosuppressants, 120 thiazides, 609
Hyperopia, 535
Hyperosmolar hyperglycemic state,
<b>347</b> DM type 2, 346
Hyperosmolarity, 590
Hyperparathyroidism, <b>345</b>
calcium pyrophosphate deposition disease, 467
cinacalcet for, 355
lab values in, 464
renal osteodystrophy and, 603 Hyperphagia
depression with, 561
hypothalamus and, 498 Hyperphosphatemia
hyperparathyroidism (secondary),
345
hypoparathyroidism, 344 renal osteodystrophy and, 603
Hyperpigmentation
bleomycin, 439
busulfan, 441 fludrocortisone, 354
hemochromatosis, 395
Peutz-Jeghers syndrome, 387
primary adrenal insufficiency, 349

FAS1\_2019\_21\_Index\_749-806.indd 774 11/21/19 12:27 PM

Hyperplasia, 206	thoracic aortic aneurysm and, 302	Hypogonadism	Hypotonia
adrenal, 348, 349	treatment for, 316	diagnosis of, 639	poliomyelitis, 531
parathyroid, <b>345</b> , 351	tyramine, 244, 575	estrogens for, 656	Zellweger syndrome, 47
uterine bleeding with, 633	Hypertensive crisis, 569	gynecomastia, 649	Hypoventilation, 592
Hyperplastic arteriolosclerosis, 301 Hyperplastic polyps, 387	MAO inhibitors, 575 phenoxybenzamine for, 244	hemochromatosis, 395 Kallmann syndrome, 639	Hypovolemic shock, 310 Hypoxanthine guanine
Hyperprolactinemia, 249, 328, <b>527</b>	pheochromocytoma, 350	pituitary prolactinomas, 328	phosphoribosyltransferase
anovulation, 645	Hypertensive emergency, 300, <b>318</b>	testosterone/methyltestosterone, 658	(HGPRT), 37
calcium channel blockers and,	RBC casts in, 594	zinc deficiency, 71	Hypoxemia
318	Hypertensive nephropathy, 300	Hypokalemia	alveolar gas equation, 668
risperidone and, 573	Hypertensive retinopathy, <b>537</b>	antacid use, 399	oxygen deprivation, 669
Hyperpyrexia with TCAs, 575	Hyperthermia atropine causing, 241	causes of, 590 cystic fibrosis, 60	vasoconstriction, 679 Hypoxia
Hyperresonance (chest percussion),	ecstasy intoxication, 571	on ECG, 293	apoptosis caused by, 208
682	MDMA, 571	loop diuretics, 608	contractility in, 284
pneumothorax, 680, <b>682</b>	Hyperthyroidism, 340, 342	nephrogenic DI, 338	erythropoietin and, 589
Hypersensitivity reactions, <b>112–113</b>	amiodarone and, 323	VIPomas and, 371	lung diseases, 679
acute interstitial nephritis, 601	β-blockers in, 245	Hypomanic episodes, <b>561</b>	nocturnal, 679
C3 deficiency, 107 cephalosporins, 189	drug reactions, 249 hCG elevation and, 633	Hyponatremia MDMA, 571	oxygen deprivation, 669 regions susceptible to, 210
Graves disease, 342	hydatidiform moles, 642	as paraneoplastic syndrome, 228	renal, 666
IgE antibodies, 105	Hypertriglyceridemia, 94	thiazides, 609	vasoconstriction/vasodilation and,
mast cells and, 408	acute pancreatitis and, 397	Hypo-osmolarity, 590	297
organ transplants, 119	Hypertrophic cardiomyopathy, 308,	Hypoparathyroidism, <b>344</b>	Hypoxia inducible factor 1a, 224
penicillins, 187–188	531 Damma diagna 97	Hypophosphatemia	Hypoxic stroke, 512
pneumonitis, 675 rheumatic fever, 312	Pompe disease, 87 Hypertrophic osteoarthropathy, 684	hyperparathyroidism, 345 Hypopituitarism, <b>339</b>	Hypoxic vasoconstriction (pulmonary), 668
sulfonamides, 194	cancer association, 228	Hypoplasia, 613	high altitude, 670
Hypersensitivity reaction (type II)	Hypertrophic pyloric stenosis, <b>359</b>	pulmonary, 660	Hysterectomy
rapidly progressive	Hypertrophic scars, 218	Hypopyon, 536	cardinal ligament in, 625
glomerulonephritis, 596	Hypertrophy, 206	Hyporeflexia	Hysteresis (lung and chest wall), 665
Hypersensitivity reaction (type III)	Hyperuricemia	LMN lesions, 531	T. Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Control of the Con
acute poststreptococcal glomerulonephritis, 596	drug reaction and, 250 gout and, 467	magnesium hydroxide and, 399 Hypospadias, 624	Iatrogenic abnormal uterine bleeding,
Hypersensitivity reaction type IV	kidney stones and, 598	Hypotension	633
contact dermatitis, 477	Lesch-Nyhan syndrome, 37	adrenal insufficiency, 349	Ibandronate, 486
Hypersomnia, 561	pyrazinamide, 197	aliskiren, 610	Ibuprofen, 486
Hypertension, <b>300</b> , 679	thiazides, 609	amphotericin B, 199	hemolysis in G6PD deficiency, 250
ACE inhibitors for, 610	vitamin B <sub>3</sub> toxicity, 67	angiotensin II receptor blockers,	Ibutilide, 323
acromegaly and, 339 aliskiren for, 610	Hyperventilation metabolic acidosis and alkalosis,	610 baroreceptors in, 296	ICAM-1 protein in leukocyte extravasation, 215
α-blockers for, 244	592	cardiac tamponade, 310	viral receptor, 166
angiotensin II receptor blockers	in pregnancy, 633	endotoxins, 131	I cells, 371
for, 610	therapeutic, 501	ephedrine for, 242	disease, 47
aortic dissection and, 303	Hypervitaminosis D, 464	hypermagnesemia, 591	Icosahedral viruses, 163
atherosclerosis and, 302	Hypnagogic hallucinations, 559	local anesthetics, 550	Icterohemorrhagic leptospirosis, 147
atrial fibrillation and, 295 autosomal recessive polycystic	narcolepsy, 568 Hypnopompic hallucinations, 559	magnesium hydroxide and, 399 metronidazole, 195	Idarucizumab, 435 Idealization, 555
kidney disease, 604	narcolepsy, 568	midodrine for, 242	Identification, 555
β-blockers for, 245	Hypoaldosteronism, 593	norepinephrine for, 242	Idiopathic intracranial hypertension,
Charcot-Bouchard	Hypocalcemia, 333	orthostatic, 349	521
microaneurysms, 516	acute pancreatitis and, 397	phenylephrine for, 242	Idiopathic pulmonary fibrosis, 675
episodic, 350	cinacalcet causing, 355	scombroid poisoning, 247	Idiopathic thrombocytopenic purpura
heart failure, 316 hyperaldosteronism, 349	hypermagnesemia and, 591 hyperparathyroidism, 345	sympatholytic drugs and, 243 Hypothalamic/pituitary drugs	(ITP), 427 rituximab for, 443
immunosuppressants, 120	hypoparathyroidism, 344	clinical use and adverse effects	IDL (intermediate-density
intraparenchymal hemorrhage,	renal osteodystrophy, 603	of, <b>354</b>	lipoprotein), 94
513	thyroidectomy, 343	Hypothalamic-pituitary hormones,	IFN-γ (Interferon-γ)
leflunomide, 486	tumor lysis syndrome, 435	328	cachexia and, 227
lipohyalinosis and, 514	Hypochlorhydria hypergastrinemia, 379	Hypothalamus	Ifosfamide, 441
local anesthetics, 550 loop diuretics for, 608	Hypocretin, 568	ADH secretion, 329 homeostasis and, <b>498</b>	hemorrhagic cystitis, 251 IgA and IgG deamidated gliadin
MDMA, 571	Hypodermis, 473	nuclei of, 498	peptide autoantibody, 115
microangiopathic anemia, 423	Hypofibrinogenemia, 214	reproductive hormone control, 656	IgA antibodies, 105
minoxidil, 658	Hypogammaglobulinemia, 228	sleep cycle role of, 497	anti-endomysial autoantibody, 115
PCP, 571	Hypoglossal nerve (CN XII), 506	TRH sensitivity, 331	anti-tissue transglutaminase
pheochromocytomas, 350	lesion in, 532	Hypothenar muscles, 450	autoantibody, 115
polyarteritis nodosa, 314 in pregnancy, 243, <b>643</b>	with stroke, 514 tongue, 493	Klumpke palsy, 448 Hypotheses (statistical), 262	ataxia-telangiectasia, 117 breast milk, 636
pseudoephedrine/phenylephrine,	Hypoglycemia	Hypothyroidism, 340, <b>341</b>	in celiac disease, 381
686	fructose intolerance, 80	amiodarone and, 323	hyper-IgM syndrome, 117
renal cyst disorders, 604	glucagon production with, 333	anemia, 420	passive immunity, 110
renal failure, 603	gluconeogenesis and, 78	carpal tunnel syndrome with, 459	Peyer patches and, 374
renovascular disease and, 604	insulinomas, 351	drug reaction and, 249	selective deficiency in, 116
sleep apnea, 679 thiazides for, 609	neonatal, 614 Von Gierke disease, 87	hormone replacement, 354 lithium, 574	IgA nephropathy, 596 IgA protease, 129
		,	G F,

FAS1\_2019\_21\_Index\_749-806.indd 775 11/21/19 12:27 PM

INDEX

IgD antibodies, 105 IgE antibodies, 105 ataxia-telangiectasia, 117 eczema, 47 hyper-IgM syndrome, 117 mast cells and, 408 type I hypersensitivity, 112 IgG antibodies, 105 ataxia-telangiectasia, 117 complement activation and, 106 hepatitis A (HAV), 174 multiple sclerosis, 523 as passive immunity, 110 type II hypersensitivity reaction, type III hypersensitivity reactions, IgM antibodies, 105 in biliary cirrhosis, 395 complement activation and, 106 hepatitis A (HAV), 174 hyper-IgM syndrome, 117 overproduction, 431 in sclerosing cholangitis, 395 splenic dysfunction, 98 Ileum, 362 basal electric rhythm, 362 Ileus, 386 bacterial peritonitis (spontaneous), gallstone, 396 Iliacus, 452 Iliohypogastric nerve, 452 Iliotibial band syndrome, 461 Illness anxiety disorder, 566 Iloperidone, 573 Imatinib, 433, 443 IMG registration timeframe, 6 Imipenem seizures with, 251 Imipramine, 575 Immature ego defenses, 555 Immature teratoma, 647 Immune checkpoint interactions, Immune complex, 113 Immune evasion in cancer, 221 Immune responses acute-phase reactants, 102 antibody structure and function, antigen type and memory, 105 Bordetella pertussis, 143 cell surface proteins, 110 complement, 106 cytokines, 108 hypersensitivity types, 114–115 immunoglobulin, 105 passive vs active, 110 respiratory burst, 109 Salmonella/Shigella spp, 144 transfusion reactions, 114 Immune system organs cellular components, 99 lymph nodes, 96 thymus, 98 Immunocompromised patients acyclovir/famciclovir/valacyclovir, Candida albicans in, 153 common organisms affecting, 179 Cryptococcus neoformans, 153 Cryptosporidium, 155 esophagitis in, 377

fungal infections, 186 Listeria monocytogenes, 139 Pneumocystis jirovecii, 154 Immunodeficiency syndromes flow cytometry diagnosis, 54 infections in, 118 syndromes, **116**–117 Immunoglobulin A vasculitis, 315 Immunoglobulins adaptive immunity and, 99 breast milk and, 636 isotypes of, 105 for Kawasaki disease, 314 Immunohistochemical stains, 227 Immunology, 96-122 cellular components, 98 immune responses, 104-117 immunosuppressants, **120**–122 lymphoid structures, 96-98 pathogen recognition in, 99 Immunomodulator signaling pathways, 337 Immunophenotype assessment, 54 Immunosuppressants for aplastic anemia, 421 targets, 121 transplant rejection, 120 Immunosuppression vitamin A deficiency, 66 vitamin C deficiency, 69 Immunotherapy, 121 Impaired colleague, 269 Imperforate hymen, 644 Impetigo, 136, 475 crusts with, 479 Imprinting disorders, 58 Inactivated (killed) vaccine, 111 Incidence vs prevalence, 259 in medical error corrections, 259 Inclusions Cowdry A, 166 mulberry-like (morulae), 150 Negri bodies, 171 "owl eye," 165 reticulate bodies, 148 Incomplete penetrance, 56 Incontinence (fecal/urinary), 453 Incus, 533, 620 Incus (ossicles) pharyngeal arch derivative, 620 India ink stain, 125 Indicator media, 126 Indinavir HIV therapy, 203 Indirect bilirubin, 375 Indirect cholinomimetic agonists, 240 Indirect Coombs test unbound antibody detection, 112 Indirect inguinal hernia, 370 Indirect sympathomimetics, 242 Indirect (unconjugated) hyperbilirubinemia, 393 Indomethacin, 486 for diabetes insipidus, 338 IFN-α (Interferon-α) clinical uses, 121 myopathy, 250 natural killer cells, 101 Infant development, 635 Infarction blood-brain barrier effects, 496 of bone, 463

atherosclerosis, 302

calcification in, 211

pituitary, 339 regions susceptible to, 210 types of, 210 IFN-β (Interferon-β) clinical uses, 121 natural killer cells, 101 Infections ESR in, 214 in immunodeficiency, 118 Inferior colliculi, 504 Inferior gluteal nerve, 453 Inferior mesenteric artery, 363, 364 horseshoe kidney, 579 Inferior oblique muscle, 540 Inferior rectal artery, 366 Inferior rectal vein, 365 Inferior rectus muscle, 540 Inferior sagittal sinus, 503 Inferior vena cava, 360 diaphragm, 663 gonadal drainage and, 624 Infertility clomiphene, 656 cystic fibrosis, 60 ectopic pregnancy, 641 Kallmann syndrome, 639 Kartagener syndrome, 49 leuprolide for, 656 mumps, 170 salpingitis, 185 septate uterus, 623 varicoceles, 651 IFN-γ (Interferon-γ), **108**, 116 clinical uses, 121 Infiltrative cardiomyopathy, 308 Inflammasome, 214 Inflammation acute, 214 in atherosclerosis, 302 cardinal signs, 213 chronic, 216 ESR in, 214 Extrinsic (death receptor) pathway, IL-1 in, 108 Intrinsic (mitochondrial) pathway, wound healing, 216 Inflammatory bowel disease (IBD), 382 azathioprine for, 440 colorectal cancer and, 388 erythema nodosum, 482 infliximab/adalimumab for, 487 methotrexate for, 440 sclerosing cholangitis and, 395 spondyloarthritis, 469 therapeutic antibodies, 122 Inflammatory breast disease, 649, 650 Inflammatory demyelinating polyradiculopathy, 524 Infliximab, 122, 487 for Crohn disease, 382 for ulcerative colitis, 382 Influenza, 169 orthomyxovirus, 167 pneumonia, 683 treatment/prevention, 201 Informed consent, 265 Infraspinatus muscle Erb palsy, 448 rotator cuff, 446 Infundibulopelvic ligament, 625 Ingested seafood toxins, 247 Inguinal canal, 369

Inguinal hernia, 370 Inguinal ligament, 368, 369 Inguinal triangle, 370 Inhalational injury, 676 Inhaled anesthetics, 550 Inheritance modes, 59 Inhibin Sertoli cell secretion of, 628 Inhibitors of complement activation, 106 Inhibitory pathway, 500 Injury (unintentional), 272 Innate immune system in acute inflammation, 214 Innate immunity, 99 Inositol trisphosphate (IP<sub>3</sub>), 337 Inotropes, 310 Inotropy, 286 INR (international normalized ratio), Insomnia barbiturates for, 546 nonbenzodiazepine hypnotics, 546 ramelteon for, 547 stimulants causing, 570 suvorexant, 547 Inspiratory capacity (IC), 664 Inspiratory reserve volume (IRV), 664 Insulin, **334** anabolic effects of, 334 diabetic ketoacidosis, 347 fructose bisphosphatase-2 and, 76 GIP effect on, 371 glucagon and, 333 glycogen regulation, 73, 85 hypokalemia from, 590 potassium shifts wit, 590 in pregnancy, 334 production of, 329 secretion of, 334 somatostatin and, 371 somatostatinomas and, 351 Insulin deficiency, 590 diabetes mellitus diagnosis, 346 Insulin-like growth factor 1 (IGF-1) acromegaly, 339 signaling pathways for, 337 Insulinoma, 351 insulin and C-peptide in, 334 MEN 1 syndrome, 351 pancreatic cell tumor, 351 Insulin preparations, 352 Insulin resistance, 633 acanthosis nigricans and, 482 acromegaly, 339 cortisol, 336 DM type 2, 347 GH, 329 non-alcoholic fatty liver disease, polycystic ovarian syndrome, 645 disregarding in treatment, 269 Medicare/Medicaid as, 272 types of plans, 271 Integrase inhibitors, 203 epithelial cells, 474 viral receptor, 166 Intellectual disability, 557 autism and, 557 cri-du-chat syndrome, 64 Down syndrome, 63 Lesch-Nyhan syndrome, 37 Patau syndrome, 63

FAS1\_2019\_21\_Index\_749-806.indd 776 11/21/19 12:27 PM

phenylketonuria, 84	Intestinal gastric cancer, 379	Iritis, 536	J
Williams syndrome, 64	Intestinal obstruction	Iron	JAK2 gene, 224
Intellectualization, 555	hernias, 370	absorption of, 69, 374	myeloproliferative disorders, 433
Intention tremor, 519 cerebellar lesions, 511	superior mesenteric artery	anemia, 388, <b>418</b> anemia of chronic disease, 421	Janeway lesions, 311
Interdigital tinea pedis, 152	syndrome, 363 Intimate partner violence, 269	colorectal cancer, 388	Jarisch-Herxheimer reaction, <b>148</b>
Interferons, 109	Intoxication (psychoactive drugs), 570	excess, 67	Jaundice, <b>393</b>
Interferon-γ release assay (IGRA), 140	Intracellular bacteria, <b>127</b>	in hemochromatosis, 395	biliary tract disease, 395
for tuberculosis, 140	Intracellular fluid (ICF), 581	lab values in anemia, 419	cholangitis, 368, 397 drug reaction and, 249
Interleukin 1 (IL-1), 108	Intracellular receptors	sideroblastic anemia, 419	fructose intolerance, 80
cachexia and, 227	endocrine hormone and, 337	toxicity of, 69	galactosemia, 80
endotoxins, 133	Intracranial hemorrhage, 513	toxicity treatment, 248	graft-versus-host disease, 119
Interleukin 2 (IL-2), 108	eclampsia, 643	Iron poisoning, <b>426</b>	hepatitis B, 184
cyclosporine and, 120	Intracranial hypertension	Iron studies	hepatocellular carcinoma, 392
natural killer cells and, 101 sirolimus and, 120	vitamin A toxicity, 66 idiopathic, <b>521</b>	interpretation of, 419–444 Irritable bowel syndrome (IBS)	hereditary hyperbilirubinemias,
tacrolimus and, 120	Intracranial pressure (ICP)	antispasmodic drugs, 241	394
Interleukin 2 receptor (IL-2R), 120	cerebral ischemia, 296	criteria and symptoms for, <b>383</b>	with leptospirosis, 147
Interleukin 3 (IL-3), 108	hydrocephalus, 522	Isavuconazole	newborn hemolytic disease, 405
Interleukin 4 (IL-4), 108	papilledema, 538	mucormycosis treatment, 153	pancreatic cancer, 398
Interleukin 5 (IL-5), 108	superior vena cava syndrome, 685	Ischemia, <b>210</b> , 669	TORCH infections, 182
Interleukin 6 (IL-6), 108	venous sinus thrombosis, 503	acute tubular necrosis from, 602	yellow fever, 168 Jaw jerk reflex, 507
cachexia and, 227	Intraductal papilloma, 649	atherosclerosis, 302	JC virus (John Cunningham virus)
endotoxins, 133	Intraepithelial adenocarcinoma, 644	colonic, 386	HIV-positive adults, 177
Interleukin 8 (IL-8), 108	Intraocular pressure (IOP), 536	digital, 472	immunocompromised patients,
neutrophils and, 406	Intraparenchymal hemorrhage, 513	in gastrointestinal tract, 386	118
Interleukin 10 (IL-10), 108 Interleukin 12 (IL-12), 108	Intrauterine device (IUD)	mesenteric, 386 necrosis and, 209	polyomaviruses, 164
natural killer cells and, 101	copper, 657 Intrauterine growth restriction	watershed areas, 210	Jejunal and ileal atresia, 359
receptor deficiency, 116	(IUGR)	Ischemic brain disease, <b>512</b>	Jejunum, 362
Interleukin receptor modulators	low birth weight, 635	Ischemic heart disease	Jervell and Lange-Nielsen syndrome,
naming conventions for, 254	substance abuse, 614	contraindicated antiarrhythmics,	294
Intermediate filaments	Intravascular hemolysis, 421	322	Jimson weed, 241
cytoskeletal element, 48	paroxysmal nocturnal	heart murmurs in, 291	Job syndrome, 116
Intermenstrual bleeding (IMB), 633	hemoglobinuria, 107	manifestations of, <b>304</b>	Jod-Basedow phenomenon, 342 Joint hypermobility, 51, 62
Internal capsule	Intravenous anesthetics, <b>550</b>	Ischemic priapism, 651	J point in ECG, 293
intraparenchymal hemorrhage, 513	Intraventricular hemorrhage, 512	Islet cell cytoplasmic antibodies, 115	Jugular foramen, 503
stroke effects, 514	neonatal respiratory distress	Islets of Langerhans, 325	Jugular venous distention (JVD),
Internal carotid artery cavernous sinus, 542	syndrome, 661 Intrinsic factor, <b>372</b> , 373	Isocarboxazid, 575 Isocitrate dehydrogenase	<b>309</b> , 685
Internal hemorrhoids, 366	Intrinsic hemolytic anemias, <b>422</b>	metabolic pathways, 74	Jugular venous pulse, 287
Internal iliac artery, 282	Intrinsic pathway, 208	rate determining enzyme, 73	Justice (ethics), 265
Internal iliac lymph nodes, 624	coagulation defects of, 426	Isodisomy, 57	Juvenile polyposis, 387
Internal inguinal ring, 370	heparin and, 437	Isoflurane, 550	Juxtaglomerular apparatus (JGA), <b>589</b>
Internal jugular vein, 503	Intrinsic renal failure, 601	Isolation of affect, 555	renin secretion, 588
Internal oblique muscle, 369	Introns	Isoleucine	Juxtaglomerular cells
Internal rotation	splicing out, 41	classification of, 81	tumors in, 349
arm (rotator cuff), 446	vs exons, 43	maple syrup urine disease and, 84	K
hip, 451	Intussusception, <b>385</b>	Isoniazid, <b>197</b> cytochrome P-450, 252	Kala-azar, 158
Internal spermatic fascia, 369 International Foundations of	Meckel diverticulum, 384 Inulin	hemolysis in G6PD deficiency, 250	Kallikrein
Medicine (IFOM), 12	glomerular filtration rate and, 582	hepatitis, 249	C1 esterase inhibitor deficiency,
Internuclear ophthalmoplegia, 511,	in proximal convoluted tubules,	Mycobacterium tuberculosis, 196	107
543	587	seizures, 251	neutrophil chemotaxis and, 406
Interossei muscles, 450	Inulin clearance, 582	Isoproterenol	Kallmann syndrome, 498, <b>639</b>
Klumpke palsy, 448	Invariant chain, 100	norepinephrine vs, 243	Kaposi sarcoma, 478
ulnar nerve, 447	Invasive carcinoma, 219	sympathomimetic action, 242	AIDS and, 184
Interpersonal therapy, 572	cervix, 645	Isosorbide dinitrate, 318	bacillary angiomatosis vs, 478
Interpreting study results, 261	Invasive lobular carcinoma (breast), 650	Isosorbide mononitrate, 318	HHV-8, 165 HIV-positive adults, 177
Intersex, 639 Interstitial fluid, 297	Inversion, 453	Isotretinoin cystic acne, 66	oncogenic microbes and, 226
Interstitial lung disease, 466, 675	In vivo biofilm-producing bacteria,	teratogenicity, 614	Kartagener syndrome, <b>49</b> , 280
Interstitial nephritis	128	Isovolumetric contraction, 287	obstructive lung disease, 675
acute, 601	Involuntary treatment, 267	Isovolumetric relaxation, 287	Karyotyping, <b>55</b>
as drug reaction, 251	Iodine	Itraconazole	KatG, 197
NSAID toxicity, 486	deficiency in, 341, 342	azoles, 199	Kawasaki disease, 314
penicillins, 188	infection control, 204	Sporothrix schenckii, 154	Kayser-Fleischer rings, 395
Interstitial pneumonia, 683	teratogenicity, 614	systemic mycoses, 151	K cells, 371
Interstitium	Iodophors, 204	Ivabradine, <b>324</b>	K complexes/sleep spindles, 497
leukocyte extravasation and, 215 Interventricular foramen, 281	IPEX syndrome, 102 Ipratropium, 241, <b>687</b>	IV drug use common organisms, 179	Kegel exercises, 599 Keloid scars, 218
Interventricular septal rupture, 305,	Irinotecan/topotecan, <b>442</b>	Ivermectin, 200	Keratinocytes, 216
<b>307</b>	targets of, 438	"Ivory white" plaques, 677	Keratin pearls, 684
"Intestinal angina," 386	topoisomerase (TOP) I inhibition,	IV phlebitis, 199	Keratoacanthoma, 484
Intestinal atresia, <b>359</b>	38	Ixodes ticks, 146, 149	Keratoconjunctivitis, 164

FAS1\_2019\_21\_Index\_749-806.indd 777 11/21/19 12:27 PM

INDEX

Keratoconjunctivitis sicca, 468
Keratomalacia, 66
Keratosis
actinic, 482
hyperkeratosis, 475
parakeratosis, 475
seborrheic, 477
Kernicterus, 194, 204, <b>393</b> –394
Ketamine, 550
Ketoacidosis, 72, 90
Ketoconazole, 658
cytochrome P-450, 252
gynecomastia from, 649
gynecomastia nom, 077
mechanism and clinical use, 199
Ketogenesis
diabetic ketoacidosis, 347
metabolic site, 72
rate-determining enzyme for, 73
Ketone bodies, <b>90</b>
brain metabolism, 334
in diabetic ketoacidosis, 347
production of, 90
Ketorolac, 486
Kidney disease
acute injury, 601
hypertension, 300
prenatal diagnosis of, 579
Kidneys
anatomy, <b>580</b>
blood flow regulation, 297
calcification in, 211
chronic graft nephropathy, 119
embryology of, <b>578</b>
endocrine functions, <b>589</b>
glomerular structure, <b>580</b>
hormones acting on, 590
ischemia in, 210
retroperitoneal location of, 360
sclerosis, 473
301010313, 179
colitary functioning 570
solitary functioning, 579
transplant prophylaxis, 120
transplant prophylaxis, 120 Kidney stones
transplant prophylaxis, 120 Kidney stones Crohn disease association, 382
transplant prophylaxis, 120 Kidney stones Crohn disease association, 382 electrolyte disturbances, 591
transplant prophylaxis, 120 Kidney stones Crohn disease association, 382 electrolyte disturbances, 591
transplant prophylaxis, 120 Kidney stones Crohn disease association, 382
transplant prophylaxis, 120 Kidney stones Crohn disease association, 382 electrolyte disturbances, 591 hematuria with, 594 hydronephrosis, 599
transplant prophylaxis, 120 Kidney stones Crohn disease association, 382 electrolyte disturbances, 591 hematuria with, 594 hydronephrosis, 599 hyperparathyroidism, 345
transplant prophylaxis, 120 Kidney stones Crohn disease association, 382 electrolyte disturbances, 591 hematuria with, 594 hydronephrosis, 599 hyperparathyroidism, 345 presentation and findings with, <b>598</b>
transplant prophylaxis, 120 Kidney stones Crohn disease association, 382 electrolyte disturbances, 591 hematuria with, 594 hydronephrosis, 599 hyperparathyroidism, 345 presentation and findings with, <b>598</b> risk factors for, 593
transplant prophylaxis, 120 Kidney stones Crohn disease association, 382 electrolyte disturbances, 591 hematuria with, 594 hydronephrosis, 599 hyperparathyroidism, 345 presentation and findings with, <b>598</b> risk factors for, 593 UTIs, 181
transplant prophylaxis, 120 Kidney stones Crohn disease association, 382 electrolyte disturbances, 591 hematuria with, 594 hydronephrosis, 599 hyperparathyroidism, 345 presentation and findings with, <b>598</b> risk factors for, 593 UTIs, 181 Kiesselbach plexus, 671
transplant prophylaxis, 120 Kidney stones Crohn disease association, 382 electrolyte disturbances, 591 hematuria with, 594 hydronephrosis, 599 hyperparathyroidism, 345 presentation and findings with, <b>598</b> risk factors for, 593 UTIs, 181 Kiesselbach plexus, 671 Killian triangle, 384
transplant prophylaxis, 120 Kidney stones Crohn disease association, 382 electrolyte disturbances, 591 hematuria with, 594 hydronephrosis, 599 hyperparathyroidism, 345 presentation and findings with, <b>598</b> risk factors for, 593 UTIs, 181 Kiesselbach plexus, 671 Killian triangle, 384 Kinases, 73
transplant prophylaxis, 120 Kidney stones Crohn disease association, 382 electrolyte disturbances, 591 hematuria with, 594 hydronephrosis, 599 hyperparathyroidism, 345 presentation and findings with, <b>598</b> risk factors for, 593 UTIs, 181 Kiesselbach plexus, 671 Killian triangle, 384
transplant prophylaxis, 120 Kidney stones Crohn disease association, 382 electrolyte disturbances, 591 hematuria with, 594 hydronephrosis, 599 hyperparathyroidism, 345 presentation and findings with, <b>598</b> risk factors for, 593 UTIs, 181 Kiesselbach plexus, 671 Killian triangle, 384 Kinases, 73 Kinesin movement of, 48
transplant prophylaxis, 120 Kidney stones Crohn disease association, 382 electrolyte disturbances, 591 hematuria with, 594 hydronephrosis, 599 hyperparathyroidism, 345 presentation and findings with, <b>598</b> risk factors for, 593 UTIs, 181 Kiesselbach plexus, 671 Killian triangle, 384 Kinases, 73 Kinesin movement of, 48
transplant prophylaxis, 120 Kidney stones Crohn disease association, 382 electrolyte disturbances, 591 hematuria with, 594 hydronephrosis, 599 hyperparathyroidism, 345 presentation and findings with, <b>598</b> risk factors for, 593 UTIs, 181 Kiesselbach plexus, 671 Killian triangle, 384 Kinases, 73 Kinesin movement of, 48 Kinin cascade/pathways, 412
transplant prophylaxis, 120 Kidney stones Crohn disease association, 382 electrolyte disturbances, 591 hematuria with, 594 hydronephrosis, 599 hyperparathyroidism, 345 presentation and findings with, 598 risk factors for, 593 UTIs, 181 Kiesselbach plexus, 671 Killian triangle, 384 Kinases, 73 Kinesin movement of, 48 Kinin cascade/pathways, 412 Klebsiella pneumoniae
transplant prophylaxis, 120 Kidney stones Crohn disease association, 382 electrolyte disturbances, 591 hematuria with, 594 hydronephrosis, 599 hyperparathyroidism, 345 presentation and findings with, 598 risk factors for, 593 UTIs, 181 Kiesselbach plexus, 671 Killian triangle, 384 Kinases, 73 Kinesin movement of, 48 Kinin cascade/pathways, 412 Klebsiella pneumoniae cephalosporins, 189
transplant prophylaxis, 120 Kidney stones Crohn disease association, 382 electrolyte disturbances, 591 hematuria with, 594 hydronephrosis, 599 hyperparathyroidism, 345 presentation and findings with, 598 risk factors for, 593 UTIs, 181 Kiesselbach plexus, 671 Killian triangle, 384 Kinases, 73 Kinesin movement of, 48 Kinin cascade/pathways, 412 Klebsiella pneumoniae cephalosporins, 189 encapsulation, 127
transplant prophylaxis, 120 Kidney stones Crohn disease association, 382 electrolyte disturbances, 591 hematuria with, 594 hydronephrosis, 599 hyperparathyroidism, 345 presentation and findings with, 598 risk factors for, 593 UTIs, 181 Kiesselbach plexus, 671 Killian triangle, 384 Kinases, 73 Kinesin movement of, 48 Kinin cascade/pathways, 412 Klebsiella pneumoniae cephalosporins, 189 encapsulation, 127 UTIs caused by, 181
transplant prophylaxis, 120 Kidney stones Crohn disease association, 382 electrolyte disturbances, 591 hematuria with, 594 hydronephrosis, 599 hyperparathyroidism, 345 presentation and findings with, 598 risk factors for, 593 UTIs, 181 Kiesselbach plexus, 671 Killian triangle, 384 Kinases, 73 Kinesin movement of, 48 Kinin cascade/pathways, 412 Klebsiella pneumoniae cephalosporins, 189 encapsulation, 127 UTIs caused by, 181 Klebsiella spp, 145
transplant prophylaxis, 120 Kidney stones Crohn disease association, 382 electrolyte disturbances, 591 hematuria with, 594 hydronephrosis, 599 hyperparathyroidism, 345 presentation and findings with, 598 risk factors for, 593 UTIs, 181 Kiesselbach plexus, 671 Killian triangle, 384 Kinases, 73 Kinesin movement of, 48 Kinin cascade/pathways, 412 Klebsiella pneumoniae cephalosporins, 189 encapsulation, 127 UTIs caused by, 181 Klebsiella spp, 145 alcoholism, 179
transplant prophylaxis, 120 Kidney stones Crohn disease association, 382 electrolyte disturbances, 591 hematuria with, 594 hydronephrosis, 599 hyperparathyroidism, 345 presentation and findings with, 598 risk factors for, 593 UTIs, 181 Kiesselbach plexus, 671 Killian triangle, 384 Kinases, 73 Kinesin movement of, 48 Kinin cascade/pathways, 412 Klebsiella pneumoniae cephalosporins, 189 encapsulation, 127 UTIs caused by, 181 Klebsiella spp, 145 alcoholism, 179 currant jelly sputum, 145, 186
transplant prophylaxis, 120 Kidney stones Crohn disease association, 382 electrolyte disturbances, 591 hematuria with, 594 hydronephrosis, 599 hyperparathyroidism, 345 presentation and findings with, 598 risk factors for, 593 UTIs, 181 Kiesselbach plexus, 671 Killian triangle, 384 Kinases, 73 Kinesin movement of, 48 Kinin cascade/pathways, 412 Klebsiella pneumoniae cephalosporins, 189 encapsulation, 127 UTIs caused by, 181 Klebsiella spp, 145 alcoholism, 179
transplant prophylaxis, 120 Kidney stones Crohn disease association, 382 electrolyte disturbances, 591 hematuria with, 594 hydronephrosis, 599 hyperparathyroidism, 345 presentation and findings with, 598 risk factors for, 593 UTIs, 181 Kiesselbach plexus, 671 Killian triangle, 384 Kinases, 73 Kinesin movement of, 48 Kinin cascade/pathways, 412 Klebsiella pneumoniae cephalosporins, 189 encapsulation, 127 UTIs caused by, 181 Klebsiella spp, 145 alcoholism, 179 currant jelly sputum, 145, 186
transplant prophylaxis, 120 Kidney stones Crohn disease association, 382 electrolyte disturbances, 591 hematuria with, 594 hydronephrosis, 599 hyperparathyroidism, 345 presentation and findings with, 598 risk factors for, 593 UTIs, 181 Kiesselbach plexus, 671 Killian triangle, 384 Kinases, 73 Kinesin movement of, 48 Kinin cascade/pathways, 412 Klebsiella pneumoniae cephalosporins, 189 encapsulation, 127 UTIs caused by, 181 Klebsiella spp, 145 alcoholism, 179 currant jelly sputum, 145, 186 nosocomial infections, 185 pneumonia, 683
transplant prophylaxis, 120 Kidney stones Crohn disease association, 382 electrolyte disturbances, 591 hematuria with, 594 hydronephrosis, 599 hyperparathyroidism, 345 presentation and findings with, 598 risk factors for, 593 UTIs, 181 Kiesselbach plexus, 671 Killian triangle, 384 Kinases, 73 Kinesin movement of, 48 Kinin cascade/pathways, 412 Klebsiella pneumoniae cephalosporins, 189 encapsulation, 127 UTIs caused by, 181 Klebsiella spp, 145 alcoholism, 179 currant jelly sputum, 145, 186 nosocomial infections, 185 pneumonia, 683 urease-positive, 127
transplant prophylaxis, 120 Kidney stones Crohn disease association, 382 electrolyte disturbances, 591 hematuria with, 594 hydronephrosis, 599 hyperparathyroidism, 345 presentation and findings with, 598 risk factors for, 593 UTIs, 181 Kiesselbach plexus, 671 Killian triangle, 384 Kinases, 73 Kinesin movement of, 48 Kinin cascade/pathways, 412 Klebsiella pneumoniae cephalosporins, 189 encapsulation, 127 UTIs caused by, 181 Klebsiella spp, 145 alcoholism, 179 currant jelly sputum, 145, 186 nosocomial infections, 185 pneumonia, 683 urease-positive, 127 urinary tract infections, 600
transplant prophylaxis, 120 Kidney stones Crohn disease association, 382 electrolyte disturbances, 591 hematuria with, 594 hydronephrosis, 599 hyperparathyroidism, 345 presentation and findings with, 598 risk factors for, 593 UTIs, 181 Kiesselbach plexus, 671 Killian triangle, 384 Kinases, 73 Kinesin movement of, 48 Kinin cascade/pathways, 412 Klebsiella pneumoniae cephalosporins, 189 encapsulation, 127 UTIs caused by, 181 Klebsiella spp, 145 alcoholism, 179 currant jelly sputum, 145, 186 nosocomial infections, 185 pneumonia, 683 urease-positive, 127 urinary tract infections, 600 Klinefelter syndrome, 638
transplant prophylaxis, 120 Kidney stones Crohn disease association, 382 electrolyte disturbances, 591 hematuria with, 594 hydronephrosis, 599 hyperparathyroidism, 345 presentation and findings with, 598 risk factors for, 593 UTIs, 181 Kiesselbach plexus, 671 Killian triangle, 384 Kinases, 73 Kinesin movement of, 48 Kinin cascade/pathways, 412 Klebsiella pneumoniae cephalosporins, 189 encapsulation, 127 UTIs caused by, 181 Klebsiella spp, 145 alcoholism, 179 currant jelly sputum, 145, 186 nosocomial infections, 185 pneumonia, 683 urease-positive, 127 urinary tract infections, 600 Klinefelter syndrome, 638 chromosome association, 64
transplant prophylaxis, 120 Kidney stones Crohn disease association, 382 electrolyte disturbances, 591 hematuria with, 594 hydronephrosis, 599 hyperparathyroidism, 345 presentation and findings with, 598 risk factors for, 593 UTIs, 181 Kiesselbach plexus, 671 Killian triangle, 384 Kinases, 73 Kinesin movement of, 48 Kinin cascade/pathways, 412 Klebsiella pneumoniae cephalosporins, 189 encapsulation, 127 UTIs caused by, 181 Klebsiella spp, 145 alcoholism, 179 currant jelly sputum, 145, 186 nosocomial infections, 185 pneumonia, 683 urease-positive, 127 urinary tract infections, 600 Klinefelter syndrome, 638 chromosome association, 64 gynecomastia, 649
transplant prophylaxis, 120 Kidney stones Crohn disease association, 382 electrolyte disturbances, 591 hematuria with, 594 hydronephrosis, 599 hyperparathyroidism, 345 presentation and findings with, 598 risk factors for, 593 UTIs, 181 Kiesselbach plexus, 671 Killian triangle, 384 Kinases, 73 Kinesin movement of, 48 Kinin cascade/pathways, 412 Klebsiella pneumoniae cephalosporins, 189 encapsulation, 127 UTIs caused by, 181 Klebsiella spp, 145 alcoholism, 179 currant jelly sputum, 145, 186 nosocomial infections, 185 pneumonia, 683 urease-positive, 127 urinary tract infections, 600 Klinefelter syndrome, 638 chromosome association, 64 gynecomastia, 649 Klumpke palsy, 448
transplant prophylaxis, 120 Kidney stones Crohn disease association, 382 electrolyte disturbances, 591 hematuria with, 594 hydronephrosis, 599 hyperparathyroidism, 345 presentation and findings with, 598 risk factors for, 593 UTIs, 181 Kiesselbach plexus, 671 Killian triangle, 384 Kinases, 73 Kinesin movement of, 48 Kinin cascade/pathways, 412 Klebsiella pneumoniae cephalosporins, 189 encapsulation, 127 UTIs caused by, 181 Klebsiella spp, 145 alcoholism, 179 currant jelly sputum, 145, 186 nosocomial infections, 185 pneumonia, 683 urease-positive, 127 urinary tract infections, 600 Klinefelter syndrome, 638 chromosome association, 64 gynecomastia, 649 Klumpke palsy, 448 Klüver-Bucy syndrome, 511
transplant prophylaxis, 120 Kidney stones Crohn disease association, 382 electrolyte disturbances, 591 hematuria with, 594 hydronephrosis, 599 hyperparathyroidism, 345 presentation and findings with, 598 risk factors for, 593 UTIs, 181 Kiesselbach plexus, 671 Killian triangle, 384 Kinases, 73 Kinesin movement of, 48 Kinin cascade/pathways, 412 Klebsiella pneumoniae cephalosporins, 189 encapsulation, 127 UTIs caused by, 181 Klebsiella spp, 145 alcoholism, 179 currant jelly sputum, 145, 186 nosocomial infections, 185 pneumonia, 683 urease-positive, 127 urinary tract infections, 600 Klinefelter syndrome, 638 chromosome association, 64 gynecomastia, 649 Klumpke palsy, 448 Klüver-Bucy syndrome, 511 Knee examination, 454
transplant prophylaxis, 120 Kidney stones Crohn disease association, 382 electrolyte disturbances, 591 hematuria with, 594 hydronephrosis, 599 hyperparathyroidism, 345 presentation and findings with, 598 risk factors for, 593 UTIs, 181 Kiesselbach plexus, 671 Killian triangle, 384 Kinases, 73 Kinesin movement of, 48 Kinin cascade/pathways, 412 Klebsiella pneumoniae cephalosporins, 189 encapsulation, 127 UTIs caused by, 181 Klebsiella spp, 145 alcoholism, 179 currant jelly sputum, 145, 186 nosocomial infections, 185 pneumonia, 683 urease-positive, 127 urinary tract infections, 600 Klinefelter syndrome, 638 chromosome association, 64 gynecomastia, 649 Klumpke palsy, 448 Klüver-Bucy syndrome, 511 Knee examination, 454 Knee injuries/conditions
transplant prophylaxis, 120 Kidney stones Crohn disease association, 382 electrolyte disturbances, 591 hematuria with, 594 hydronephrosis, 599 hyperparathyroidism, 345 presentation and findings with, 598 risk factors for, 593 UTIs, 181 Kiesselbach plexus, 671 Killian triangle, 384 Kinases, 73 Kinesin movement of, 48 Kinin cascade/pathways, 412 Klebsiella pneumoniae cephalosporins, 189 encapsulation, 127 UTIs caused by, 181 Klebsiella spp, 145 alcoholism, 179 currant jelly sputum, 145, 186 nosocomial infections, 185 pneumonia, 683 urease-positive, 127 urinary tract infections, 600 Klinefelter syndrome, 638 chromosome association, 64 gynecomastia, 649 Klumpke palsy, 448 Klüver-Bucy syndrome, 511 Knee examination, 454 Knee injuries/conditions Baker cyst, 460
transplant prophylaxis, 120 Kidney stones Crohn disease association, 382 electrolyte disturbances, 591 hematuria with, 594 hydronephrosis, 599 hyperparathyroidism, 345 presentation and findings with, 598 risk factors for, 593 UTIs, 181 Kiesselbach plexus, 671 Killian triangle, 384 Kinases, 73 Kinesin movement of, 48 Kinin cascade/pathways, 412 Klebsiella pneumoniae cephalosporins, 189 encapsulation, 127 UTIs caused by, 181 Klebsiella spp, 145 alcoholism, 179 currant jelly sputum, 145, 186 nosocomial infections, 185 pneumonia, 683 urease-positive, 127 urinary tract infections, 600 Klinefelter syndrome, 638 chromosome association, 64 gynecomastia, 649 Klumpke palsy, 448 Klüver-Bucy syndrome, 511 Knee examination, 454 Knee injuries/conditions

ligament and meniscus, 460 Osgood-Schlatter disease, 461 prepatellar bursitis, 460 Knees
common conditions of, <b>460</b> Knock-out/Knock-in genes, 56 KOH preparation, 152 Koilocytes condylomata acuminata, 184
Koilocytosis, 477 Koplik spots, 183 Korsakoff syndrome, 66, 558, <b>571</b> Krabbe disease, <b>88</b> , 524 KRAS gene, 224
adenomatous colonic polyps and, 387
lung cancer and, 684 Krukenberg tumors, 379 Kübler-Ross grief model, 562 Kulchitsky cells, 684 Kuru, 178
Kussmaul respirations in diabetic ketoacidosis, 347 Kussmaul sign, <b>316</b>
Kwashiorkor, 71 Kyphoscoliosis, 531 Kyphosis
in homocystinuria, 84 K <sub>m</sub> , 230
Labetalol, 245 hypertension in pregnancy, 316
hypertensive emergency, 318 Labia, 625 Labile cells, 46 Lachman test, 454
Lac operons, <b>40</b> Lacrimation reflex, 507 Lactase deficiency, <b>81</b>
Lactation, <b>636</b> oxytocin's role in, 328 progesterone and, 630
prolactin and, 330 Sheehan syndrome and, 339 Lactational mastitis, 649
Lactic acid dehydrogenase, 77 Lactic acidosis ethanol metabolism and, 72
exercise and, 670 MELAS syndrome, 59
pyruvate dehydrogenase complex deficiency, 77 Lactoferrin
in neutrophils, 406 in respiratory burst, 109 Lactose-fermenting enteric bacteria,
126, <b>144</b> Lactose intolerance, 381 Lactose metabolism
genetic response to environmental change, 40 Lactulose
for hepatic encephalopathy, 391 Lacunar infarcts, 514 Ladd bands, 385 Lambert-Eaton myasthenic syndrome
472 autoantibody, 115 as paraneoplastic syndrome, 228
small cell lung cancer, 684 Lamina propria Peyer patches in, 374
in Whipple disease, 381 Lamins, 48

Lamivudine, 203
HIV therapy, 203 Lamotrigine
epilepsy, 544
rash caused by 750
Lancet-shaped diplococci, 136 Landmarks (anatomical)
for dermatomes, <b>510</b>
midclavicular line, 663
pudendal nerve block, 453 Langerhans cell histiocytosis, <b>434</b>
pulmonary, 6/5 Lansoprazole, 399 Laplace law, <b>284</b> , 661 Large cell carcinoma, 684 Large-vessel vasculitis
Large cell carcinoma, 684
Large-vessel vasculitis
presentation and pathology, 314 Larva migrans, 159 Laryngopharyngeal reflux, 377 Laryngospasm, 359
Laryngopharyngeal reflux, 377
_aryngospasm, 359 drug-induced, 569
Larynx, 662
Larynx muscles, 620
Latanoprost, 552
Latent errors, 274
drug-induced, 569 Larynx, 662 Larynx muscles, 620 Lassa fever encephalitis, 167 Latanoprost, 552 Latent errors, 274 Lateral cerebellar lesions, 499 Lateral collateral ligament (LCL)
mjury, 121
Lateral corticospinal tract, 508, <b>509</b> , 514
ateral epicondylitis, 459 ateral femoral cutaneous nerve, 452 ateral geniculate nucleus (LGN),
400
Lateral medullary syndrome, 514
Lateral nucleus (hypothalamus), 498
Lateral medullary syndrome, 514 Lateral nucleus (hypothalamus), 498 Lateral pterygoid muscle, 507 Lateral rectus muscle, 540 Lateral spinothalamic tract, 508 Lateral thoracic artery, 455 Lateral ventricles
Lateral spinothalamic tract, 508
Lateral thoracic artery, 455
optic radiation, 542 ventricular system, 504
ventricular system, 504
LD50 (lethal median dose), 234
ventricular system, 504 Laxatives, <b>401</b> LD50 (lethal median dose), 234 LDH tumor burden indicator, 226
tumor burden indicator, 226 LDL (low-density lipoprotein), 94
PCSK9 enzyme, 93
receptor binding, 93
Leaden paralysis, 561 Lead poisoning
anemia with, 419
foot drop, 419 mechanism, 425
memory loss with, 425
sideroblastic anemia, 419 treatment of, 248, <b>419</b>
Lead-time bias, 261
Lead-time bias, 261 Leber hereditary optic neuropathy, 59 Lecithinase, 133, 138 Lecithin-cholesterol acetyltransferase
Lecitninase, 155, 158 Lecithin-cholesterol acetyltransferase
(LCAI)
activation of, 93 Lecithin-cholesterol acyltransferase,
93
Lectin pathway (complement
activation), 106 Ledipasvir, 204
Ledipasvir, 204 Leflunomide, <b>486</b>
dihydroorotate dehydrogenase inhibition, 36
Left anterior descending artery
coronary circulation, 283
myocardial infarction and, 305

Left bundle branch, 293
Left bundle branch, 293
Left circumflex coronary artery, 283
Left heart disease, 679
I felt a felt 200
Left heart failure, 309
Left horn of sinus venosus, 281
Left main coronary artery, 283
Left marginal artery, 283
Left shift, 424
Left-to-right shunts, 299
Lett-to-right shulls, 277
Legg-Calvé-Perthes disease, 461, 463
Legionella pneumophila, <b>143</b>
Legionella spp
atypical organism, 179
culture requirements, 126
facultative intracellular organisms,
127
Gram stain of, 125
macrolides, 193
nosocomial infection, 185
intracellular organism, 127
pnoumonia 682
pneumonia, 683
silver stain, 125
Legionnaires' disease, 143
Leiomyama (fibrail) 640
Leiomyoma (fibroid), 648
nomenclature for, 220
uterine bleeding with, 633
Leiomyosarooma 220 640
Leiomyosarcoma, 220, 648
Leishmaniasis, 158, 200
Length-time bias, 261
Lens
collagen in, 50
infantile cataracts, 80
Lens subluxation
Elastin syndrome, 52
in homocystinuria, 52, <b>84</b>
Lenticulostriate artery, 514
Lentiform nucleus, 500
Lenthorn nucleus, 700
Leonine facies, 141
Leprosy (Hansen disease), <b>141</b>
Leptin, 336
hypothalamus, 498
hypothalamus, 498 Leptospira spp
hypothalamus, 498 Leptospira spp
hypothalamus, 498 <i>Leptospira</i> spp Gram stain of, 125
hypothalamus, 498 Leptospira spp Gram stain of, 125 spirochete, 146
hypothalamus, 498  Leptospira spp Gram stain of, 125 spirochete, 146 zoonotic infections, 149
hypothalamus, 498  Leptospira spp Gram stain of, 125 spirochete, 146 zoonotic infections, 149
hypothalamus, 498 Leptospira spp Gram stain of, 125 spirochete, 146 zoonotic infections, 149 Leptospira interrogans, <b>147</b>
hypothalamus, 498 Leptospira spp Gram stain of, 125 spirochete, 146 zoonotic infections, 149 Leptospira interrogans, 147 Leptospirosis, 149
hypothalamus, 498 Leptospira spp Gram stain of, 125 spirochete, 146 zoonotic infections, 149 Leptospira interrogans, 147 Leptospirosis, 149 symptoms of, 147
hypothalamus, 498  Leptospira spp Gram stain of, 125 spirochete, 146 zoonotic infections, 149 Leptospira interrogans, 147 Leptospirosis, 149 symptoms of, 147 Lesch-Nyhan syndrome
hypothalamus, 498  Leptospira spp Gram stain of, 125 spirochete, 146 zoonotic infections, 149 Leptospira interrogans, 147 Leptospirosis, 149 symptoms of, 147 Lesch-Nyhan syndrome
hypothalamus, 498  Leptospira spp Gram stain of, 125 spirochete, 146 zoonotic infections, 149 Leptospira interrogans, 147 Leptospirosis, 149 symptoms of, 147 Lesch-Nyhan syndrome inheritance, 61
hypothalamus, 498  Leptospira spp Gram stain of, 125 spirochete, 146 zoonotic infections, 149  Leptospira interrogans, 147  Leptospirosis, 149 symptoms of, 147  Lesch-Nyhan syndrome inheritance, 61 purine salvage deficiency, 37
hypothalamus, 498  Leptospira spp Gram stain of, 125 spirochete, 146 zoonotic infections, 149 Leptospira interrogans, 147 Leptospirosis, 149 symptoms of, 147 Lesch-Nyhan syndrome inheritance, 61 purine salvage deficiency, 37 Leser-Trélat sign, 228, 477
hypothalamus, 498  Leptospira spp Gram stain of, 125 spirochete, 146 zoonotic infections, 149  Leptospira interrogans, 147  Leptospirosis, 149 symptoms of, 147  Lesch-Nyhan syndrome inheritance, 61 purine salvage deficiency, 37
hypothalamus, 498  Leptospira spp Gram stain of, 125 spirochete, 146 zoonotic infections, 149  Leptospira interrogans, 147 Leptospirosis, 149 symptoms of, 147 Lesch-Nyhan syndrome inheritance, 61 purine salvage deficiency, 37 Leser-Trélat sign, 228, 477 stomach cancer, 379
hypothalamus, 498  Leptospira spp Gram stain of, 125 spirochete, 146 zoonotic infections, 149  Leptospira interrogans, 147  Leptospirosis, 149 symptoms of, 147  Lesch-Nyhan syndrome inheritance, 61 purine salvage deficiency, 37  Leser-Trélat sign, 228, 477 stomach cancer, 379  Lesser omental sac, 361
hypothalamus, 498 Leptospira spp Gram stain of, 125 spirochete, 146 zoonotic infections, 149 Leptospira interrogans, 147 Leptospirosis, 149 symptoms of, 147 Lesch-Nyhan syndrome inheritance, 61 purine salvage deficiency, 37 Leser-Trélat sign, 228, 477 stomach cancer, 379 Lesser omental sac, 361 Letrozole, 656
hypothalamus, 498  Leptospira spp Gram stain of, 125 spirochete, 146 zoonotic infections, 149  Leptospira interrogans, 147  Leptospirosis, 149 symptoms of, 147  Lesch-Nyhan syndrome inheritance, 61 purine salvage deficiency, 37  Leser-Trélat sign, 228, 477 stomach cancer, 379  Lesser omental sac, 361
hypothalamus, 498 Leptospira spp Gram stain of, 125 spirochete, 146 zoonotic infections, 149 Leptospira interrogans, 147 Leptospirosis, 149 symptoms of, 147 Lesch-Nyhan syndrome inheritance, 61 purine salvage deficiency, 37 Leser-Trélat sign, 228, 477 stomach cancer, 379 Lesser omental sac, 361 Letrozole, 656 Leucine
hypothalamus, 498 Leptospira spp Gram stain of, 125 spirochete, 146 zoonotic infections, 149 Leptospira interrogans, 147 Leptospirosis, 149 symptoms of, 147 Lesch-Nyhan syndrome inheritance, 61 purine salvage deficiency, 37 Leser-Trélat sign, 228, 477 stomach cancer, 379 Lesser omental sac, 361 Letrozole, 656 Leucine classification of, 81
hypothalamus, 498 Leptospira spp Gram stain of, 125 spirochete, 146 zoonotic infections, 149 Leptospira interrogans, 147 Leptospirosis, 149 symptoms of, 147 Lesch-Nyhan syndrome inheritance, 61 purine salvage deficiency, 37 Leser-Trélat sign, 228, 477 stomach cancer, 379 Lesser omental sac, 361 Letrozole, 656 Leucine classification of, 81 maple syrup urine disease and, 84
hypothalamus, 498 Leptospira spp Gram stain of, 125 spirochete, 146 zoonotic infections, 149 Leptospira interrogans, 147 Leptospirosis, 149 symptoms of, 147 Lesch-Nyhan syndrome inheritance, 61 purine salvage deficiency, 37 Leser-Trélat sign, 228, 477 stomach cancer, 379 Lesser omental sac, 361 Letrozole, 656 Leucine classification of, 81
hypothalamus, 498 Leptospira spp Gram stain of, 125 spirochete, 146 zoonotic infections, 149 Leptospira interrogans, 147 Leptospirosis, 149 symptoms of, 147 Lesch-Nyhan syndrome inheritance, 61 purine salvage deficiency, 37 Leser-Trélat sign, 228, 477 stomach cancer, 379 Lesser omental sac, 361 Letrozole, 656 Leucine classification of, 81 maple syrup urine disease and, 84 Leucovorin, 440 Leukemias, 432
hypothalamus, 498 Leptospira spp Gram stain of, 125 spirochete, 146 zoonotic infections, 149 Leptospira interrogans, 147 Leptospirosis, 149 symptoms of, 147 Lesch-Nyhan syndrome inheritance, 61 purine salvage deficiency, 37 Leser-Trélat sign, 228, 477 stomach cancer, 379 Lesser omental sac, 361 Letrozole, 656 Leucine classification of, 81 maple syrup urine disease and, 84 Leucovorin, 440 Leukemias, 432
hypothalamus, 498 Leptospira spp Gram stain of, 125 spirochete, 146 zoonotic infections, 149 Leptospira interrogans, 147 Leptospirosis, 149 symptoms of, 147 Lesch-Nyhan syndrome inheritance, 61 purine salvage deficiency, 37 Leser-Trélat sign, 228, 477 stomach cancer, 379 Lesser omental sac, 361 Letrozole, 656 Leucine classification of, 81 maple syrup urine disease and, 84 Leucovorin, 440 Leukemias, 432 carcinogens, 225
hypothalamus, 498 Leptospira spp Gram stain of, 125 spirochete, 146 zoonotic infections, 149 Leptospira interrogans, 147 Leptospirosis, 149 symptoms of, 147 Lesch-Nyhan syndrome inheritance, 61 purine salvage deficiency, 37 Leser-Trélat sign, 228, 477 stomach cancer, 379 Lesser omental sac, 361 Letrozole, 656 Leucine classification of, 81 maple syrup urine disease and, 84 Leucovorin, 440 Leukemias, 432 carcinogens, 225 cell type, 220
hypothalamus, 498 Leptospira spp Gram stain of, 125 spirochete, 146 zoonotic infections, 149 Leptospira interrogans, 147 Leptospirosis, 149 symptoms of, 147 Lesch-Nyhan syndrome inheritance, 61 purine salvage deficiency, 37 Leser-Trélat sign, 228, 477 stomach cancer, 379 Lesser omental sac, 361 Letrozole, 656 Leucine classification of, 81 maple syrup urine disease and, 84 Leucovorin, 440 Leukemias, 432 carcinogens, 225 cell type, 220 cyclophosphamide for, 441
hypothalamus, 498 Leptospira spp Gram stain of, 125 spirochete, 146 zoonotic infections, 149 Leptospira interrogans, 147 Leptospirosis, 149 symptoms of, 147 Lesch-Nyhan syndrome inheritance, 61 purine salvage deficiency, 37 Leser-Trélat sign, 228, 477 stomach cancer, 379 Lesser omental sac, 361 Letrozole, 656 Leucine classification of, 81 maple syrup urine disease and, 84 Leucovorin, 440 Leukemias, 432 carcinogens, 225 cell type, 220 cyclophosphamide for, 441
hypothalamus, 498 Leptospira spp Gram stain of, 125 spirochete, 146 zoonotic infections, 149 Leptospira interrogans, 147 Leptospirosis, 149 symptoms of, 147 Lesch-Nyhan syndrome inheritance, 61 purine salvage deficiency, 37 Leser-Trélat sign, 228, 477 stomach cancer, 379 Lesser omental sac, 361 Letrozole, 656 Leucine classification of, 81 maple syrup urine disease and, 84 Leucovorin, 440 Leukemias, 432 carcinogens, 225 cell type, 220 cyclophosphamide for, 441 cytarabine for, 440
hypothalamus, 498 Leptospira spp Gram stain of, 125 spirochete, 146 zoonotic infections, 149 Leptospira interrogans, 147 Leptospirosis, 149 symptoms of, 147 Lesch-Nyhan syndrome inheritance, 61 purine salvage deficiency, 37 Leser-Trélat sign, 228, 477 stomach cancer, 379 Lesser omental sac, 361 Letrozole, 656 Leucine classification of, 81 maple syrup urine disease and, 84 Leucovorin, 440 Leukemias, 432 carcinogens, 225 cell type, 220 cyclophosphamide for, 441 cytarabine for, 440 doxorubicin for, 439
hypothalamus, 498 Leptospira spp Gram stain of, 125 spirochete, 146 zoonotic infections, 149 Leptospira interrogans, 147 Leptospirosis, 149 symptoms of, 147 Lesch-Nyhan syndrome inheritance, 61 purine salvage deficiency, 37 Leser-Trélat sign, 228, 477 stomach cancer, 379 Lesser omental sac, 361 Letrozole, 656 Leucine classification of, 81 maple syrup urine disease and, 84 Leucovorin, 440 Leukemias, 432 carcinogens, 225 cell type, 220 cyclophosphamide for, 441 cytarabine for, 440 doxorubicin for, 439 epidemiology, 222
hypothalamus, 498 Leptospira spp Gram stain of, 125 spirochete, 146 zoonotic infections, 149 Leptospira interrogans, 147 Leptospirosis, 149 symptoms of, 147 Lesch-Nyhan syndrome inheritance, 61 purine salvage deficiency, 37 Leser-Trélat sign, 228, 477 stomach cancer, 379 Lesser omental sac, 361 Letrozole, 656 Leucine classification of, 81 maple syrup urine disease and, 84 Leucovorin, 440 Leukemias, 432 carcinogens, 225 cell type, 220 cyclophosphamide for, 441 cytarabine for, 440 doxorubicin for, 439 epidemiology, 222
hypothalamus, 498 Leptospira spp Gram stain of, 125 spirochete, 146 zoonotic infections, 149 Leptospira interrogans, 147 Leptospirosis, 149 symptoms of, 147 Lesch-Nyhan syndrome inheritance, 61 purine salvage deficiency, 37 Leser-Trélat sign, 228, 477 stomach cancer, 379 Lesser omental sac, 361 Letrozole, 656 Leucine classification of, 81 maple syrup urine disease and, 84 Leucovorin, 440 Leukemias, 432 carcinogens, 225 cell type, 220 cyclophosphamide for, 441 cytarabine for, 440 doxorubicin for, 439 epidemiology, 222 etoposide/teniposide for, 442
hypothalamus, 498 Leptospira spp Gram stain of, 125 spirochete, 146 zoonotic infections, 149 Leptospira interrogans, 147 Leptospirosis, 149 symptoms of, 147 Lesch-Nyhan syndrome inheritance, 61 purine salvage deficiency, 37 Leser-Trélat sign, 228, 477 stomach cancer, 379 Lesser omental sac, 361 Letrozole, 656 Leucine classification of, 81 maple syrup urine disease and, 84 Leucovorin, 440 Leukemias, 432 carcinogens, 225 cell type, 220 cyclophosphamide for, 441 cytarabine for, 440 doxorubicin for, 439 epidemiology, 222 etoposide/teniposide for, 442 immunohistochemical stain for,
hypothalamus, 498 Leptospira spp Gram stain of, 125 spirochete, 146 zoonotic infections, 149 Leptospira interrogans, 147 Leptospirosis, 149 symptoms of, 147 Lesch-Nyhan syndrome inheritance, 61 purine salvage deficiency, 37 Leser-Trélat sign, 228, 477 stomach cancer, 379 Lesser omental sac, 361 Letrozole, 656 Leucine classification of, 81 maple syrup urine disease and, 84 Leucovorin, 440 Leukemias, 432 carcinogens, 225 cell type, 220 cyclophosphamide for, 441 cytarabine for, 440 doxorubicin for, 440 doxorubicin for, 439 epidemiology, 222 etoposide/teniposide for, 442 immunohistochemical stain for, 227
hypothalamus, 498  Leptospira spp Gram stain of, 125 spirochete, 146 zoonotic infections, 149 Leptospira interrogans, 147 Leptospirosis, 149 symptoms of, 147 Lesch-Nyhan syndrome inheritance, 61 purine salvage deficiency, 37 Leser-Trélat sign, 228, 477 stomach cancer, 379 Lesser omental sac, 361 Letrozole, 656 Leucine classification of, 81 maple syrup urine disease and, 84 Leucovorin, 440 Leukemias, 432 carcinogens, 225 cell type, 220 cyclophosphamide for, 441 cytarabine for, 440 doxorubicin for, 439 epidemiology, 222 etoposide/teniposide for, 442 immunohistochemical stain for, 227 lymphoma comparison, 429
hypothalamus, 498  Leptospira spp Gram stain of, 125 spirochete, 146 zoonotic infections, 149 Leptospira interrogans, 147 Leptospirosis, 149 symptoms of, 147 Lesch-Nyhan syndrome inheritance, 61 purine salvage deficiency, 37 Leser-Trélat sign, 228, 477 stomach cancer, 379 Lesser omental sac, 361 Letrozole, 656 Leucine classification of, 81 maple syrup urine disease and, 84 Leucovorin, 440 Leukemias, 432 carcinogens, 225 cell type, 220 cyclophosphamide for, 441 cytarabine for, 440 doxorubicin for, 439 epidemiology, 222 etoposide/teniposide for, 442 immunohistochemical stain for, 227 lymphoma comparison, 429
hypothalamus, 498  Leptospira spp Gram stain of, 125 spirochete, 146 zoonotic infections, 149 Leptospira interrogans, 147 Leptospirosis, 149 symptoms of, 147 Lesch-Nyhan syndrome inheritance, 61 purine salvage deficiency, 37 Leser-Trélat sign, 228, 477 stomach cancer, 379 Lesser omental sac, 361 Letrozole, 656 Leucine classification of, 81 maple syrup urine disease and, 84 Leucovorin, 440 Leukemias, 432 carcinogens, 225 cell type, 220 cyclophosphamide for, 441 cytarabine for, 440 doxorubicin for, 439 epidemiology, 222 etoposide/teniposide for, 442 immunohistochemical stain for, 227 lymphoma comparison, 429 mucormycosis, 153
hypothalamus, 498  Leptospira spp Gram stain of, 125 spirochete, 146 zoonotic infections, 149 Leptospira interrogans, 147 Leptospirosis, 149 symptoms of, 147 Lesch-Nyhan syndrome inheritance, 61 purine salvage deficiency, 37 Leser-Trélat sign, 228, 477 stomach cancer, 379 Lesser omental sac, 361 Letrozole, 656 Leucine classification of, 81 maple syrup urine disease and, 84 Leucovorin, 440 Leukemias, 432 carcinogens, 225 cell type, 220 cyclophosphamide for, 441 cytarabine for, 440 doxorubicin for, 439 epidemiology, 222 etoposide/teniposide for, 442 immunohistochemical stain for, 227 lymphoma comparison, 429 mucormycosis, 153 nomenclature for, 220
hypothalamus, 498  Leptospira spp Gram stain of, 125 spirochete, 146 zoonotic infections, 149  Leptospira interrogans, 147 Leptospirosis, 149 symptoms of, 147 Lesch-Nyhan syndrome inheritance, 61 purine salvage deficiency, 37 Leser-Trélat sign, 228, 477 stomach cancer, 379 Lesser omental sac, 361 Letrozole, 656 Leucine classification of, 81 maple syrup urine disease and, 84 Leucovorin, 440 Leukemias, 432 carcinogens, 225 cell type, 220 cyclophosphamide for, 441 cytarabine for, 440 doxorubicin for, 439 epidemiology, 222 etoposide/teniposide for, 442 immunohistochemical stain for, 227 lymphoma comparison, 429 mucormycosis, 153 nomenclature for, 220 oncogenic microbes, 225
hypothalamus, 498  Leptospira spp Gram stain of, 125 spirochete, 146 zoonotic infections, 149  Leptospira interrogans, 147 Leptospirosis, 149 symptoms of, 147 Lesch-Nyhan syndrome inheritance, 61 purine salvage deficiency, 37 Leser-Trélat sign, 228, 477 stomach cancer, 379 Lesser omental sac, 361 Letrozole, 656 Leucine classification of, 81 maple syrup urine disease and, 84 Leucovorin, 440 Leukemias, 432 carcinogens, 225 cell type, 220 cyclophosphamide for, 441 cytarabine for, 440 doxorubicin for, 439 epidemiology, 222 etoposide/teniposide for, 442 immunohistochemical stain for, 227 lymphoma comparison, 429 mucormycosis, 153 nomenclature for, 220 oncogenic microbes, 225 suppressor genes, 224
hypothalamus, 498  Leptospira spp Gram stain of, 125 spirochete, 146 zoonotic infections, 149  Leptospira interrogans, 147 Leptospirosis, 149 symptoms of, 147 Lesch-Nyhan syndrome inheritance, 61 purine salvage deficiency, 37 Leser-Trélat sign, 228, 477 stomach cancer, 379 Lesser omental sac, 361 Letrozole, 656 Leucine classification of, 81 maple syrup urine disease and, 84 Leucovorin, 440 Leukemias, 432 carcinogens, 225 cell type, 220 cyclophosphamide for, 441 cytarabine for, 440 doxorubicin for, 439 epidemiology, 222 etoposide/teniposide for, 442 immunohistochemical stain for, 227 lymphoma comparison, 429 mucormycosis, 153 nomenclature for, 220 oncogenic microbes, 225 suppressor genes, 224
hypothalamus, 498  Leptospira spp Gram stain of, 125 spirochete, 146 zoonotic infections, 149  Leptospira interrogans, 147 Leptospirosis, 149 symptoms of, 147 Lesch-Nyhan syndrome inheritance, 61 purine salvage deficiency, 37 Leser-Trélat sign, 228, 477 stomach cancer, 379 Lesser omental sac, 361 Letrozole, 656 Leucine classification of, 81 maple syrup urine disease and, 84 Leucovorin, 440 Leukemias, 432 carcinogens, 225 cell type, 220 cyclophosphamide for, 441 cytarabine for, 440 doxorubicin for, 439 epidemiology, 222 etoposide/teniposide for, 442 immunohistochemical stain for, 227 lymphoma comparison, 429 mucormycosis, 153 nomenclature for, 220 oncogenic microbes, 225

FAS1\_2019\_21\_Index\_749-806.indd 778 11/21/19 12:27 PM

Leukocoria, 538	Linear viruses, 163	cystic fibrosis, 60	LPS endotoxin, 124, 131, 133, 145
Leukocyte adhesion deficiency, <b>117</b> ,	Lines of Zahn, 672	hepatosteatosis, 72	LTB <sub>4</sub> (Leukotriene B4), 406, 485
215	Lineweaver-Burk plot, 230	hereditary, 394	Lumbar puncture, 507, 521
Leukocyte alkaline phosphatase (LAP), 406	Linezolid, <b>193</b> highly resistant organisms, 198	ischemia in, 210 metastases to, 223	Lumbosacral radiculopathy, 455 Lumbrical muscles, 450
Leukocyte esterase, 181, 600	protein synthesis inhibition, 191	serum markers, 390	Klumpke palsy and, 448
Leukocytes	Lingula (lung), 663	target cells in, 415	median and ulnar nerves, 447
extravasation, 214, <b>215</b>	Linkage disequilibrium, 57	Wilson disease and, 395	Lumefantrine, 200
leukemias, 432	Liothyronine (T3), <b>354</b>	Liver failure	Lunate bone, 449
in urine, <b>181</b> , 594, 600	Lipase	Budd-Chiari syndrome and, 392	Lung abscesses, <b>685</b>
Leukocytoclastic vasculitis, 173	pancreatic secretions, 373	movement disorder in, 519	Lung and chest wall expansion, 665
Leukocytosis, 213	in pancreatitis, 397	Liver fluke	Lung cancer
diabetic ketoacidosis, 347	Lipid-lowering agents	hyperbilirubinemia with, 393	asbestosis and, 677
nosocomial infections, 185 Leukodystrophies, 494, 524	mechanism and adverse effects, <b>320</b> –321	as oncogenic microbe, 226 Liver function tests	carcinogens causing, 225 cisplatin/carboplatin for, 442
Leukoerythroblastic reaction, 424	Lipid metabolism	cholestatic pattern of, 395	erlotinib for, 442
Leukopenias, <b>424</b>	fatty acids, 73	serum markers for, 390	hypercalcemia and, 228
cytarabine, 440	Lipids	Liver markers	incidence/mortality in, 222
ganciclovir, 202	key enzymes in, 93	in alcohol use, 570	metastases to, 223
trimethoprim, 194	transport of, <b>92</b> –93	Liver tumors, 392	non-small cell, 684
Leukoplakia, 479	Lipodystrophy	Living wills, 266	oncogenes and, 224
Leukotrienes	protease inhibitors, 203	Loa loa, <b>159</b>	paraneoplastic syndromes and,
basophils and, 408	tesamorelin for, 328	Loading dose, 231	228
cortisol effects, 336 Levator veli palatini muscle, 620	Lipofuscin, <b>211</b> Lipoic acid, 76	Lobar pneumonia natural history of, 683	presentation and complications, <b>684</b>
Levetiracetam, 544	Lipolysis	organisms and characteristics, 683	small cell, 684
Levodopa, 548, <b>549</b>	cortisol and, 336	physical findings with, 680	topotecan for, 442
Levofloxacin	insulin and, 334	Lobular carcinoma (breast), 650	Lung diseases
fluoroquinolones, 195	sympathetic receptors and, 238	Local anesthetics, <b>550</b>	obstructive, 674–675
Pseudomonas aeruginosa, 143	thyroid hormone and, 331	Localized amyloidosis, 212	restrictive, 675
Levomilnacipran, 575	Lipomas, 220	Locked-in syndrome	Lungs
Levonorgestrel, 657	Lipophilic drug	osmotic demyelination syndrome,	anatomical relationships, <b>663</b>
Levothyroxine, <b>354</b> Lewy bodies, 520, 521	drug metabolism of, 232 Lipoprotein lipase, 93	524 stroke, 515	blood flow regulation, 297 development of, <b>660</b>
dementia, <b>521</b>	Lipoproteins, 93	Locus ceruleus, 495	physical findings, 680
Leydig cells	functions of, <b>94</b>	Locus heterogeneity, 57	sclerosis of, 473
cryptorchidism, 651	Liposarcomas, 220	Löffler endocarditis, 308	transfusion-related injury, 114
endocrine function, 628, 638	Lipoteichoic acid	Löffler medium, 126	Lung volumes, 664
genital embryology, 622	cytoplasmic membrane, 124	Corynebacterium diphtheriae, 139	Lung zones, 669
tumors of, 653	Liquefactive necrosis, 209	Lomustine, 441	Lupus
LFA-1 antigens, 215	Liraglutide, 353	Lone Star tick (disease vector), 149	autoimmune hemolytic anemia
Libido in geriatric patients, 270	Lisch nodules, 525 Lisdexamfetamine, 572	Long-chain fatty acid (LCFA) metabolism of, 89	and, 423 azathioprine for, 440
testosterone and, 636	Lisinopril, 610	Long QT syndrome	drug-induced, 115
Libman-Sacks endocarditis, 470	Lispro, 352	congenital, 294	isoniazid, 197
Lice	Lissencephaly, <b>491</b>	ranolazine, 319	lymphopenia, 424
disease vectors, 149	Listeria monocytogenes	sudden cardiac death, 304	marantic endocarditis in, 311
head/scalp, 161	β-hemolysis, 135	Long thoracic nerve	microangiopathic hemolytic
treatment, 200	neonates, 182	arm abduction, 446	anemia,, 423
Lichen planus, 173, 475, <b>482</b> Lichen sclerosus, 644	penicillins for, 188 transmission of, <b>139</b>	neurovascular pairing, 455 Loop diuretics, <b>608</b>	nephritis, 470 neutropenia, 424
Lichen simplex chronicus, 644	Listeria spp	for heart failure, 309	Lupus anticoagulant, 115
Liddle syndrome, 586	facultative intracellular organisms,	toxicity of, 251	Lupus-like syndrome
markers in, 591	127	Loop of Henle, 608	α-methyldopa, 243
Lidocaine, 322, 550	intracellular organism, 127	Bartter syndrome and, 586	hydralazine, 318
Life support	Lithium	ethacrynic acid effect on, 608	procainamide, 322
withdrawal, 269	diabetes insipidus and, 249, 338	"loose associations," 559	Lurasidone, 573
Li-Fraumeni syndrome osteosarcomas, 465	hypothyroidism, 341	Looser zones (osteomalacia), 463	Luteal phase of menstrual cycle, 632
tumor suppressor genes in, 46, 224	mechanism and use, <b>574</b> prenatal exposure, <b>298</b> , 300	Loperamide, <b>400</b> , 551 Lopinavir	Luteinizing hormone (LH) clomiphene effect, 656
Ligaments	teratogenicity, 614	HIV therapy, 203	contraception, 657
female reproductive anatomy, 625	therapeutic index of, 234	Loratadine, 686	estrogen/progesterone, 630
gastrointestinal anatomy, 361	thyroid functions with, 249	Lorazepam	hCG and, 617
Ligamentum arteriosum, 282	toxicity of, 569	alcohol withdrawal, 572	ovulation, 631
Ligamentum teres hepatis, 282, <b>361</b>	Live attenuated vaccines, 111	Losartan, 610	PCOS, 645
Ligamentum venosum, 282	Liver	Low birth weight, <b>635</b>	premature ovarian failure, 636
Ligand receptors, 208 Lightheadedness, 534	blood supply and innervation of, 364 in gastrointestinal anatomy, 361	Löwenstein-Jensen agar/medium, 126 Lower esophageal sphincter (LES)	secretion of, 327 sex development disorders, 639
Likelihood ratio (LR), <b>257</b>	lipid transport and, 92	achalasia and, 376	signaling pathways of, 337
Limbic system, <b>499</b>	tissue architecture, <b>367</b>	in Barrett esophagus, 377	spermatogenesis, 628
Limited scleroderma (CREST	Liver/biliary disease	nitric oxide and, 371	testosterone, 658
syndrome), 115, 473	acanthocytes in, 414	Lower extremity nerves, <b>452</b> –453	Lyme disease
Linagliptin, 353	alcoholic, 391	Lower left quadrant (LLQ) pain, 383	animal transmission, 149
Lindane, 200	anemia, 420	Lower motor neuron (LMN) lesions,	AV block in, 295
Linea alba, 369 Linear ulcers, 377	autoimmune, 389, 392, 395 cirrhosis, 71, 80, <b>389</b>	530, 531 facial nerve, 532	Borrelia burgdorferi, <b>146</b> ceftriaxone, 189
Emical diccis, 7//	Cittiosis, / 1, 00, <b>307</b>	racial fictive, 772	certifiazone, 107

FAS1\_2019\_21\_Index\_749-806.indd 779 11/21/19 12:27 PM

Lymphadenopathy Corynebacterium diphtheriae, 132 hilar, 675-676 Lymphogranuloma venereum, 184 mediastinal, 676 mononucleosis, 165 rubella, 169, 182-183 serum sickness, 113 syphilis, 147, 184 tinea capitis, 152 Toxoplasma gondii, 182 Trypanosoma brucei, 156 in viral infections, 96 Lymphatic filariasis (elephantiasis) Wuchereria bancrofti, 159 Lymph drainage gonadal, 624 superficial inguinal nodes, 624 Lymph nodes absent or scanty, 116 drainage sites, 96-97 structure and function, 96 T cell differentiation, 102 tumor metastases, 223 Lymphocyte-depleted lymphoma, 429 Lymphocyte-rich lymphoma, 429 Lymphocytes, 409 breast milk and, 636 CLL/small cell lymphocytic lymphoma, 432 corticosteroid effect on, 424 lymph nodes, 96 non-Hodgkin lymphoma, 430 spleen, 98 thymus, 98 Lymphocytic choriomeningitis virus (LCMV), 167 Lymphocytic infiltrates Bordetella pertussis, 143 Lymphocytosis, 98 Lymphogranuloma venereum, 184 Chlamydia trachomatis, 149 Lymphoid hyperplasia, 383 Lymphoid neoplasms, 432 Lymphoid structures, 96-97 Peyer patches, 362, 374 Lymphomas carcinogens causing, 225 celiac disease and, 381 cyclophosphamide for, 441 cytarabine for, 440 doxorubicin for, 439 EBV and, 165 etoposide/teniposide for, 442 Hodgkin, 429 hypercalcemia and, 228 leukemia comparison, 429 methotrexate for, 440 nomenclature for, 220 non-Hodgkin, 430 oncogene for, 208, 224 oncogenic microbes, 226 paraneoplastic syndromes with, 228 of stomach, 379 testicular, 653 Lymphopenias, 424 ataxia-telangiectasia, 117 corticosteroid effect on, 424 Lynch syndrome, 388 mismatch repair and, 40 Lyonization (x-inactivation) Barr body formation, 61 Lysergic acid diethylamide (LSD), 571 classification of, 81 in cystinuria, 85

kidney stones, 598 for pyruvate dehydrogenase complex deficiency, 77 Lysogenic phage infection, 130 Lysosomal storage diseases, 47 causes and effects of, 88 Lysosomal trafficking regulator gene, Lysosomal α-1,4-glucosidase, 87 Lysozyme innate immunity, 99 in neutrophils, 406 LYST gene, 117 Lytic bone lesions adult T-cell lymphoma and, 430 Langerhans cell histiocytosis, 434 MacConkey agar, 126, 144 "Machine-like" murmur, 291 Macroangiopathic hemolytic anemia, Macrocytic anemia, 420 Macroglobulinemia, 431 Macrolides cytochrome P-450 and, 252 hypertrophic pyloric stenosis and, 359 Legionella pneumophila, 143 mechanism and use, **193** Mycoplasma pneumoniae, 150 naming convention for, 253 protein synthesis inhibition, 191 torsades de pointes, 248 Macroorchidism, 62 Macro-ovalocytes, 415 Macrophages, 407 alveolar, 662 apoptosis and, 208 binding of, 104 breast milk and, 636 cell surface proteins, 110 cytokine secretion, 108 endotoxin activation, 133 innate immunity, 99 in lymph node, 96 lymphocyte interaction, **102** in MI, 305 necrosis and, 209 pneumoconioses, 677 splenic, 98 in wound healing, 216 Macrosomia, 614 Macula densa juxtaglomerular apparatus, 589 Macular cherry-red spot, 88, 538 Macular degeneration, 536 Macules, 475 melanocytic nevus, 477 Maculopapular rash graft-versus-host disease, 119 measles, 170 syphilis, 147 Magnesium antacid use, 399 antiarrhythmic treatment, 324 cardiac glycoside toxicity, 321 in laxatives, 401 PTH regulation, 332 torsades de pointes and, 294 Magnesium hydroxide, 399 Magnesium sulfate preeclampsia/eclampsia, 643

Maintenance dose, 231

Maintenance stage, substance

addiction, 568

Major basic protein (MBP), 408 Major depressive disorder (MDD) diagnostic symptoms for, 561 peripartum onset, 562 vortioxetine use, 576 Malabsorption syndromes, 381-382 fat-soluble vitamin deficiencies, 65 inflammatory bowel disease, 382 Malaria artesunate for, 200 Plasmodium, 157 quinidine/quinine for, 200 Malassezia spp, 152, 476 Malathion, 200 Male/female genital homologs, 623 Male genital embryology, 622 Male reproductive anatomy, 626 Male sexual response, 627 Malformation, 613 Malignancy marantic endocarditis in, 311 uterine bleeding with, 633 Malignancy/hyperplasia uterine bleeding with, 633 Malignant hypertension microangiopathic hemolytic anemia, 423 Malignant hyperthermia, 550-551 Malignant mesothelioma, 227 Malignant tumors, 220 bones, 465 Malingering, 566 Malleus (ossicles), 533, 620 Mallory bodies in alcoholic hepatitis, 391 Mallory-Weiss syndrome, 377 Malnutrition, 71 superior mesenteric artery syndrome and, 363 Malrotation, **385** "Maltese cross" appearance, 157, 594 MALT lymphomas Helicobacter pylori, 146 oncogenic microbes and, 226 Sjögren syndrome, 468 Mammary glands, 613 Mammillary bodies, 511 limbic system, 499 Wernicke-Korsakoff syndrome, 571 Mandibular process, 620 Mango flies (disease vector), 159 Manic episode, **560** Man-in-the-barrel syndrome, 502 Mannitol, 607 Mantle cell lymphomas, 430, 434 Mantle zone spleen, 98 Maple syrup urine disease, 84 Marantic endocarditis, 228, 311 Marasmus, 71 Maraviroc, 203 Marburg hemorrhagic fever, 167 Marcus Gunn pupils, 539 multiple sclerosis, 523 Marfanoid habitus homocystinuria, 84 MEN 2B syndrome and, 351 Marfan syndrome aortic dissection and, 303 cardiac defect association, 300 cataracts, 535 chromosome association, 64 elastin and, 52 heart murmur with, 291 thoracic aortic aneurysm and, 302 Marginal zone lymphoma, 430, 434

Marijuana intoxication and withdrawal, 571 Marine omega-3 fatty acids, 320 Masseter muscle, 507 Mast cells, 408 IgE antibody and, 105 Mast cell stabilizers, 687 Mastectomy, 448 Mastication muscles, 507 Mastoid air cells, 621 Mastoiditis brain abscesses, 180 Wegener granulomatosis, 315 Maternal diabetes cardiac defect association, 300 Maternal PKU, 84 Maternal (postpartum) blues, 562 Maternal pregnancy complication, Mature cystic teratoma, 647 Mature ego defenses, 555 Maxillary artery, 619 Maxillary process, 620 Mayer-Rokitansky-Küster-Hauser syndrome, 622 McArdle disease, 87 McBurney point, 383 McCune-Albright syndrome, 57 McMurray test, 454 MDMA (ecstasy), 571 Mean (statistics), 262 Mean arterial pressure, 501 equation for, 285 Measles, 183 paramyxovirus, 167, 169 rubeola virus, 170 unvaccinated children, 186 vitamin A for, 66 Measurement bias, 260 Measures of central tendency, 262 Measures of dispersion, 262 Mebendazole, 200 microtubules and, 48 mecA gene penicillin resistance and, 135 Meckel diverticulum, **384**, 618 Meconium ileus, 386 cystic fibrosis, 60 MECP2 gene, 62 Medial calcific sclerosis, 301 Medial cerebellar lesions, 499 Medial collateral ligament (MCL) injury in "unhappy triad," 460 Medial epicondylitis, 459 Medial femoral circumflex artery, Medial geniculate nucleus (MGN), 498 Medial lemniscus, 514 Medial longitudinal fasciculus (MLF), 511, 543 Medial malleolus, 455 Medial medullary syndrome, 514 Medial meniscal tear, 460 Medial pterygoid muscle, 507 Medial rectus muscle, 540 Medial tibial stress syndrome, 461 Medial umbilical ligament, 282, 369 Median (statistics), 262 "Median claw," 451 Median nerve carpal tunnel syndrome, 459 injury to, 447 neurovascular pairing, 455 Median umbilical ligament, 369

FAS1\_2019\_21\_Index\_749-806.indd 780 11/21/19 12:27 PM

index 781

Mediastinal lymphadenopathy, 676
Mediastinal pathology, 672
Mediastinitis, 672
in pulmonary anthrax, 137 Medical abortion
ethical situations, 268
methotrexate for, 440
Medical errors analysis of, <b>274</b>
assessment of, 268
types of, 274
Medical insurance plans, 271 Medical power of attorney, 266
Medicare/Medicaid, 272
Medication errors, 274 Medication noncompliance, 268
Medium-chain acyl-CoA
dehydrogenase deficiency
89 Medium-vessel vasculitis
presentation and pathology, 314
Medroxyprogesterone, 657
Medulla (brain) adrenal cortex and, <b>327</b>
cranial nerves and nuclei, 505
development of, 490
spinal tracts and, 509
strokes in, 514–515 Medulla (lymph nodes)
lymph nodes, 96
thymus, 102 Medullary breast carcinomas, 650
Medullary cystic kidney disease,
604
Medullary thyroid carcinomas, 343, 351
Medulloblastoma, 350, 528
"Medusa head" appearance, 137
Mefloquine, 157 Megacolon
Chagas disease, 158
in Hirschsprung disease, 384
Megakaryocytes in essential thrombocythemia, 433
Megaloblastic anemia, 420
cytarabine, 440
Diphyllobothrium latum, 160 drug reaction and, 250
orotic aciduria, 420
trimethoprim, 194
tropical sprue, 381 vitamin B <sub>9</sub> deficiency, 68
vitamin B <sub>12</sub> deficiency, 69
Megestrol, 657
Meglitinides, 353 Meissner corpuscles, 494
Meissner plexus, 384
Melanocytes
tumor nomenclature in, 220 Melanocyte-stimulating hormone
(MSH)
function of, 328 secretion of, 327
signaling pathways of, 337
Melanocytic nevus, 477
Melanoma, 484
common metastases, 223 immunohistochemical stain for,
227
nomenclature for, 220 oncogene, 224
origin of, 220
recombinant cytokines for
metastatic, 121 tumor suppressor gene, 224
Melarsoprol, 156, 200
* '

Melasma (chloasma), 476
MELAS syndrome, 59
Melatonin circadian rhythms and, 497
Melatonin receptor agonist
Ramelteon as, 547
Melena
Meckel diverticulum, 384, 618
polyarteritis nodosa, 314
Meloxicam, 486
Memantine, 549
Membrane attack complex (MAC),
104
complement and, 106 Membranoproliferative
glomerulonephritis
(MPGN), 596
hepatitis B and C, 173
Membranous glomerular disorders,
594
hepatitis B and C, 173
Membranous interventricular
septum, 281
Membranous nephropathy, 597
primary autoantibody, 115
Membranous ossification, 458
Membranous urethra injury, 627 Membranous ventricular septum, 281
Memory
neural structures and, 499
Memory loss
anti-NMDA receptor encephalitis,
228
lead poisoning, 425
Wernicke-Korsakoff syndrome, 511
MEN1 gene, 224, 352
Ménétrier disease, <b>379</b>
Ménière disease, 534
Menin, 224
Menin, 224 Meninges, <b>496</b>
Menin, 224 Meninges, <b>496</b> Meningiomas, 526
Menin, 224 Meninges, <b>496</b> Meningiomas, 526 Psammoma bodies in, 227
Menin, 224 Meninges, <b>496</b> Meningiomas, 526 Psammoma bodies in, 227 Meningitis
Menin, 224 Meninges, <b>496</b> Meningiomas, 526 Psammoma bodies in, 227 Meningitis ceftriaxone, 189
Menin, 224 Meninges, 496 Meningiomas, 526 Psammoma bodies in, 227 Meningitis ceftriaxone, 189 chloramphenicol, 192 coccidioidomycosis, 151
Menin, 224 Meninges, 496 Meningiomas, 526 Psammoma bodies in, 227 Meningitis ceftriaxone, 189 chloramphenicol, 192 coccidioidomycosis, 151 common causes, 180
Menin, 224 Meninges, 496 Meningiomas, 526 Psammoma bodies in, 227 Meningitis ceftriaxone, 189 chloramphenicol, 192 coccidioidomycosis, 151 common causes, 180 Cryptococcus neoformans, 153
Menin, 224 Meninges, 496 Meningiomas, 526 Psammoma bodies in, 227 Meningitis ceftriaxone, 189 chloramphenicol, 192 coccidioidomycosis, 151 common causes, 180 Cryptococcus neoformans, 153 CSF findings in, 180
Menin, 224 Meninges, 496 Meningiomas, 526 Psammoma bodies in, 227 Meningitis ceftriaxone, 189 chloramphenicol, 192 coccidioidomycosis, 151 common causes, 180 Cryptococcus neoformans, 153 CSF findings in, 180 fluconazole, 199
Menin, 224 Meninges, 496 Meningiomas, 526 Psammoma bodies in, 227 Meningitis ceftriaxone, 189 chloramphenicol, 192 coccidioidomycosis, 151 common causes, 180 Cryptococcus neoformans, 153 CSF findings in, 180 fluconazole, 199 flucytosine, 199
Menin, 224 Meninges, 496 Meningiomas, 526 Psammoma bodies in, 227 Meningitis ceftriaxone, 189 chloramphenicol, 192 coccidioidomycosis, 151 common causes, 180 Cryptococcus neoformans, 153 CSF findings in, 180 fluconazole, 199 flucytosine, 199 Haemophilus influenzae, 142
Menin, 224 Meninges, 496 Meningiomas, 526 Psammoma bodies in, 227 Meningitis ceftriaxone, 189 chloramphenicol, 192 coccidioidomycosis, 151 common causes, 180 Cryptococcus neoformans, 153 CSF findings in, 180 fluconazole, 199 flucytosine, 199 Haemophilus influenzae, 142 headaches with, 518
Menin, 224 Meninges, 496 Meningiomas, 526 Psammoma bodies in, 227 Meningitis ceftriaxone, 189 chloramphenicol, 192 coccidioidomycosis, 151 common causes, 180 Cryptococcus neoformans, 153 CSF findings in, 180 fluconazole, 199 flucytosine, 199 Haemophilus influenzae, 142 headaches with, 518 HIV-positive adults, 177
Menin, 224 Meninges, 496 Meningiomas, 526 Psammoma bodies in, 227 Meningitis ceftriaxone, 189 chloramphenicol, 192 coccidioidomycosis, 151 common causes, 180 Cryptococcus neoformans, 153 CSF findings in, 180 fluconazole, 199 flucytosine, 199 Haemophilus influenzae, 142 headaches with, 518 HIV-positive adults, 177 Listeria monocytogenes, 139
Menin, 224 Meninges, 496 Meningiomas, 526 Psammoma bodies in, 227 Meningitis ceftriaxone, 189 chloramphenicol, 192 coccidioidomycosis, 151 common causes, 180 Cryptococcus neoformans, 153 CSF findings in, 180 fluconazole, 199 flucytosine, 199 Haemophilus influenzae, 142 headaches with, 518 HIV-positive adults, 177
Menin, 224 Meninges, 496 Meningiomas, 526 Psammoma bodies in, 227 Meningitis ceftriaxone, 189 chloramphenicol, 192 coccidioidomycosis, 151 common causes, 180 Cryptococcus neoformans, 153 CSF findings in, 180 fluconazole, 199 flucytosine, 199 Haemophilus influenzae, 142 headaches with, 518 HIV-positive adults, 177 Listeria monocytogenes, 139 meningococci, 142 mumps, 170 in neonates, 182
Menin, 224 Meninges, 496 Meningiomas, 526 Psammoma bodies in, 227 Meningitis ceftriaxone, 189 chloramphenicol, 192 coccidioidomycosis, 151 common causes, 180 Cryptococcus neoformans, 153 CSF findings in, 180 fluconazole, 199 flucytosine, 199 Haemophilus influenzae, 142 headaches with, 518 HIV-positive adults, 177 Listeria monocytogenes, 139 meningococci, 142 mumps, 170 in neonates, 182 rifamycin prophylaxis, 196
Menin, 224 Meninges, 496 Meningiomas, 526 Psammoma bodies in, 227 Meningitis ceftriaxone, 189 chloramphenicol, 192 coccidioidomycosis, 151 common causes, 180 Cryptococcus neoformans, 153 CSF findings in, 180 fluconazole, 199 flucytosine, 199 Haemophilus influenzae, 142 headaches with, 518 HIV-positive adults, 177 Listeria monocytogenes, 139 meningococci, 142 mumps, 170 in neonates, 182 rifamycin prophylaxis, 196 Streptococcus pneumoniae, 136
Menin, 224 Meninges, 496 Meningiomas, 526 Psammoma bodies in, 227 Meningitis ceftriaxone, 189 chloramphenicol, 192 coccidioidomycosis, 151 common causes, 180 Cryptococcus neoformans, 153 CSF findings in, 180 fluconazole, 199 flucytosine, 199 Haemophilus influenzae, 142 headaches with, 518 HIV-positive adults, 177 Listeria monocytogenes, 139 meningococci, 142 mumps, 170 in neonates, 182 rifamycin prophylaxis, 196 Streptococcus pneumoniae, 136 Streptococcus agalactiae, 137
Menin, 224 Meninges, 496 Meningiomas, 526 Psammoma bodies in, 227 Meningitis ceftriaxone, 189 chloramphenicol, 192 coccidioidomycosis, 151 common causes, 180 Cryptococcus neoformans, 153 CSF findings in, 180 fluconazole, 199 flucytosine, 199 Haemophilus influenzae, 142 headaches with, 518 HIV-positive adults, 177 Listeria monocytogenes, 139 meningococci, 142 mumps, 170 in neonates, 182 rifamycin prophylaxis, 196 Streptococcus pneumoniae, 136 Streptococcus agalactiae, 137 unvaccinated children, 186
Menin, 224 Meninges, 496 Meningiomas, 526 Psammoma bodies in, 227 Meningitis ceftriaxone, 189 chloramphenicol, 192 coccidioidomycosis, 151 common causes, 180 Cryptococcus neoformans, 153 CSF findings in, 180 fluconazole, 199 flucytosine, 199 Haemophilus influenzae, 142 headaches with, 518 HIV-positive adults, 177 Listeria monocytogenes, 139 meningococci, 142 mumps, 170 in neonates, 182 rifamycin prophylaxis, 196 Streptococcus pneumoniae, 136 Streptococcus agalactiae, 137 unvaccinated children, 186 Meningocele, 491
Menin, 224 Meninges, 496 Meningiomas, 526 Psammoma bodies in, 227 Meningitis ceftriaxone, 189 chloramphenicol, 192 coccidioidomycosis, 151 common causes, 180 Cryptococcus neoformans, 153 CSF findings in, 180 fluconazole, 199 flucytosine, 199 Haemophilus influenzae, 142 headaches with, 518 HIV-positive adults, 177 Listeria monocytogenes, 139 meningococci, 142 mumps, 170 in neonates, 182 rifamycin prophylaxis, 196 Streptococcus pneumoniae, 136 Streptococcus agalactiae, 137 unvaccinated children, 186 Meningocele, 491 Meningococcal prophylaxis, 198
Menin, 224 Meninges, 496 Meningiomas, 526 Psammoma bodies in, 227 Meningitis ceftriaxone, 189 chloramphenicol, 192 coccidioidomycosis, 151 common causes, 180 Cryptococcus neoformans, 153 CSF findings in, 180 fluconazole, 199 flucytosine, 199 Haemophilus influenzae, 142 headaches with, 518 HIV-positive adults, 177 Listeria monocytogenes, 139 meningococci, 142 mumps, 170 in neonates, 182 rifamycin prophylaxis, 196 Streptococcus pneumoniae, 136 Streptococcus agalactiae, 137 unvaccinated children, 186 Meningocele, 491 Meningococcal prophylaxis, 198 Meningococcal vaccine, 127
Menin, 224 Meninges, 496 Meningiomas, 526 Psammoma bodies in, 227 Meningitis ceftriaxone, 189 chloramphenicol, 192 coccidioidomycosis, 151 common causes, 180 Cryptococcus neoformans, 153 CSF findings in, 180 fluconazole, 199 flucytosine, 199 Haemophilus influenzae, 142 headaches with, 518 HIV-positive adults, 177 Listeria monocytogenes, 139 meningococci, 142 mumps, 170 in neonates, 182 rifamycin prophylaxis, 196 Streptococcus pneumoniae, 136 Streptococcus agalactiae, 137 unvaccinated children, 186 Meningococcal prophylaxis, 198 Meningococcal vaccine, 127 Meningococcemia
Menin, 224 Meninges, 496 Meningiomas, 526 Psammoma bodies in, 227 Meningitis ceftriaxone, 189 chloramphenicol, 192 coccidioidomycosis, 151 common causes, 180 Cryptococcus neoformans, 153 CSF findings in, 180 fluconazole, 199 flucytosine, 199 Haemophilus influenzae, 142 headaches with, 518 HIV-positive adults, 177 Listeria monocytogenes, 139 meningococci, 142 mumps, 170 in neonates, 182 rifamycin prophylaxis, 196 Streptococcus pneumoniae, 136 Streptococcus pneumoniae, 136 Meningococcal prophylaxis, 198 Meningococcal prophylaxis, 198 Meningococcal prophylaxis, 198 Meningococcemia endotoxins, 131 Meningococci, 131, 142
Menin, 224 Meninges, 496 Meningiomas, 526 Psammoma bodies in, 227 Meningitis ceftriaxone, 189 chloramphenicol, 192 coccidioidomycosis, 151 common causes, 180 Cryptococcus neoformans, 153 CSF findings in, 180 fluconazole, 199 flucytosine, 199 Haemophilus influenzae, 142 headaches with, 518 HIV-positive adults, 177 Listeria monocytogenes, 139 meningococci, 142 mumps, 170 in neonates, 182 rifamycin prophylaxis, 196 Streptococcus pneumoniae, 136 Streptococcus pneumoniae, 136 Streptococcus pneumoniae, 136 Meningococcal vaccine, 127 Meningococcal vaccine, 127 Meningococcemia endotoxins, 131 Meningococci, 131, 142 Meningoencephalitis
Menin, 224 Meninges, 496 Meningiomas, 526 Psammoma bodies in, 227 Meningitis ceftriaxone, 189 chloramphenicol, 192 coccidioidomycosis, 151 common causes, 180 Cryptococcus neoformans, 153 CSF findings in, 180 fluconazole, 199 flucytosine, 199 Haemophilus influenzae, 142 headaches with, 518 HIV-positive adults, 177 Listeria monocytogenes, 139 meningococci, 142 mumps, 170 in neonates, 182 rifamycin prophylaxis, 196 Streptococcus agalactiae, 137 unvaccinated children, 186 Meningococcal prophylaxis, 198 Meningococcal vaccine, 127 Meningococcemia endotoxins, 131 Meningococci, 131, 142 Meningococci, 132 Meningococci, 131, 142 Meningoencephalitis HSV-2, 182
Menin, 224 Meninges, 496 Meningiomas, 526 Psammoma bodies in, 227 Meningitis ceftriaxone, 189 chloramphenicol, 192 coccidioidomycosis, 151 common causes, 180 Cryptococcus neoformans, 153 CSF findings in, 180 fluconazole, 199 flucytosine, 199 Haemophilus influenzae, 142 headaches with, 518 HIV-positive adults, 177 Listeria monocytogenes, 139 meningococci, 142 mumps, 170 in neonates, 182 rifamycin prophylaxis, 196 Streptococcus agalactiae, 137 unvaccinated children, 186 Meningocele, 491 Meningococcal prophylaxis, 198 Meningococcal vaccine, 127 Meningococcemia endotoxins, 131 Meningococci, 131, 142 Meningoencephalitis HSV-2, 182 Naegleria fowleri, 156
Menin, 224 Meninges, 496 Meningiomas, 526 Psammoma bodies in, 227 Meningitis ceftriaxone, 189 chloramphenicol, 192 coccidioidomycosis, 151 common causes, 180 Cryptococcus neoformans, 153 CSF findings in, 180 fluconazole, 199 flucytosine, 199 Haemophilus influenzae, 142 headaches with, 518 HIV-positive adults, 177 Listeria monocytogenes, 139 meningococci, 142 mumps, 170 in neonates, 182 rifamycin prophylaxis, 196 Streptococcus pneumoniae, 136 Streptococcus agalactiae, 137 unvaccinated children, 186 Meningococcal prophylaxis, 198 Meningococcal prophylaxis, 198 Meningococcal vaccine, 127 Meningococcal vaccine, 127 Meningococci, 131, 142 Meningoencephalitis HSV-2, 182 Naegleria fowleri, 156 West Nile virus, 167
Menin, 224 Meninges, 496 Meningiomas, 526 Psammoma bodies in, 227 Meningitis ceftriaxone, 189 chloramphenicol, 192 coccidioidomycosis, 151 common causes, 180 Cryptococcus neoformans, 153 CSF findings in, 180 fluconazole, 199 flucytosine, 199 Haemophilus influenzae, 142 headaches with, 518 HIV-positive adults, 177 Listeria monocytogenes, 139 meningococci, 142 mumps, 170 in neonates, 182 rifamycin prophylaxis, 196 Streptococcus pneumoniae, 136 Streptococcus agalactiae, 137 unvaccinated children, 186 Meningocele, 491 Meningococcal prophylaxis, 198 Meningococci, 131, 142 Meningococci, 131, 142 Meningoencephalitis HSV-2, 182 Naegleria fowleri, 156 West Nile virus, 167 Meningomyelocele, 491
Menin, 224 Meninges, 496 Meningiomas, 526 Psammoma bodies in, 227 Meningitis ceftriaxone, 189 chloramphenicol, 192 coccidioidomycosis, 151 common causes, 180 Cryptococcus neoformans, 153 CSF findings in, 180 fluconazole, 199 flucytosine, 199 Haemophilus influenzae, 142 headaches with, 518 HIV-positive adults, 177 Listeria monocytogenes, 139 meningococci, 142 mumps, 170 in neonates, 182 rifamycin prophylaxis, 196 Streptococcus pneumoniae, 136 Streptococcus agalactiae, 137 unvaccinated children, 186 Meningocele, 491 Meningococcal vaccine, 127 Meningococci, 131, 142 Meningococci, 131, 142 Meningoencephalitis HSV-2, 182 Naegleria fowleri, 156 West Nile virus, 167 Meningomyelocele, 491 Menkes disease
Menin, 224 Meninges, 496 Meningiomas, 526 Psammoma bodies in, 227 Meningitis ceftriaxone, 189 chloramphenicol, 192 coccidioidomycosis, 151 common causes, 180 Cryptococcus neoformans, 153 CSF findings in, 180 fluconazole, 199 flucytosine, 199 Haemophilus influenzae, 142 headaches with, 518 HIV-positive adults, 177 Listeria monocytogenes, 139 meningococci, 142 mumps, 170 in neonates, 182 rifamycin prophylaxis, 196 Streptococcus pneumoniae, 136 Streptococcus agalactiae, 137 unvaccinated children, 186 Meningococel, 491 Meningococcal prophylaxis, 198 Meningococcal prophylaxis, 198 Meningococcemia endotoxins, 131 Meningococcemia endotoxins, 131 Meningococci, 131, 142 Meningoencephalitis HSV-2, 182 Naegleria fowleri, 156 West Nile virus, 167 Meningomyelocele, 491 Menkes disease mechanism and symptoms, 51
Menin, 224 Meninges, 496 Meningiomas, 526 Psammoma bodies in, 227 Meningitis ceftriaxone, 189 chloramphenicol, 192 coccidioidomycosis, 151 common causes, 180 Cryptococcus neoformans, 153 CSF findings in, 180 fluconazole, 199 flucytosine, 199 Haemophilus influenzae, 142 headaches with, 518 HIV-positive adults, 177 Listeria monocytogenes, 139 meningococci, 142 mumps, 170 in neonates, 182 rifamycin prophylaxis, 196 Streptococcus pneumoniae, 136 Streptococcus agalactiae, 137 unvaccinated children, 186 Meningocele, 491 Meningococcal vaccine, 127 Meningococci, 131, 142 Meningococci, 131, 142 Meningoencephalitis HSV-2, 182 Naegleria fowleri, 156 West Nile virus, 167 Meningomyelocele, 491 Menkes disease

Melasma (chloasma), 476

Menopause, <b>636</b>
hormone replacement therapy, 657
primary ovarian insufficiency, 645
Turner syndrome, 638
Menorrhagia, 633
anemia with, 418
Menstrual cycle estrogens for, 656
heavy bleeding (AUB/HMB), 633
phases of, <b>632</b>
Meperidine, 551
Mepivacaine, 550
Mercury poisoning, 248
Merkel discs, 494
Merlin protein, 224
MERS (Middle East respiratory syndrome), 167
Mesalamine, 382
Mesangial cells
juxtaglomerular apparatus, 589
Mesencephalon, 490
Mesenchymal tumors
nomenclature of, 220
Mesenteric arteries, 363
Mesenteric ischemia, 386
Mesocortical pathway, 499 Mesoderm, 490
branchial arches derivation, 619
derivatives of, 613
Mesolimbic pathway, 499
Mesometrium, 625
Mesonephric (Wolffian) duct, 622
Mesonephros, 578
Mesosalpinx, 625 Mesothelioma, <b>678</b>
carcinogens causing, 225
Psammoma bodies in, 227
Mesovarium, 625
Mestranol, 656
Meta-analysis, 263, <b>264</b>
Metabolic acidosis, 592 adrenal insufficiency, 349
renal failure, 603
symptoms of, 593
symptoms of, 593 Metabolic alkalosis, 592
symptoms of, 593 Metabolic alkalosis, 592 hyperaldosteronism, 349
symptoms of, 593 Metabolic alkalosis, 592 hyperaldosteronism, 349 in hypertrophic pyloric stenosis,
symptoms of, 593 Metabolic alkalosis, 592 hyperaldosteronism, 349 in hypertrophic pyloric stenosis, 359
symptoms of, 593 Metabolic alkalosis, 592 hyperaldosteronism, 349 in hypertrophic pyloric stenosis, 359 loop diuretics, 608
symptoms of, 593 Metabolic alkalosis, 592 hyperaldosteronism, 349 in hypertrophic pyloric stenosis, 359
symptoms of, 593 Metabolic alkalosis, 592 hyperaldosteronism, 349 in hypertrophic pyloric stenosis, 359 loop diuretics, 608 nephron transport, 586
symptoms of, 593 Metabolic alkalosis, 592 hyperaldosteronism, 349 in hypertrophic pyloric stenosis, 359 loop diuretics, 608 nephron transport, 586 thiazides, 609 Metabolic disorders fructose, 80
symptoms of, 593 Metabolic alkalosis, 592 hyperaldosteronism, 349 in hypertrophic pyloric stenosis, 359 loop diuretics, 608 nephron transport, 586 thiazides, 609 Metabolic disorders fructose, 80 galactose, 80
symptoms of, 593 Metabolic alkalosis, 592 hyperaldosteronism, 349 in hypertrophic pyloric stenosis, 359 loop diuretics, 608 nephron transport, 586 thiazides, 609 Metabolic disorders fructose, 80 galactose, 80 glycogen storage, 87
symptoms of, 593 Metabolic alkalosis, 592 hyperaldosteronism, 349 in hypertrophic pyloric stenosis, 359 loop diuretics, 608 nephron transport, 586 thiazides, 609 Metabolic disorders fructose, 80 galactose, 80 glycogen storage, 87 lysosomal storage diseases, 88–89
symptoms of, 593 Metabolic alkalosis, 592 hyperaldosteronism, 349 in hypertrophic pyloric stenosis, 359 loop diuretics, 608 nephron transport, 586 thiazides, 609 Metabolic disorders fructose, 80 galactose, 80 glycogen storage, 87 lysosomal storage diseases, 88–89 Metabolic fuel use, <b>91</b>
symptoms of, 593 Metabolic alkalosis, 592 hyperaldosteronism, 349 in hypertrophic pyloric stenosis, 359 loop diuretics, 608 nephron transport, 586 thiazides, 609 Metabolic disorders fructose, 80 galactose, 80 glycogen storage, 87 lysosomal storage diseases, 88–89 Metabolic fuel use, <b>91</b> Metabolic syndrome
symptoms of, 593 Metabolic alkalosis, 592 hyperaldosteronism, 349 in hypertrophic pyloric stenosis, 359 loop diuretics, 608 nephron transport, 586 thiazides, 609 Metabolic disorders fructose, 80 galactose, 80 glycogen storage, 87 lysosomal storage diseases, 88–89 Metabolic fuel use, <b>91</b>
symptoms of, 593 Metabolic alkalosis, 592 hyperaldosteronism, 349 in hypertrophic pyloric stenosis, 359 loop diuretics, 608 nephron transport, 586 thiazides, 609 Metabolic disorders fructose, 80 galactose, 80 glycogen storage, 87 lysosomal storage diseases, 88–89 Metabolic fuel use, <b>91</b> Metabolic syndrome with antipsychotic drugs, 573 non-alcoholic fatty liver disease and, 391
symptoms of, 593 Metabolic alkalosis, 592 hyperaldosteronism, 349 in hypertrophic pyloric stenosis, 359 loop diuretics, 608 nephron transport, 586 thiazides, 609 Metabolic disorders fructose, 80 galactose, 80 glycogen storage, 87 lysosomal storage diseases, 88–89 Metabolic fuel use, <b>91</b> Metabolic syndrome with antipsychotic drugs, 573 non-alcoholic fatty liver disease and, 391 Metabolism, 72–94
symptoms of, 593 Metabolic alkalosis, 592 hyperaldosteronism, 349 in hypertrophic pyloric stenosis, 359 loop diuretics, 608 nephron transport, 586 thiazides, 609 Metabolic disorders fructose, 80 galactose, 80 glycogen storage, 87 lysosomal storage diseases, 88–89 Metabolic fuel use, <b>91</b> Metabolic syndrome with antipsychotic drugs, 573 non-alcoholic fatty liver disease and, 391 Metabolism, 72–94 amino acid derivatives, 83
symptoms of, 593 Metabolic alkalosis, 592 hyperaldosteronism, 349 in hypertrophic pyloric stenosis, 359 loop diuretics, 608 nephron transport, 586 thiazides, 609 Metabolic disorders fructose, 80 galactose, 80 glycogen storage, 87 lysosomal storage diseases, 88–89 Metabolic fuel use, <b>91</b> Metabolic syndrome with antipsychotic drugs, 573 non-alcoholic fatty liver disease and, 391 Metabolism, 72–94 amino acid derivatives, 83 amino acids, 81
symptoms of, 593 Metabolic alkalosis, 592 hyperaldosteronism, 349 in hypertrophic pyloric stenosis, 359 loop diuretics, 608 nephron transport, 586 thiazides, 609 Metabolic disorders fructose, 80 galactose, 80 glycogen storage, 87 lysosomal storage diseases, 88–89 Metabolic fuel use, 91 Metabolic syndrome with antipsychotic drugs, 573 non-alcoholic fatty liver disease and, 391 Metabolism, 72–94 amino acid derivatives, 83 amino acids, 81 apolipoproteins, 93
symptoms of, 593 Metabolic alkalosis, 592 hyperaldosteronism, 349 in hypertrophic pyloric stenosis, 359 loop diuretics, 608 nephron transport, 586 thiazides, 609 Metabolic disorders fructose, 80 galactose, 80 glycogen storage, 87 lysosomal storage diseases, 88–89 Metabolic fuel use, <b>91</b> Metabolic syndrome with antipsychotic drugs, 573 non-alcoholic fatty liver disease and, 391 Metabolism, 72–94 amino acid derivatives, 83 amino acids, 81
symptoms of, 593 Metabolic alkalosis, 592 hyperaldosteronism, 349 in hypertrophic pyloric stenosis, 359 loop diuretics, 608 nephron transport, 586 thiazides, 609 Metabolic disorders fructose, 80 galactose, 80 glycogen storage, 87 lysosomal storage diseases, 88–89 Metabolic fuel use, 91 Metabolic syndrome with antipsychotic drugs, 573 non-alcoholic fatty liver disease and, 391 Metabolism, 72–94 amino acid derivatives, 83 amino acids, 81 apolipoproteins, 93 cellular sites of, 72 disorders of, 81, 84–85 drugs, 232
symptoms of, 593 Metabolic alkalosis, 592 hyperaldosteronism, 349 in hypertrophic pyloric stenosis, 359 loop diuretics, 608 nephron transport, 586 thiazides, 609 Metabolic disorders fructose, 80 galactose, 80 glycogen storage, 87 lysosomal storage diseases, 88–89 Metabolic fuel use, 91 Metabolic syndrome with antipsychotic drugs, 573 non-alcoholic fatty liver disease and, 391 Metabolism, 72–94 amino acid derivatives, 83 amino acids, 81 apolipoproteins, 93 cellular sites of, 72 disorders of, 81, 84–85 drugs, 232 dyslipidemias, 94
symptoms of, 593 Metabolic alkalosis, 592 hyperaldosteronism, 349 in hypertrophic pyloric stenosis, 359 loop diuretics, 608 nephron transport, 586 thiazides, 609 Metabolic disorders fructose, 80 galactose, 80 glycogen storage, 87 lysosomal storage diseases, 88–89 Metabolic fuel use, 91 Metabolic syndrome with antipsychotic drugs, 573 non-alcoholic fatty liver disease and, 391 Metabolism, 72–94 amino acid derivatives, 83 amino acids, 81 apolipoproteins, 93 cellular sites of, 72 disorders of, 81, 84–85 drugs, 232 dyslipidemias, 94 ethanol, 72, 232
symptoms of, 593 Metabolic alkalosis, 592 hyperaldosteronism, 349 in hypertrophic pyloric stenosis, 359 loop diuretics, 608 nephron transport, 586 thiazides, 609 Metabolic disorders fructose, 80 galactose, 80 glycogen storage, 87 lysosomal storage diseases, 88–89 Metabolic fuel use, 91 Metabolic syndrome with antipsychotic drugs, 573 non-alcoholic fatty liver disease and, 391 Metabolism, 72–94 amino acid derivatives, 83 amino acids, 81 apolipoproteins, 93 cellular sites of, 72 disorders of, 81, 84–85 drugs, 232 dyslipidemias, 94 ethanol, 72, 232 fatty acid, 89
symptoms of, 593 Metabolic alkalosis, 592 hyperaldosteronism, 349 in hypertrophic pyloric stenosis, 359 loop diuretics, 608 nephron transport, 586 thiazides, 609 Metabolic disorders fructose, 80 galactose, 80 glycogen storage, 87 lysosomal storage diseases, 88–89 Metabolic fuel use, 91 Metabolic syndrome with antipsychotic drugs, 573 non-alcoholic fatty liver disease and, 391 Metabolism, 72–94 amino acid derivatives, 83 amino acids, 81 apolipoproteins, 93 cellular sites of, 72 disorders of, 81, 84–85 drugs, 232 dyslipidemias, 94 ethanol, 72, 232 fatty acid, 89 fuel use, 91
symptoms of, 593 Metabolic alkalosis, 592 hyperaldosteronism, 349 in hypertrophic pyloric stenosis, 359 loop diuretics, 608 nephron transport, 586 thiazides, 609 Metabolic disorders fructose, 80 galactose, 80 glycogen storage, 87 lysosomal storage diseases, 88–89 Metabolic fuel use, 91 Metabolic syndrome with antipsychotic drugs, 573 non-alcoholic fatty liver disease and, 391 Metabolism, 72–94 amino acid derivatives, 83 amino acids, 81 apolipoproteins, 93 cellular sites of, 72 disorders of, 81, 84–85 drugs, 232 dyslipidemias, 94 ethanol, 72, 232 fatty acid, 89 fuel use, 91 gluconeogenesis, 78
symptoms of, 593 Metabolic alkalosis, 592 hyperaldosteronism, 349 in hypertrophic pyloric stenosis, 359 loop diuretics, 608 nephron transport, 586 thiazides, 609 Metabolic disorders fructose, 80 galactose, 80 glycogen storage, 87 lysosomal storage diseases, 88–89 Metabolic fuel use, 91 Metabolic syndrome with antipsychotic drugs, 573 non-alcoholic fatty liver disease and, 391 Metabolism, 72–94 amino acid derivatives, 83 amino acids, 81 apolipoproteins, 93 cellular sites of, 72 disorders of, 81, 84–85 drugs, 232 dyslipidemias, 94 ethanol, 72, 232 fatty acid, 89 fuel use, 91

rate-determining enzymes, 73 summary of pathways, 74 TCA cycle, 7 tyrosine catabolism, 83 urea cycle, 82 Metacarpal neck fracture, 459 Metacarpophalangeal (MCP) joints, Metachromatic granules Corynebacterium diphtheriae diagnosis, 139 Metachromatic leukodystrophy, 88, Metalloproteinases, 216 Metal storage diseases, 210 Metanephros, 578 Metaphase, 46 Metaplasia, 206 benign breast disease, 649 esophagus, 378 intestinal, 379 specialized intestinal, 378 Metastases common, 223 Metastasis, 219, 223 gastric cancer, 379 heart tumors from, 316 liver cancer, 392 lung, cancer, 684 Metastatic calcification, 211 Metastatic melanoma vemurafenib for, 444 Metatarsophalangeal (MTP) joints gout, 467 Metencephalon, 490 Metformin, 353 diarrhea with, 249 Methacholine, 240 Methadone, 551 heroin addiction, 576 intoxication and withdrawal, 570 Methamphetamine, 572 Methanol toxicity, 248 Methemoglobin, 666 toxicity treatment, 248 Methemoglobinemia, 666 local anesthetics and, 550 Methicillin, 249 Methimazole, 354 agranulocytosis, 250 aplastic anemia, 250 teratogenicity, 614 Methionine classification of, 81 start codons, 44 sulfonamides and, 194 Methotrexate, 440 folate deficiency, 420 hydatidiform moles, 642 megaloblastic anemia, 250 pulmonary fibrosis, 251 pyrimidine synthesis and, 36 rheumatoid arthritis, 466 targets of, 438 teratogenicity, 614 vitamin B<sub>9</sub> deficiency, 68 as weak acid, 233 Methoxyflurane, 550 Methylation histones, 45 Methyldopa Coombs-positive hemolytic anemia, 250 hypertension in pregnancy, 316 Methylene blue, 248

FAS1\_2019\_21\_Index\_749-806.indd 781 11/21/19 12:27 PM

pyruvate, 77

Methylenetetrahydrofolate reductase (MTHFR) deficiency, 84 Methylmalonic acid vitamin B<sub>12</sub> deficiency, 69 vitamin B<sub>9</sub> deficiency, 68 Methylmalonyl-CoA mutase, 69 Methylmercury teratogenicity, 614 Methylnaltrexone, 551 Methylphenidate AĎĤD, 557, 572 CNS stimulant, 572 Methyltestosterone, 658 Methylxanthines, 687 Metoclopramide, 400 Parkinson-like syndrome, 251 tardive dyskinesia, 251 Metolazone, 609 Metoprolol, 245, 323 Metronidazole bacterial vaginosis, 148 clindamycin vs, 192 Clostridium difficile, 138 for Crohn disease, 382 disulfiram-like reaction, 251 Giardia lamblia, 155 Helicobacter pylori, 146 mechanism and use, 195 vaginal infections, 181 vaginitis, 158 Mevalonate synthesis, 320 Mexiletine, 322 Meyer loop, 542 MHC (major histocompatibility complex) I and II, 100 Micafungin, 200 Michaelis-Menten kinetics, 230 Miconazole, 199 Microalbuminuria, 346 Microangiopathic hemolytic anemia (MAHA), 423 hypertensive emergency and, intravascular hemolysis in, 421 Microarrays, 54 Microbiology, 123-204 antimicrobials, 187-204 bacteriology, 124-134 clinical bacteriology, 134-150 mycology, 151-154 oncogenic organisms, 226 parasitology, 155–161 systems, 178–186 virology, 162-177 Microbiome in innate immunity, 99 Microcephaly, 63 cri-du-chat syndrome, 64 fetal alcohol syndrome, 615 maternal phenylketonuria, 84 maternal X-ray exposure, 614 Patau syndrome, 63 with zika virus, 171 Microcytic, hypochromic anemia, 418–419 Ancylostoma, 161 Microcytosis, 214 Microdeletion congenital, 64 fluorescent in situ hybridization and, 55 22q11, 116 Microfilaments, 48 Microglia, 490, 493 Micrognathia Edwards syndrome, 63

Pierre Robin sequence, 620

Micromelia, 614 Microphthalmia, 63 MicroRNA (miRNA), 42, 56 Microscopic polyangiitis, 315 Microsporum, 152 Microtubule inhibitors, 441 Microtubules, 48 drugs acting on, 48 structure and function of, 48 Micturition center, 237 Midazolam, 546, 550 Midbrain brain, 490 cranial nerve nuclei of, 505 lesions in, 511 Middlebrook medium, 126 Middle cerebral artery (MCA) cortical distribution, 502 saccular aneurysms, 516 stroke effects, 514 Middle meningeal artery epidural hematoma and, 513 Middle rectal vein, 365 Midgut blood supply/innervation of, 364 development of, 358 Midgut volvulus, 386 Midodrine, 242 Mifepristone, 657 Miglitol, 353 Migraine headaches, 518 hormonal contraception contraindication, 657 triptans for, 547 Migrating motor complexes (MMC), Migratory polyarthritis, 312 Milnacipran, 575 Mineralocorticoids adrenal insufficiency, 349 adrenal steroids and, 335 Mineral oil, 65 Minimal alveolar concentration, Minocycline, 192 Minors, consent for, 265 Minoxidil, **658** Minute ventilation, 664 cholinomimetic agents, 552 Horner syndrome, 531, 540 pupillary control, 539 sympatholytic drugs, 243 Mirabegron, 242 Mirtazapine, 244, 576 major depressive disorder, 561 Mismatch repair, 40 Misoprostol, 399 Missense mutations, 39 Mites/louse treatment, 200 Mitochondria high altitude and, 670 metabolism in, 72 Mitochondrial encephalopathy, 59 Mitochondrial inheritance, 59 Mitochondrial myopathies, 59 Mitosis, 46 griseofulvin, 200 Mitral regurgitation, 288 in MI, 305 murmurs caused by, 290, 291 Mitral stenosis, 288 murmurs caused by, 291

Mitral valve

in cardiac cycle, 287

regurgitation in, 312

Mitral valve prolapse, 291 fragile X syndrome, 62 Marfan syndrome, 52 renal cyst disorders and, 604 Mittelschmerz, 631 Mixed cellularity lymphoma, 429 Mixed connective tissue disease, 470 autoantibody, 115 Raynaud phenomenon, 472 Mixed cryoglobulinemia, 315 Mixed transcortical aphasia, 516 MMR vaccine, 170 Mobitz AV blocks, 295 Moccasin distribution (tinea pedis), 152 Modafinil, 568 Mode (statistics), 262 Molecular mimicry autoimmune response in rheumatic fever, 129 Molecular motor proteins, 48 Molluscum contagiosum, 164, 479 Mönckeberg sclerosis, 301 "Monday disease," 318 Monoamine oxidase (MAO) inhibitors atypical depression, 561 mechanism and clinical use, 575 Parkinson disease, 549 selegiline/rasagiline, 549 tyramine and, 244 Monobactams, 190 Pseudomonas aeruginosa, 143 Monoclonal antibodies drug names for, 254 Monoclonal immunoglobulin (Ig) overproduction, 431 Monocytes, 407 innate immunity, 99 morulae in, 150 Monospot test, 165 Monozygotic ("identical") twins, 616 Montelukast, 687 Mood oxytocin's role in regulating, 328 Mood disorder, 560 readmissions with, 272 Mood stabilizing drugs, 561 Morbidly adherent placenta, 640 Moro reflex, 510, 635 Morphine, 551 for acute coronary syndromes, 307 intoxication and withdrawal, 570 Morphogenesis of heart, 280-281 errors in, 613 Morulae, 150 Mosaic bone architecture, 464 Mosaicism, 57 Mosquitoes (disease vectors) lymphatic filariasis, 159 malaria, 157 Zika virus, 171 Motilin, 371 Motion sickness, 241 Motor cortex, 514 descending spinal tracts, 509 topographic representation, 502 ventral lateral thalamus and, 498 Motor innervation derivation of, 620 lower extremity, 452 tongue, 493 Motor neuron signs, 529 Movement disorders, 519 dopaminergic pathways and, 499 Moxifloxacin, 195 M phase, 46

MPO-ANCA/p-ANCA autoantibody, 115 M protein rheumatic fever and, 136 as virulence factor, 129 mRNA aminoglycosides, 191 hepatitis viruses, 172 pre-mRNA splicing, 42 processing, 41 protease inhibitors, 203 stop codons, 44 MRSA (methicillin-resistant Staphylococcus aureus) cephalosporins, 189 highly resistant, 198 nosocomial infections, 135 oxazolidinones, 193 vancomycin, 190 mTOR sirolimus (rapamycin) inhibition of, 120 Mucicarmine stain polysaccharide capsule staining, 125 Mucinous cystadenocarcinoma, 646 Mucinous cystadenoma, 646 Mucociliary escalator, 662 Mucocutaneous lymph node syndrome, 314 Mucoepidermoid carcinomas, 376 Mucopolysaccharides Periodic acid-Schiff stain, 125 Mucopolysaccharidoses, 88 Mucormycosis diabetic ketoacidosis, 347 Mucor spp amphotericin B for, 199 opportunistic infection, 153 Mucosa, 362 Mucosal cells, 372 Mucosal neuromas, 351 Mucosal polyps, 387 Mucositis methotrexate, 440 Mucus, 238 "Muddy brown" casts (urine), 594 Mulberry molars, 147 Müllerian duct agenesis, 622 anomalies of, 623 derivatives of, 622 Müllerian inhibitory factor (MIF), 622 Sertoli cell production, 628 Multicystic dysplastic kidney, 578, 579 Multidrug resistance protein 1 , (MDR1), 227 Multifactorial pulmonary hypertension, 679 Multiorgan drug reactions, 251 Multiple endocrine neoplasias (MEN syndromes), 351 Zollinger-Ellison syndrome, 351 Multiple gestations, 633 Multiple myeloma bortezomib/carfilzomib in, 443 common metastases, 223 ESR in, 214 metastatic calcification, 211 monoclonal gammopathy transition to, 431 plasma cell dyscrasia, 409 Multiple personality disorder, 558 Multiple sclerosis, **523** drug therapy for, 551 HLA-DR2 and, 100 internuclear ophthalmoplegia, 543

FAS1\_2019\_21\_Index\_749-806.indd 782 11/21/19 12:27 PM

natalizumab for, 122
recombinant cytokines for, 121 Mumps, <b>170</b>
acute pancreatitis with, 397
paramyxovirus, 167, 169 Munchausen syndrome, 566
Munchausen syndrome by proxy, 566
Murphy sign, 396 Muscarinic acetylcholine (ACh)
receptors, 236 Muscarinic agonists, 237
Muscarinic antagonists, 237, 241, 687
multiple sclerosis, 523 neuromuscular blocking drugs,
550, 551
Parkinson disease, 548 Muscarinic receptor
detrusor muscle, in, 237
Muscle conduction/contraction skeletal, 456
smooth muscle, 457 Muscle proprioceptors, <b>458</b>
Muscles
atrophy of, 42 in starvation, 91
metabolism in, 86
ragged red fibers in, 59 Muscle spindled, 458
Muscular dystrophies, 61
frameshift mutation, 61 X-linked recessive disorder, 61
Muscularis externa, 362 Muscular ventricular septum, 281
Musculocutaneous nerve
injury presentation, 447 Musculoskeletal drug reactions, 250
Musculoskeletal paraneoplastic
syndromes, 228 Musculoskeletal system
anatomy, 446–454 common conditions, <b>461</b>
pathology, 459–467
pharmacology, 485–487 Mutase, 73
Mutations BRAF, 432
BRCA1 gene, 56
COL3AI, 51 de novo, 62
drug resistance mechanisms, 196
in HbS and HbC, 410 JAK2, 433
locus heterogeneity in, 57
muscular dystrophies, 61 myelodysplastic syndromes, 432
non-Hodgkin lymphoma, 430 in PBPs, 187
same locus, 57
STAT3, 116 thalassemia and, 418
tumor suppressor genes, 46, 525
WT1 deletion, 606 Myalgias
Ebola virus, 171 fluoroquinolones, 195
genital herpes, 184
Jarisch-Herxheimer reaction, 148 Leptospira interrogans, 147
Lyme disease, 146
meningitis, 186 <i>Trichinella spiralis</i> , 159, 161
trichinosis, 159 vasculitides, 314
Myasthenia gravis, 472
autoantibody, 115 diagnosis of, 240
0 / "

HLA subtype association, 100
neostigmine for, 240
as paraneoplastic syndrome, 228
pyridostigmine for, 240
restrictive lung diseases, 675
MYCL1 gene, 224
MYCN gene, 224
Mycobacterial cells, 196 Mycobacterium spp, <b>140</b>
Gram stain, 125
intracellular organism, 127
Ziehl-Neelsen stain, 125
Mycobacterium avium-intracellulare,
140
HIV-positive adults, 177
prophylaxis with HIV, 198
vertebral osteomyelitis, 180
Mycobacterium leprae
animal transmission, 149
diagnosis, 141
rifamycins/dapsone, 196
Mycobacterium marinum, 140
Mycobacterium pneumoniae, 126
Mycobacterium scrofulaceum, 140
Mycobacterium spp
facultative intracellular organisms,
127
Mycobacterium tuberculosis
culture requirements for, 126
osteomyelitis, 180
reactivation site, 140
symptoms of, 140
therapeutic agents, 196, 197
Mycolic acid
isoniazid, 197
synthesis of, 196 Mycology, 151–154
Mycophenolate mofetil, 120
inosine monophosphate dehydrogenase inhibition, 36
Mycoplasma spp
atypical organisms, 179
Gram stain, 125
macrolides, 193
pneumonia caused by, <b>150</b> , 179, 683
tetracyclines, 192
Mycoses
cutaneous, 152
systemic, 151
Mycosis fungoides, 430
Mydriasis
glaucoma treatment and, 552
G-protein-linked second receptor,
238
muscarinic antagonists for, 241
pupillary control, 539
saccular aneurysm, 516
Myelencephalon, 490
Myelin, <b>494</b>
Myeloblasts (peripheral smear), 432
Myelodysplastic syndromes, <b>432</b>
sideroblastic anemia, 419
Myelofibrosis, 433
Myeloid neoplasms, 432
Myelomeningocele, 63, 492
Myeloperoxidase, 109
H <sub>2</sub> O <sub>2</sub> degradation, 128
in neutrophils, 406 Myeloproliferative disorders
in AML, 432
chronic, 433
hydroxyurea for, 442
Myeloschisis, 491
Myelosuppression
alkylating agents, 441
antimetabolites, 440

drugs causing, 444 hydroxyurea, 442
irinotecan/topotecan, 442 Myenteric plexus, 362
Mylohyoid muscle, 620
Myocardial action potential, <b>292</b> Myocardial depression, 550
Myocardial infarction (MI), 304 antiarrhythmics after, 322
β-blockers for, 245
complications of, <b>307</b> diabetes mellitus, 346
diagnosis of, 306
on ECG, 293 ECG localization of STEMI, 306
evolution of, 305
heart failure caused by, 309 heparin for, 436
homocystinuria, 84
hypertensive emergency and, 300 shock caused by, 310
thrombolytics for, 437
Myocardial O <sub>2</sub> consumption/ demand, 284
angina treatment, 319 Myocarditis, <b>313</b>
adenovirus, 164
coxsackievirus, 167 diphtheria, 139
picornaviruses, 167
Toxocara canis, 159 Myoclonic seizures, 517
Myoclonus, 519, 521
Myofibroblasts, 216 Myoglobin, 665
ooxygen-hemoglobin dissociation
curve, 666 Myoglobinuria
acute tubular necrosis, 602
McArdle disease, 87 Myonecrosis, 138
Myopathy
daptomycin, 195 drug reaction and, 250
Myophosphorylase, 87 Myopia, 535
retinal detachment, 537
Myotonic dystrophy, <b>61</b> cataracts and, 535
Myxedema
thyroid hormones for, 354 Myxomas, 316
Myxomatous degeneration, 291
N
N-acetylglucosaminyl-1-
phosphotransferase, 47 N-acetylcysteine, <b>686</b>
for acetaminophen toxicity, 248 for cystic fibrosis, 60
NADH (reduced nicotinamide
adenine dinucleotide) electron transport chain, 78
fructose metabolism, 80
TCA cycle, 77 Nadolol, 245
NADPH (reduced nicotinamide
adenine dinucleotide phosphate)
ethanol metabolism, 72
HMP shunt and, 79 respiratory burst and, 109
universal electron acceptors, 75
Naegleria fowleri, 156 Nafcillin
characteristics of, 188

Nails
clubbing, 60
glomus tumors under, 478
hemorrhages in bed of, 311
with psoriatic arthritis, 469
Naïve T cell activation, 103
Naked viral genome infectivity, <b>163</b>
Nalbuphine, 551
Naloxone
dextromethorphan overdose, 686
heroin detoxification, 576
for opioid toxicity, 248, 551
opioid toxicity, 570
Naltrexone
alcoholism, 571
heroin detoxification, 576
opioid toxicity, 551
2-naphthylamine, 225
Naproxen, 486
acute gout drugs, 487
Narcissistic personality disorder, 565
Narcolepsy
amphetamines for, 242
characteristics/treatment, <b>568</b>
hypnagogic/hypnopompic
hallucinations, 568
Narrow-angle glaucoma, 536
Nasal congestion, 686
Nasal decongestion
ephedrine for, 242
Nasal polyps
cystic fibrosis, 60
Nasal septum perforation, 315
Nasopharyngeal carcinoma
EBV and, 165
oncogenic microbes and, 226
Natalizumab, 122
multiple sclerosis, 523 Nateglinide, 353
National Board of Medical Examiners
(NBME), 2, 11
Natriuresis, 588
Natriuretic peptide, 296
Natural killer (NK) cells, 101, <b>409</b>
cell surface proteins, 110
function of, 409
innate immunity, 99
Nausea
adverse drug effects, 400
antiemetics for, 401
with appendicitis, 383
biliary colic, 396
with MI, 305
migraine headaches, 518
ranolazine, 319
renal failure, 603
vitamin A toxicity, 66
vitamin C toxicity, 69
Nebivolol, 245
Necator spp
disease associations, 161
infection routes, 158
Necator americanus, 159
Neck and head cancer, 671
cetuximab for, 442
Necrosis, 209
acute pancreatitis, 397
Arthus reaction, 113
benign tumors, 220
Budd-Chiari syndrome, 392
calcification, 211
enterocolitis, 386
femoral head, 120, 461, 463
fibrinoid, 466
glioblastoma multiforme, 526
hepatic, 485

FAS1\_2019\_21\_Index\_749-806.indd 783 11/21/19 12:27 PM

INDEX

Necrosis (continued)	jaundice in, 393	Neuroblastomas, <b>350</b>	IL-8 and, 108
hernias and, 370	kernicterus, 194, 204	incidence and mortality, 222	innate immunity, 99
jaw, 486	Listeria monocytogenes in, 139	oncogenes and, 224	left shift, 424
mesenteric ischemia, 386	low birth weight, 635	paraneoplastic syndromes with, 228	in leukocyte adhesion deficiency,
nonalcoholic fatty liver disease,	meningitis in, 182	Neurocutaneous disorders, <b>525</b>	117
391	necrotizing enterocolitis and, 386		LTB4, 485
		Neurodegenerative disorders,	
saponification, 209	obesity risk factors, 636	<b>520</b> –522	megaloblastic anemia, 420
scaphoid avascular, 449	pneumonia in, 149	drug therapy for, <b>549</b>	in MI, 305
transplant reaction, 119	primitive reflexes in, 510	Neuroectoderm, 490	necrosis and, 209
warfarin, 436	sickle cell anemia in, 422	derivatives of, 612	nonmegaloblastic anemia, 420
Necrotizing enterocolitis, 386	Streptococcus agalactiae in, 137	pituitary gland, 327	pseudo-Pelger-Huet anomaly, 432
Necrotizing fasciitis, 479	TORCH manifestations in, 182	Neuroendocrine tumors, <b>350</b>	stimulation of, 44
Streptococcus pyogenes (Group A	Neoplasia	Neurofibromatosis, 535	wound healing, 216
strep), 136	pathology of, <b>219</b> –226, 518	chromosome association, 64	Nevi, 220
Necrotizing glomerulonephritis, 315	Neoplastic progression, 219	inheritance, 60	Nevirapine
Negative predictive value (NPV), 257	Neoplastic transformation, 216	tumor suppressor genes and, 224	cytochrome P-450 and, 252
Negative punishment, 554	adenomatous polyps, 387	typesI and II, 525	HIV therapy, 203
Negative reinforcement, 554	Neostigmine, 240	variable expressivity, 56	NF1/NF2 genes, 224
Negative skew distribution, 262	Nephritic-nephrotic syndrome	Neurofilaments	N-formylmethionine (fMet), 44
Negative-stranded viruses, <b>168</b>	etiology and presentation, 595	cytoskeletal element, 48	NF-κB, 120
Neglect (child), 556	Nephritic syndrome, <b>596</b> –597	immunohistochemical stain for,	Niacin 240
Negri bodies, 171	etiology and presentation, 595	227	cutaneous flushing, 248
Neisseria gonorrhoeae	Nephritis, 608	Neurogenic ileus, 240	gout, 250
culture requirements, 126	Nephroblastoma, <b>606</b>	Neurohypophysis, 327	hyperglycemia, 249
epididymitis and orchitis, 654	Nephrocalcinosis, 211	hypothalamus and, 498	myopathy caused by, 250
osteomyelitis, 180	Nephrogenic diabetes insipidus, 211,	Neuroleptic malignant syndrome	Nicardipine, 318
septic arthritis, 468	338	(NMS), 551, 569	Nicotinamides, 75
STI, 184	lithium toxicity, 569	Neurological signs	Nicotine
UTIs with, 600	treatment, 609	proximal upper and lower	intoxication and withdrawal, <b>571</b>
Neisseria meningitidis	Nephrolithiasis, 606	extremity, 502	teratogenicity, 614
chloramphenicol, 192	calcium oxalate, 69	Neurologic drug reactions, 251	Nicotinic acetylcholine receptors,
culture requirements, 126	Nephron physiology, <b>585</b>	Neurology and special senses,	166, <b>236</b>
encapsulation, 127	Nephropathy	490–544	Niemann-Pick disease, 88
meningitis, 180	diabetes mellitus, 346	anatomy/physiology, 493-515	Nifedipine, 316, <b>318</b> , 643
penicillin G/V for, 187	hypertension and, 300	embryology, 490–492	Nifurtimox, 158, 200
Waterhouse-Friderichsen			
	protease inhibitors, 203	ophthalmology, 534–541	Night terrors
syndrome, 349	transplant rejection, 119	otology, <b>533–534</b>	benzodiazepines for, 497
Neisseria spp	Nephrotic syndrome, <b>597</b>	pathology, 511–518	Nigrostriatal pathway, 499
C5-C9 deficiencies, 107	early-onset, 606	pharmacology, 544-551	Nikolsky sign
cephalosporins, 189	ESŘ in, 214	Neuromuscular blocking drugs, <b>551</b>	blistering skin disorders, 480
fluoroquinolones, 195	etiology and presentation, 595	Neuromuscular disorders	scalded skin syndrome, 479
gram-negative algorithm, 142	fatty casts in, 594	paraneoplastic syndromes, 228	Nilotinib, 443
	TBG and, 331		
IgA protease, 129		Neuromuscular junction	Nimodipine, <b>318</b> , 513
intracellular organism, 127	Nephrotoxicity	skeletal muscle, 236	Nipple
transformation in, 130	aminoglycosides, 191	diseases of, 472	intraductal papilloma, 649
Nelson syndrome, <b>348</b>	amphotericin B, 199	Neurons, 493	lactational mastitis, 649
Nematodes, 159	cidofovir, 202	in ascending spinal tracts, 509	Nissl bodies, 46
infection routes, 158	cisplatin/carboplatin, 442	local anesthetics, 550	Nissl substance
Neomycin	cladribine, 440	origins of, 490	chromatolysis, 495
aminoglycosides, 191	drug reaction and, 251	Parkinson disease, 548	neurons, 493
Neonatal abstinence syndrome, <b>615</b>	drugs causing, 444	primary motor cortex, 509	Nitazoxanide, 155
Neonatal conjunctivitis	immunosuppressants, 120	Neuron-specific enolase, 226, 350	Nitrates, 319
Chlamydia trachomatis, 149	inhaled anesthetics, 550	Neuropathic pain, 515	mechanism and clinical use, <b>318</b>
Neonatal pneumonia	streptomycin, 197	Neuropathy	Nitric oxide, 371
Group B streptococci, 179	sulfonamides, 194	diabetes mellitus, 346	free radical injury and, 210
Neonatal respiratory distress	Nerve blockade (local anesthetics),	Neurosyphilis, 147	Nitrites
syndrome (NRDS), <b>661</b>	550	Neurotoxicity	urinary tract infections, 181
Neonates	Nerve fibers, 495	cladribine, 440	Nitroblue tetrazolium dye reduction
abstinence syndrome, 615	Nerves	immunosuppressants, 120	test, 117
Apgar score, 634	lower extremity, 452, 453	methylmercury exposure, 614	Nitrofurantoin
Candida albicans in, 153	upper extremity, 446, 447	methylxanthines, 687	hemolysis in G6PD deficiency, 250
coagulation cascade in, 413	Nerve trunk, 495	vincristine, 441	pulmonary fibrosis, 251
conjunctivitis, 142, 149	Nesiritide, 296	Neurotransmitters	Nitroglycerin, 318
deprivation effects, 556	Neural crest	bacterial toxin effects, 132	acute coronary syndromes, 307
esophageal atresia in, 359	derivatives of, 613	changes with disease, 495	angina, 304
flora with C-section, 178	Neural crest cells, 490, 494	vomiting center receptors, 496	Nitroprusside, 318
galactosemia in, 80	Neural development, <b>490</b>	Neurovascular pairing, <b>455</b>	Nitrosamines
gastroenteritis, 168	Neural plate, 490	Neutralization (antibody), 104	as carcinogens, 225
gray baby syndrome in, 192	Neural tube, 490	Neutropenia, 424	stomach cancer and, 379
hemolytic anemia in, 422	derivatives, 613	ganciclovir, 202	Nitrosoureas, 441
herpes in, 164	formation, 612	rheumatoid arthritis, 466	Nitrous oxide, 550
hyperthermia in, 241	Neural tube defects, <b>491</b>	ticlopidine, 437	Nizatidine, 399
hypertrophic pyloric stenosis in,	maternal diabetes, 614	Neutrophils, 406	NMDA receptor antagonist
359	prevention, 68	chemotaxis, 44, 106, 133, 406, 485,	ketamine as, 550
indirect inguinal hernia in, 370	valproic acid, 544	487, 691	memantine as, 549
intraventricular hemorrhage, <b>512</b>	Neuraminidase, 169–170	corticosteroid effect on, <b>424</b>	N-myc oncogene, 350
	,	· · · · · · · · · · · · · · · · · · ·	/ 9 -7

FAS1\_2019\_21\_Index\_749-806.indd 784 11/21/19 12:27 PM

# INDEX

NNRTIs, 203	peptic ulcer disease and, 380	Null hypothesis, 263
Nocardia spp	rheumatoid arthritis, 466	Number needed to harm (NNH),
aerobic culture requirements, 126 comparison with <i>Actinomyces</i> spp,	tor sialadenitis, 376	258
139	Non-ST-segment elevation MI (NSTEMI)	Number needed to treat (NNT), 258
effects and treatment, 139	diagnosis of, 306	Nursemaid's elbow, 461
necrosis and, 209	STEMI vs, 304	Nutcracker syndrome, 363
sulfonamides for, 194	treatment, 307	Nutmeg liver, 309, 392
urease-positive, 127 Ziehl-Neelsen stain, 125	Noradrenergic drugs, 574 Norepinephrine (NE)	Nutrition, 65–72 Nyctalopia, 66
Nocturia, 654	adrenal medulla secretion, 327	Nystagmus
Nocturnal enuresis, 329	amphetamines and, 239	cerebellum, 499
Nodes of Ranvier, 494	bupropion effect on, 576	common lesions with, 511
Nodular phlebitis, 314 Nodular sclerosis lymphoma, 429	changes with disease, 495 circadian rhythm, 497	Friedreich ataxia, 531 internuclear ophthalmoplegia,
Noise-induced hearing loss, 533	direct sympathomimetic, 242	543
Nonadherent patients, 268	isoproterenol vs, <b>243</b>	PCP, 571
Nonalcoholic fatty liver disease, 389,	male sexual response, 627	phenytoin, 544
390, <b>391</b> , 392 Nonbacterial endocarditis, 311	MAO inhibitor effects, 575 opioid effect on, 551	stroke and, 514 Nystatin, <b>199</b>
Nonbacterial thrombotic	pheochromocytoma secretion, 350	Tystatiii, 199
endocarditis, 228	release regulation, 239	0
Nonbenzodiazepine hypnotics, <b>546</b>	REM sleep and, 497	Obesity
Noncaseating granulomas sarcoidosis, 676	vitamin B <sub>6</sub> and, 67 Norethindrone, 657	amphetamine for, 242
Noncommunicating hydrocephalus,	Norfloxacin, 195	anovulation with, 645 cholelithiasis and, 396
522	Normal distribution, 262	DM type 2 and, 347
Noncompetitive agonists, 234	Normal flora	esophageal cancer and, 378
Noncompetitive antagonist, 234	colonic, 137 female genital tract, 136	hypertension risk factors, 300
Noncompetitive inhibitors, 230 Noncompliant patients, 268	GI tract, 127	hypoventilation syndrome, 679 lateral femoral cutaneous nerve,
Nondepolarizing neuromuscular	neonates, <b>178</b>	452
blocking drugs, 551	oropharynx, 136	osteoarthritis/rheumatoid arthritis,
Nondominant parietal cortex lesions,	skin, 135	466
511 Non-frameshift mutations	Normal pressure hydrocephalus, 522 Normal splitting, 289	renal cell carcinoma association, 605
deletions, 61	Normocytic anemia, <b>421</b>	sleep apnea, 679
Nonhemolytic, normocytic anemia,	Norovirus, 167	stress incontinence and, 599
421	Northern blot, 53	Obligate intracellular organisms,
Non-Hodgkin lymphoma, <b>430</b> corticosteroids, 120	Nortriptyline, 575 Nosocomial infections, 274	127 Observational studies, <b>256</b>
Hashimoto thyroiditis and, 341	Acinetobacter baumannii, 142	errors in, 260–261
hepatitis C, 173	Ebola, 171	Observer-expectancy bias, 260
HIV-positive adults, 177	enterococci, 137	Obsessive-compulsive disorder
Hodgkin lymphoma vs, 429 oncogenes and, 224	Klebsiella, 145	(OCD)
rituximab for, 443	MRSA, 135 pneumonias, 179	diagnostic criteria/treatment, <b>563</b> drug therapy for, 572
vinca alkaloids for, 441	Pseudomonas aeruginosa, 143	SSRIs for, 575
Nonhomologous end joining, 40	risk factors, 185	Tourette syndrome and, 557
Nonmaleficence (ethics), 265	UTIs as, 181	venlafaxine for, 575
Nonmegaloblastic macrocytic anemia, 420	Notochord, <b>490</b> , 612–613 postnatal derivative of, 282	Obsessive-compulsive personality disorder, 566
Nonnormal distributions, 262	Novobiocin	Obstructive jaundice, 398
Nonoverlapping genetic code, 37	gram-positive antibiotic test, 134	Obstructive lung diseases, 674-675
Nonreceptor tyrosine kinase, 337	Staphylococcus epidermidis, 135	flow volume loops in, 673
Non-REM sleep stages, 497 Nonselective antagonists, 245	NRTIs, 203 NS3/4A inhibitors, 204	Obstructive shock, 310 Obstructive sleep apnea, 679
Nonsense mutations, 39	NS5A inhibitors, 204	pulsus paradoxus in, 310
Nonsteroidal anti-inflammatory drugs	NS5B inhibitors, 204	Obturator nerve, 452
(NSAIDs), <b>486</b>	Nuchal translucency, 63	Occipital cortex, 515
acute pericarditis, 313 aplastic anemia, 250	Nucleic acids pathogen-associated molecular	Occipital lobe, 501 Occipital sinus, 503
Beers criteria, 247	pattogen-associated molecular pattern (PAMP), 99	Occult bleeding, 387
calcium pyrophosphate deposition	Nucleosome, 34	FOBT for, 388
disease, 467	Nucleotide excision repair, 40	Octreotide, 371, <b>400</b>
colorectal cancer	Nucleotides, <b>35</b>	acromegaly, 339
chemopreventative, 389 esophagitis from, 377	deamination reactions, 35 synthesis, 72	GH excess, 329 hypothalamic/pituitary drugs, 354
gastritis with, 379	Nucleus accumbens, 495	Ocular motility, <b>540</b>
GFR effects of, 589	Nucleus ambiguus, 506	Oculomotor nerve (CN III), 506
gout, <b>467</b> , 487	Nucleus cuneatus, 509	ocular motility, <b>540</b>
headaches, 518 interstitial nephritis, 249	Nucleus pulposus collagen in, 50	palsy of, 513, <b>541</b> pupillary contraction, 539
loop diuretics and, 608	fetal precursor, 282	Odds ratio (OR), 256, <b>258</b>
misoprostol use with, 399	Nucleus tractus solitarius (NTS),	Ofloxacin, 195
osteoarthritis, 466	496	Okazaki fragments, 38

"OK gesture," 451 Olanzapine, 573 Olfaction hallucinations, 559 limbic system in, 499 Olfactory nerve (CN I), 506 Oligoclonal bands, 523 Oligodendrocytes, **494** Oligodendroglia, 490 in multiple sclerosis, 494 Oligodendrogliomas, 526 Oligohydramnios, 578, 641 Oligomenorrhea, 633 Oligomycin, 78 Oligospermia, 400 Olive-shaped mass, 359 Omalizumab, 122, **687** Ombitasvir, 204 Omental foramen, 361 Omeprazole, 399 Omphalocele, 358 Omphalomesenteric cysts, 384 Omphalomesenteric (vitelline) duct, 618 Onchocerca volvulus, 159 Oncocytoma (renal), 605 Oncogenes, 224 Oncogenic microbes, 226 Ondansetron, 400 torsades de pointes, 248 1,25-(OH)<sub>2</sub>D<sub>3</sub> kidney endocrine function, 589 "100-day cough," 132 Onion skin periosteal reaction, 465 Onychomycosis terbinafine, 199 tinea unguium, 152 Oocysts acid-fast stain, 155 Toxoplasmosis, 156 Ziehl-Neelsen stain, 125 Oogenesis, 631 Oophorectomy, 625 Open-angle glaucoma, 536 carbachol for, 240 pilocarpine for, 240 Operant conditioning, **554** Ophthalmology, 534–541 Ophthalmoplegia cavernous sinus syndrome, 542 common lesions with, 511 internuclear, 543 Wernicke-Korsakoff syndrome, Opioid analgesics, 551 agonists, 551 Beers criteria, 247 detoxification and relapse prevention, 576 intoxication and withdrawal, 570 mechanism and use, 551 mixed agonist/antagonist analgesics, 552 receptor binding, 234 sleep apnea, 679 toxicity treatment, 248 Opisthotonos tetanospasmin, 138 Opponens digiti minimi muscle, 450 Opponens pollicis muscle, 450 Opportunistic fungal infections, 153-154 Oppositional defiant disorder, 557 Opposition (thumb), **450**, 451 Opsoclonus-myoclonus syndrome, **228**, 350

FAS1\_2019\_21\_Index\_749-806.indd 785 11/21/19 12:27 PM

INDEX

Opsonization, <b>104</b> , 106
antibodies in, 112
complement in, 106
encapsulated organisms, 98
Optic disc
papilledema in, 538
Optic nerve (CN II), 506 embryologic derivation, 613
Optic neuritis, 523
Optic neuropathy, 197
Optochin
gram-positive antibiotic test, 134
Oral advance directives, 266
Oral contraceptives (OCPs)
hepatic adenomas and, 392
prolactin effects on, 330 reproductive hormones, 656
SHBG effects on, 337
venous sinus thrombosis with, 503
Oral glucose tolerance test, 346
Oral hairy leukoplakia, 177
Oral/intestinal ganglioneuromatosis,
351
Oral rehydration therapy, 146
Oral thrush, 177 Orange body fluids, 196
Orchiectomy, 651
Orchiopexy, 651
Orchitis, 170, <b>654</b>
Orexigenic effect, 336
Orexin, 568
hypocretin receptor antagonist,
Suvorexant as, 547
Organ failure, in acute pancreatitis,
397 Organia acidemias <b>85</b>
Organic acidemias, <b>85</b> Organ of Corti, 533
Organogenesis
embryologic derivatives, 612, <b>613</b>
errors in, 613
errors in, 613 fetal development, 612
fetal development, 612 teratogens, 614
fetal development, 612 teratogens, 614 Organophosphates
fetal development, 612 teratogens, 614 Organophosphates toxicity treatment, 248
fetal development, 612 teratogens, 614 Organophosphates toxicity treatment, 248 Organ transplants
fetal development, 612 teratogens, 614 Organophosphates toxicity treatment, 248 Organ transplants azathioprine for, 440
fetal development, 612 teratogens, 614 Organophosphates toxicity treatment, 248 Organ transplants azathioprine for, 440 cytomegalovirus, 186
fetal development, 612 teratogens, 614 Organophosphates toxicity treatment, 248 Organ transplants azathioprine for, 440
fetal development, 612 teratogens, 614 Organophosphates toxicity treatment, 248 Organ transplants azathioprine for, 440 cytomegalovirus, 186 hairy leukoplakia and, 479 kidneys, 580 WBC casts, 594
fetal development, 612 teratogens, 614 Organophosphates toxicity treatment, 248 Organ transplants azathioprine for, 440 cytomegalovirus, 186 hairy leukoplakia and, 479 kidneys, 580 WBC casts, 594 Organum vasculosum of the lamina
fetal development, 612 teratogens, 614 Organophosphates toxicity treatment, 248 Organ transplants azathioprine for, 440 cytomegalovirus, 186 hairy leukoplakia and, 479 kidneys, 580 WBC casts, 594 Organum vasculosum of the lamina terminalis (OVLT), 498
fetal development, 612 teratogens, 614 Organophosphates toxicity treatment, 248 Organ transplants azathioprine for, 440 cytomegalovirus, 186 hairy leukoplakia and, 479 kidneys, 580 WBC casts, 594 Organum vasculosum of the lamina terminalis (OVLT), 498 Orientation, <b>557</b>
fetal development, 612 teratogens, 614 Organophosphates toxicity treatment, 248 Organ transplants azathioprine for, 440 cytomegalovirus, 186 hairy leukoplakia and, 479 kidneys, 580 WBC casts, 594 Organum vasculosum of the lamina terminalis (OVLT), 498 Orientation, 557 Origin of replication, 38
fetal development, 612 teratogens, 614 Organophosphates toxicity treatment, 248 Organ transplants azathioprine for, 440 cytomegalovirus, 186 hairy leukoplakia and, 479 kidneys, 580 WBC casts, 594 Organum vasculosum of the lamina terminalis (OVLT), 498 Orientation, <b>557</b> Origin of replication, 38 Orlistat, <b>400</b>
fetal development, 612 teratogens, 614 Organophosphates toxicity treatment, 248 Organ transplants azathioprine for, 440 cytomegalovirus, 186 hairy leukoplakia and, 479 kidneys, 580 WBC casts, 594 Organum vasculosum of the lamina terminalis (OVLT), 498 Orientation, 557 Origin of replication, 38
fetal development, 612 teratogens, 614 Organophosphates toxicity treatment, 248 Organ transplants azathioprine for, 440 cytomegalovirus, 186 hairy leukoplakia and, 479 kidneys, 580 WBC casts, 594 Organum vasculosum of the lamina terminalis (OVLT), 498 Orientation, 557 Origin of replication, 38 Orlistat, 400 diarrhea, 249 Ornithine
fetal development, 612 teratogens, 614 Organophosphates toxicity treatment, 248 Organ transplants azathioprine for, 440 cytomegalovirus, 186 hairy leukoplakia and, 479 kidneys, 580 WBC casts, 594 Organum vasculosum of the lamina terminalis (OVLT), 498 Orientation, 557 Origin of replication, 38 Orlistat, 400 diarrhea, 249 Ornithine cystinuria, 85 kidney stones and, 598
fetal development, 612 teratogens, 614 Organophosphates toxicity treatment, 248 Organ transplants azathioprine for, 440 cytomegalovirus, 186 hairy leukoplakia and, 479 kidneys, 580 WBC casts, 594 Organum vasculosum of the lamina terminalis (OVLT), 498 Orientation, 557 Origin of replication, 38 Orlistat, 400 diarrhea, 249 Ornithine cystinuria, 85 kidney stones and, 598 urea cycle, 82
fetal development, 612 teratogens, 614 Organophosphates toxicity treatment, 248 Organ transplants azathioprine for, 440 cytomegalovirus, 186 hairy leukoplakia and, 479 kidneys, 580 WBC casts, 594 Organum vasculosum of the lamina terminalis (OVLT), 498 Orientation, 557 Origin of replication, 38 Orlistat, 400 diarrhea, 249 Ornithine cystinuria, 85 kidney stones and, 598 urea cycle, 82 Ornithine transcarbamylase, 74
fetal development, 612 teratogens, 614 Organophosphates toxicity treatment, 248 Organ transplants azathioprine for, 440 cytomegalovirus, 186 hairy leukoplakia and, 479 kidneys, 580 WBC casts, 594 Organum vasculosum of the lamina terminalis (OVLT), 498 Orientation, 557 Origin of replication, 38 Orlistat, 400 diarrhea, 249 Ornithine cystinuria, 85 kidney stones and, 598 urea cycle, 82 Ornithine transcarbamylase, 74 Ornithine transcarbamylase
fetal development, 612 teratogens, 614 Organophosphates toxicity treatment, 248 Organ transplants azathioprine for, 440 cytomegalovirus, 186 hairy leukoplakia and, 479 kidneys, 580 WBC casts, 594 Organum vasculosum of the lamina terminalis (OVLT), 498 Orientation, 557 Origin of replication, 38 Orlistat, 400 diarrhea, 249 Ornithine cystinuria, 85 kidney stones and, 598 urea cycle, 82 Ornithine transcarbamylase, 74 Ornithine transcarbamylase deficiency, 61, 83
fetal development, 612 teratogens, 614 Organophosphates toxicity treatment, 248 Organ transplants azathioprine for, 440 cytomegalovirus, 186 hairy leukoplakia and, 479 kidneys, 580 WBC casts, 594 Organum vasculosum of the lamina terminalis (OVLT), 498 Orientation, 557 Origin of replication, 38 Orlistat, 400 diarrhea, 249 Ornithine cystinuria, 85 kidney stones and, 598 urea cycle, 82 Ornithine transcarbamylase, 74 Ornithine transcarbamylase deficiency, 61, 83 Orotic acid, 83
fetal development, 612 teratogens, 614 Organophosphates toxicity treatment, 248 Organ transplants azathioprine for, 440 cytomegalovirus, 186 hairy leukoplakia and, 479 kidneys, 580 WBC casts, 594 Organum vasculosum of the lamina terminalis (OVLT), 498 Orientation, 557 Origin of replication, 38 Orlistat, 400 diarrhea, 249 Ornithine cystinuria, 85 kidney stones and, 598 urea cycle, 82 Ornithine transcarbamylase, 74 Ornithine transcarbamylase deficiency, 61, 83 Orotic acid, 83 Orotic aciduria, 420
fetal development, 612 teratogens, 614 Organophosphates toxicity treatment, 248 Organ transplants azathioprine for, 440 cytomegalovirus, 186 hairy leukoplakia and, 479 kidneys, 580 WBC casts, 594 Organum vasculosum of the lamina terminalis (OVLT), 498 Orientation, 557 Origin of replication, 38 Orlistat, 400 diarrhea, 249 Ornithine cystinuria, 85 kidney stones and, 598 urea cycle, 82 Ornithine transcarbamylase, 74 Ornithine transcarbamylase deficiency, 61, 83 Orotic acid, 83 Orotic aciduria, 420 "Orphan Annie" eyes (nuclei), 343 Orthomyxoviruses, 168
fetal development, 612 teratogens, 614 Organophosphates toxicity treatment, 248 Organ transplants azathioprine for, 440 cytomegalovirus, 186 hairy leukoplakia and, 479 kidneys, 580 WBC casts, 594 Organum vasculosum of the lamina terminalis (OVLT), 498 Orientation, 557 Origin of replication, 38 Orlistat, 400 diarrhea, 249 Ornithine cystinuria, 85 kidney stones and, 598 urea cycle, 82 Ornithine transcarbamylase, 74 Ornithine transcarbamylase deficiency, 61, 83 Orotic acid, 83 Orotic acid, 83 Orotic aciduria, 420 "Orphan Annie" eyes (nuclei), 343 Orthomyxoviruses, 168 characteristics of, 167, 168
fetal development, 612 teratogens, 614 Organophosphates toxicity treatment, 248 Organ transplants azathioprine for, 440 cytomegalovirus, 186 hairy leukoplakia and, 479 kidneys, 580 WBC casts, 594 Organum vasculosum of the lamina terminalis (OVLT), 498 Orientation, 557 Origin of replication, 38 Orlistat, 400 diarrhea, 249 Ornithine cystinuria, 85 kidney stones and, 598 urea cycle, 82 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase deficiency, 61, 83 Orotic acid, 83 Orotic aciduria, 420 "Orphan Annie" eyes (nuclei), 343 Orthomyxoviruses, 168 characteristics of, 167, 168 influenza viruses, 169
fetal development, 612 teratogens, 614 Organophosphates toxicity treatment, 248 Organ transplants azathioprine for, 440 cytomegalovirus, 186 hairy leukoplakia and, 479 kidneys, 580 WBC casts, 594 Organum vasculosum of the lamina terminalis (OVLT), 498 Orientation, 557 Origin of replication, 38 Orlistat, 400 diarrhea, 249 Ornithine cystinuria, 85 kidney stones and, 598 urea cycle, 82 Ornithine transcarbamylase, 74 Ornithine transcarbamylase deficiency, 61, 83 Orotic acid, 83 Orotic aciduria, 420 "Orphan Annie" eyes (nuclei), 343 Orthomyxoviruses, 168 characteristics of, 167, 168 influenza viruses, 169 Orthopedic conditions, 460
fetal development, 612 teratogens, 614 Organophosphates toxicity treatment, 248 Organ transplants azathioprine for, 440 cytomegalovirus, 186 hairy leukoplakia and, 479 kidneys, 580 WBC casts, 594 Organum vasculosum of the lamina terminalis (OVLT), 498 Orientation, 557 Origin of replication, 38 Orlistat, 400 diarrhea, 249 Ornithine cystinuria, 85 kidney stones and, 598 urea cycle, 82 Ornithine transcarbamylase, 74 Ornithine transcarbamylase deficiency, 61, 83 Orotic acid, 83 Orotic aciduria, 420 "Orphan Annie" eyes (nuclei), 343 Orthomyxoviruses, 168 characteristics of, 167, 168 influenza viruses, 169 Orthopedic conditions, 460 lower extremity, 460, 461
fetal development, 612 teratogens, 614 Organophosphates toxicity treatment, 248 Organ transplants azathioprine for, 440 cytomegalovirus, 186 hairy leukoplakia and, 479 kidneys, 580 WBC casts, 594 Organum vasculosum of the lamina terminalis (OVLT), 498 Orientation, 557 Origin of replication, 38 Orlistat, 400 diarrhea, 249 Ornithine cystinuria, 85 kidney stones and, 598 urea cycle, 82 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 76 Ornithine transcarbamylase, 76 Ornithine transcarbamylase, 76 Ornithine transcarbamylase, 76 Ornithine transcarbamylase, 76 Ornithine transcarbamylase, 76 Ornithine transcarbamylase, 76 Ornithine transcarbamylase, 76 Ornithine transcarbamylase, 76 Ornithine transcarbamylase, 76 Ornithine transcarbamylase, 76 Ornithine transcarbamylase, 76 Ornithine transcarbamylase, 76 Ornithine transcarbamylase, 76 Ornithine transcarbamylase, 76 Ornithine transcarbamylase, 76 Ornithine transcarbamylase, 76 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transca
fetal development, 612 teratogens, 614 Organophosphates toxicity treatment, 248 Organ transplants azathioprine for, 440 cytomegalovirus, 186 hairy leukoplakia and, 479 kidneys, 580 WBC casts, 594 Organum vasculosum of the lamina terminalis (OVLT), 498 Orientation, 557 Origin of replication, 38 Orlistat, 400 diarrhea, 249 Ornithine cystinuria, 85 kidney stones and, 598 urea cycle, 82 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 76 Ornithine transcarbamylase, 76 Ornithine transcarbamylase, 76 Ornithine transcarbamylase, 76 Ornithine transcarbamylase, 76 Ornithine transcarbamylase, 76 Ornithine transcarbamylase, 76 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transca
fetal development, 612 teratogens, 614 Organophosphates toxicity treatment, 248 Organ transplants azathioprine for, 440 cytomegalovirus, 186 hairy leukoplakia and, 479 kidneys, 580 WBC casts, 594 Organum vasculosum of the lamina terminalis (OVLT), 498 Orientation, 557 Origin of replication, 38 Orlistat, 400 diarrhea, 249 Ornithine cystinuria, 85 kidney stones and, 598 urea cycle, 82 Ornithine transcarbamylase, 74 Ornithine transcarbamylase deficiency, 61, 83 Orotic acid, 83 Orotic aciduria, 420 "Orphan Annie" eyes (nuclei), 343 Orthomyxoviruses, 168 characteristics of, 167, 168 influenza viruses, 169 Orthopedic conditions, 460 lower extremity, 460, 461 Orthopnea, 309 Orthostatic hypotension adrenal insufficiency, 349
fetal development, 612 teratogens, 614 Organophosphates toxicity treatment, 248 Organ transplants azathioprine for, 440 cytomegalovirus, 186 hairy leukoplakia and, 479 kidneys, 580 WBC casts, 594 Organum vasculosum of the lamina terminalis (OVLT), 498 Orientation, 557 Origin of replication, 38 Orlistat, 400 diarrhea, 249 Ornithine cystinuria, 85 kidney stones and, 598 urea cycle, 82 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 76 Ornithine transcarbamylase, 76 Ornithine transcarbamylase, 76 Ornithine transcarbamylase, 76 Ornithine transcarbamylase, 76 Ornithine transcarbamylase, 76 Ornithine transcarbamylase, 76 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transcarbamylase, 74 Ornithine transca

Ortolani maneuver, 461
Oseltamivir, 201
Osgood-Schlatter disease, 461
Osler nodes, 311 Osler-Weber-Rendu syndrome, 316
Osmotic demyelination syndrome, 524
SIADH and, 338
Osmotic diarrhea, 381 Osmotic laxatives, 401
Ossicles, 533
conductive hearing loss and, 51 Ossification, 458
Osteitis deformans, <b>463</b>
Osteitis fibrosa cystica, <b>345</b> , 459, 464 Osteoarthritis, 466
celecoxib for, 486
vs rheumatoid arthritis, <b>466</b>
Osteoarthropathy, hypertrophic
cancer association, 228
Osteoblastoma, 464 Osteoblasts, 459
bone formation, 458
cortisol effect on, 336
Paget disease of bone, 463
teriparatide effect on, 487
Osteochondroma, 464 Osteoclasts, 459
bisphosphonate effects, 486
bone formation, 458
osteopetrosis, 463
Paget disease of bone, 463
Osteodystrophy renal, 345, <b>603</b>
Osteogenesis imperfecta
bisphosphonates, 486
collagen and, 50
collagen synthesis and structure in, <b>51</b>
Osteogenic sarcoma, 463, 465
Osteoma, 220, 464–465
nomenclature for, 220
Osteomalacia hypophosphatemia, 591
lab values with rickets, 464
rickets, 463
Osteomyelitis, <b>180</b>
Pseudomonas aeruginosa, 143 sickle cell anemia, 422
Staphylococcus aureus, 135
Osteonecrosis, <b>463</b> , 486
Osteopenia, 463
Osteopetrosis, <b>463</b> , 464 Osteophytes, 466
Osteoporosis, <b>462</b>
bisphosphonates, 486
corticosteroids, 120
denosumab, 122 drug reaction and, 250
estrogen, 459
Gaucher disease, 88
heparin, 436
homocystinuria, 84 hormone replacement therapy, 657
lab values in, 464
pituitary prolactinomas, 328
raloxifene, 443, 656
teriparatide for, 487
thiazides for, 609 Osteosarcoma, 220, 464–465
Otitis media
brain abscesses with, 180
Haemophilus influenzae, 128, <b>142</b>
Langerhans cell histiocytosis, 434 Streptococcus pneumoniae, 136
Wegener granulomatosis and, 315

Otology 533
Otology, 533 Ototoxicity
aminoglycosides, <b>191</b> , 204, 614
cisplatin/carboplatin, 442
drug reaction and, 251
ethacrynic acid, 608
loop diuretics, 608
Duabain
sodium-potassium pump and, 49
Outcome (quality measurement),
273
Outer membrane, 124
Outflow tract formation, 281 Outpatient follow-up, 272
Oval fat bodies," 594
Ovarian artery, 625
Ovarian cancer
breastfeeding and, 636
cisplatin/carboplatin for, 442
epidemiology of, 643
hypercalcemia and, 228
irinotecan/topotecan for, 442
Lynch syndrome and, 388
oncogenes and, 224
paclitaxel for, 441
Psammoma bodies in, 227
tumor suppressor genes and, 224
Ovarian cycle, 632
Ovarian cysts, <b>646</b> Ovarian ligament, 625
Ovarian neoplasms
classification and characteristics
646
epithelial tumors, 646
germ cell tumors, 647
sex cord stromal tumors, 647
Ovarian teratomas
paraneoplastic syndrome, 228
Ovaries
anatomy of, 625
descent of, 624
epithelial histology, 626
estrogen production, 630
lymphatic drainage, 624 Overflow incontinence, 599
Overuse injury
elbow, <b>459</b>
knee, 461
radial nerve, 447
wrist, 459
Ovotesticular disorder, 638
Ovulation
anovulation causes, 645
progesterone and, 630
prolactin effect on, 330
regulation of, <b>631</b>
Ovulatory uterine bleeding, 633
Owl eyes" inclusions, 165, 429
Oxacillin characteristics of, 188
Dvaliplatip 442
Dvazenam 546
Oxaliplatin, <b>442</b> Oxazepam, 546 Oxazolidinones
mechanism and use, 193
Oxidative burst, 109
Oxidative phosphorylation, 78
metabolic site, 72
poisons, 78
Oxybutynin, 237, <b>241</b>
Dxygen
deprivation, 669
in blood, <b>666</b>
for carbon monoxide poisoning,
248
cluster headaches, 518 exercise and, 670
energies and, 0/0

	hemoglobin, 665
	toxicity, 210 Oxygen-hemoglobin dissociation
	curve, <b>666</b> Oxytocin
	functions of, 328 hypothalamus production, 498
~	lactation and, 636
9	pituitary gland and, 327 signaling pathways for, 337
	P
	P-450, 197
	P2Y12 receptor inhibitors and, 437
	thrombogenesis and, 411 P53 gene mutation
	dominant negative mutation, 56
	Pacemaker action potential, <b>292</b> Pacinian corpuscles, 494
	Paclitaxel, 441 microtubules and, 48
	targets of, 438
	Paget disease in breast, 650
1	Paget disease (extramammary), 644 Paget disease of bone, 463
	bisphosphonates, 486 lab values in, 464
	osteosarcomas and, 465
,	woven bone in, 458 Pain
	with headaches, 518 loss in syringomyelia, 492
	post-stroke syndrome, 515 receptors for, 494
	spinal tracts for, 509
	thalamic nuclei and, 498 treatment in multiple sclerosis,
	523 unilateral visual loss and, 523
	Pale (anemic) infarct, 210
	Paliperidone, 573 Palivizumab, 122
	pneumonia prophylaxis, 169 Pallor in aplastic anemia, 421
	Palmar interossei, 450 Palmar reflex, 510
	PALM-COEIN uterine bleeding
	classification, 633 PALP, 653
	Panacinar emphysema, 392, <b>674</b> p-ANCA
	sclerosing cholangitis and, 395 ulcerative colitis, 382
	Pancoast tumor, <b>685</b>
	lung cancer, 684 superior vena cava syndrome, 685
	thoracic outlet syndrome, 448 Pancreas
	annular, 360 biliary structures and, 368
	blood supply and innervation of,
	364 buds, 360
	divisum, 360 embryology, <b>360</b>
	Pancreatic cancer
	5-fluorouracil for, 440 adenocarcinomas, <b>398</b>
	biliary cirrhosis and, 395 carcinogens causing, 225
	hyperbilirubinemia with, 393 oncogenes and, 224
	paraneoplastic syndromes with, 228
	tumor suppressor genes and, 224

FAS1\_2019\_21\_Index\_749-806.indd 786 11/21/19 12:27 PM

Pancreatic ducts, 360, 368	Parame
Pancreatic insufficiency, <b>381</b> , 397	
Pancreatic islet cell tumors, <b>351</b>	extra
Pancreatic lipase, 93	Parame
Pancreatic secretions, <b>373</b> Pancreatitis	Parame
acute, 397	1 aranne
acute respiratory distress syndrome	Paramy
and, 678	chara
alcoholism, 571	croup
chronic, 397 corticosteroids and, 249	mum
drug reactions and, 249	Paraneo Paranoi
hyperchylomicronemia, 94	LSD
hyperparathyroidism, 345	Parasite
hypertriglyceridemia, 94	infec
mumps, 170	
necrosis and, 209 NRTIs, 203	Parasitio
valproic acid, 544	Danasita
Pancytopenia, 421	Parasito Parasyn
Chédiak-Higashi syndrome, 117	crani
cytarabine, 440	male
Gaucher disease, 88	recep
leishmaniasis, 158 osteopetrosis and, 463	VIP a
with immunosuppressants, 120	Parathy
Panic disorder	hype: MEN
drug therapy for, 572	Parathy
SSRIs for, 563, <b>575</b>	Parathy
symptoms and treatment, <b>563</b>	phary
venlafaxine for, 575 Panitumumab, <b>442</b>	Parathy
Panniculitis, 482	1
Pantoprazole, 399	bone bone
Pantothenic acid, 67	calcit
Papillary carcinomas, 220	calcii
Papillary cystadenoma lymphomatosum, 376	in hy
Papillary muscle	osteo
blood supply to, 307	Paget signa
rupture, 305, <b>307</b>	thym
Papillary thyroid carcinomas, 343 carcinogens for, 225	Paraum
Psammoma bodies in, 227	Paraven
Papilledema, 521, <b>538</b>	Parenta
hypertensive emergency and, 300	Paresth vitan
Papillomas, 220	Parietal
Papillomaviruses characteristics of, 164	Parietal
DNA viruses, 163	Parietal
genome, 163	Parietal
Pappenheimer bodies, 416	Parinau
Papules, 475	Parkins benz
capillary, 478 molluscum contagiosum, 479	dopa
Para-aminohippuric acid (PAH), 582	Lewy
Para-aortic lymph nodes, 624	meto
Paracoccidioidomycosis, 151	
Paracortex (lymph node), 96	nigro restir
Paracrine, 589 Paradoxical splitting, 289	seboi
Paraesophageal hiatal hernia, 370	
Parainfluenza	thera
croup, 170	trihe
paramyxovirus, 167, 169	ubiqı Parkina
Parakeratosis, 475 Paralysis	Parkins Parotid
conversion disorder and, 566	embi
of face, 514	enlar
Guillain-Barré syndrome, 524	stone
poliovirus, 186	tumo
rabies, 171 stroke effects, 514	Parotitis mum
unvaccinated children, 186	Paroxet
Paralytic ileus, 441	Paroxys
•	•

aramedian pontine reticular
formation
extraocular movements, 497 aramedian pontine reticular
formation lesions, 511
aramesonephric (Müllerian) duct, 622
aramyxoviruses, <b>169</b> characteristics of, 167, 168
croup, 170
croup, 170 mumps, 170
araneoplastic syndromes, <b>228</b> , 605 aranoia
LSD, 571
arasites infections with immunodeficiency,
118
arasitic infections myocarditis with, 313
myocarditis with, 313 arasitology, 155– <b>161</b>
arasympathetic nervous system
male erection, 627
arasympathetic nervous system cranial nerves, supply of, 236 male erection, 627 receptor targets, 236 VIP and, 371
arathyroid adenomas
hyperparathyroidism caused by, 345
MEN 1/MEN 2A syndromes, 351 arathyroid disease diagnosis, 343
arathyroid glands
pharyngeal pouch derivation, 621 arathyroid hormone (PTH), <b>332</b> ,
590
bone disorders, 464 bone formation, 459
calcitonin and, 333
calcium homeostasis and, 333 in hyperparathyroidism, 345
osteomalacia/rickets, 463
Paget disease of bone, 463 signaling pathways of, 337
thymic aplasia, 116
araumbilical vein, 365
araventricular nucleus, 498 arental consent, 265
aresthesias
vitamin B <sub>12</sub> deficiency, 69, 530 arietal cells (stomach), 372
arietal cortex lesions, 511
arietal lobe, 501 arietal peritoneum, 369
arinaud syndrome, <b>511</b> , 528
arkinson disease, 520 benztropine for, 241
dopaminergic pathways, 499
Lewy bodies, 520 metoclopramide contraindication,
400
nigrostriatal pathway and, 499 resting tremor in, 519
seborrheic dermatitis association,
476 therapy for, <b>548</b>
trihexyphenidyl, 241
ubiquitin-proteasome system in, 48 arkinson-like syndrome, 251
arotid gland
embryologic derivation, 613
enlargement of, 468 stones in, 376
tumors in, 376
arotitis mumps, 170
aroxetine, 575
aroxysmal nocturnal dyspnea, 309

Paroxysmal nocturnal
hemoglobinuria, 422
CD55 deficiency, 107
eculizumab for, 122
flow cytometry diagnosis, 54 intravascular hemolysis in, 421
Partial agonists, 234
Partial (focal) seizures, 517
drug therapy for, 544
Partial thromboplastin time (PTT), 426
Parvovirus
characteristics of, 164
DNA viruses, 163
naked viruses, 163 Parvovirus B19
hereditary spherocytosis, 422
hydrops fetalis, 182
rash, 183
Passive aggression, 555
Passive immunity, <b>110</b> Pasteurella multocida
osteomyelitis, 180
transmission, 149, 186
Patau syndrome, 63
cataracts, 535 chromosome association, 64
Patches (skin)
pityriasis rosea, 482
psoriatic arthritis, 469
Patellar reflex, 510 Patellofemoral syndrome, 461
Patent ductus arteriosus (PDA)
congenital rubella, 300
fetal alcohol syndrome, 300
heart murmur with, 291 indomethacin for, 486
mechanism and treatment, 299
neonatal respiratory distress
syndrome and, 661
Patent foramen ovale
atrial septal defect vs, 299 septal fusion failure, 280
Patent urachus, 618
Pathogen-associated molecular
patterns (PAMPs), 99
Pathogen recognition features, 99 Pathologic grief, 562
Pathology
cardiovascular, 298–312
endocrine, 338–354
gastrointestinal, 376–397 hematologic/oncologic, 404–424,
414–434
musculoskeletal/skin/connective
tissue, 459–467
neoplasia, 219–226 neurological, 511–518
psychiatric, 556–570
renal, 594–605
reproductive, 638–652
respiratory, 671–681 USMLE Step 1 preparation for,
277
Pautrier microabscess, 430
Pavlovian (classical) conditioning,
554 Payment models for healthcare, 271
P-bodies, 41
PCP (phencyclidine)
intoxication and withdrawal, 571
PCSK9, 93 PCSK9 inhibitors 320
PCSK9 inhibitors, 320 PCV13 (pneumococcal conjugate
vaccine), 127
PDSA cycle, <b>273</b>

Pearson correlation coefficient(r), <b>264</b> Peau d'orange, 650
Pectinate line, <b>366</b> Pectineus, 451, 452
Pectoriloquy (whispered), 680 Pediatric patients
arthritis in, 468 brachial plexus injury, 448
common causes of death, 272 common fractures, <b>462</b>
common orthopedic conditions, 461
cystic fibrosis, 60 dactinomycin for, 439
failure to thrive, 556 growth retardation in, 603
hemolytic disease of newborn, 405 hyperbilirubinemia (newborns), 393
infant deprivation effects, 556 intraventricular hemorrhage, 512 juvenile polyposis syndrome in, 387
leukocoria in, 538 Munchausen syndrome by proxy,
566 neglect in, 556
neuroblastomas in, 350 precocious puberty, 57, 335 primary brain tumors, 528
rashes, 183 renal malignancy in, 606
rhabdomyomas in, 316 scalded skin syndrome, 479
sleep terror disorder in, 568 strawberry hemangiomas in, 478
tetracycline side effects, 192 unvaccinated, 186 Wilms tumors in, 606
Pegloticase, 487 Pegvisomant, 339
Pellagra, 67 Pelvic inflammatory disease (PID),
185 Actinomyces spp, 139
chlamydia, 148, 184 Chlamydia trachomatis, 149
clinical features, 185 copper IUD, 657
ectopic pregnancy, 641 gonorrhea, 184
Neisseria spp, 142 Pelvic splanchnic nerves, 236
Pelvis fracture and nerve injury, 452
nerve injury with surgery, 452 Pemphigus vulgaris, 480
acantholysis and, 475 autoantibody, 115
type II hypersensitivity, 112 Pencil-in-cup deformity (X-ray), 469
Penicillamine for lead poisoning, 248
myopathy, 250 for Wilson disease, 395
Penicillin Actinomyces spp, 139
antipseudomonal, 188 Coombs-positive hemolytic
anemia, 250 penicillinase-resistant, 188
penicillinase-sensitive, 188 prophylaxis, 198
rash, 250 for rheumatic fever, 312 Penicillings registrant penicilling 188
Penicillinase-resistant penicillins, <b>188</b>

FAS1\_2019\_21\_Index\_749-806.indd 787 11/21/19 12:27 PM

788 INDEX

Penicillinase-sensitive penicillins, <b>188</b>	smudge cells, 432	Phagocytes, 117	vitamin B <sub>9</sub> deficiency, 68
Penicillin-binding proteins (PBPs)	spherocytes and agglutinated	Phagocytosis dendritic cells, 408	zero-order elimination of, 232 Pheochromocytomas, <b>350</b>
in bacteria, 124 Penicillin G, V, <b>187</b>	RBCs, 423 Peripheral edema	eosinophils, 408	MEN 2A/MEN 2B and, 351
meningococci, 142	calcium channel blockers, 318	group A streptococcal inhibition,	phenoxybenzamine for, 244
prophylaxis, 198	heart failure, 309	136	Philadelphia chromosome
Penile cancer, 226	Peripheral facial palsy, 532	M protein prevention of, 129	in myeloproliferative disorders, 43
Penis	Peripheral nerves, <b>495</b>	β-hemolytic bacteria inhibition	translocations of, 434
congenital abnormalities, <b>624</b>	Peripheral nervous system (PNS)	of, 135	Phlebitis P. 100
female homolog, 624 lymphatic drainage, 624	origins of, <b>490</b>	Phalen maneuver, 459	IV amphotericin B, 199 Phlebotomy
pathology of, <b>651</b>	Peripheral neuropathy alcoholism, 571	Pharmaceutical company sponsorship, 269	for hemochromatosis, 395
Pentamidine, 154	drug reactions and, 251	Pharmacokinetics, <b>231</b>	Phobias, <b>563</b>
Pentazocine, 551, <b>552</b>	Fabry disease, 88	Pharmacology, 230–254	agoraphobia, 563
Pentobarbital, 546	isoniazid, 197	autonomic drugs, 236–245	social anxiety disorder, 563
Pentose phosphate pathway	Krabbe disease, 88	cardiovascular, 316-322	Phocomelia, 614
functions of, <b>79</b>	NRTIs, 203	endocrine, 352–354	Phonophobia, migraine headache,
Pentostatin, 432	oxazolidinones, 193	gastrointestinal, 398–400	518 DI 1 - 72
PEP carboxykinase, 74	sorbitol, 81	hematologic/oncologic, 435–443	Phosphatases, 73
Pepsin, 372 Pepsinogen	vincristine, 444 vitamin B <sub>6</sub> deficiency, 67	musculoskeletal/skin/connective tissue, 485–487	Phosphodiesterase (PDE) inhibitors, <b>246</b> , 658, 686
location of, 373	Peripheral precocious puberty, 637	neurology, 544–551	Phosphoenolpyruvate carboxykinase
somatostatin and, 371	Peripheral resistance, 243	pharmacodynamics, 232–234	78
Peptic ulcer disease, <b>380</b>	Peripheral vascular disease, 302	pharmacokinetics, 230–231	Phosphofructokinase-1 (PFK-1)
glycopyrrolate for, 241	Peripheral vertigo, 534	psychiatric, 572-576	glycolysis and, 73
H pylori and, 146	Periplasm	renal, 607–610	metabolic pathways, 74
H <sub>2</sub> blockers for, 399	in bacteria, 124	reproductive, 655–658	Phospholipid bilayer sac
misoprostol for, 399	Peristalsis motilin receptor agonists and, 371	respiratory, 686–687	in bacteria, 124
proton pump inhibitors for, 399 Zollinger-Ellison syndrome, 352	visible, 359	toxicities and side effects, 248–251 USMLE Step 1 preparation for,	Phospholipids, 374 Phosphorus in Paget disease of bone.
Peptidoglycan	Peritoneum, 360	277	463
in gram negative bacteria, 124	hernias and, 370	Pharyngeal apparatus, <b>619</b>	Phosphorylases, 73
Peptostreptococcus spp	irritation with Mittelschmerz, 631	Pharyngeal arch derivatives, <b>620</b>	Phosphorylation, 45
alcoholism, 179	Peritonitis	1st pharyngeal arch, 620	Photophobia
Percussion (chest), 680	appendicitis, 383	2nd pharyngeal arch, 620	leptospirosis, 147
Perforation (GI), 380	diverticulitis, 383	4th–6th pharyngeal arches, 620	migraine headache, 518
necrotizing enterocolitis, 386 Perforin	spontaneous bacterial, 389, 390 Periventricular plaques, multiple	Pharyngeal cleft derivatives, <b>619</b> Pharyngeal pouch derivatives, <b>621</b>	rabies, 171 Photosensitivity
cytotoxic T cells and, 102	sclerosis, 523	1st pharyngeal pouch, 621	drugs causing, 192, 194, 250
extrinsic pathway and, 208	Permethrin, 200	2nd pharyngeal pouch, 621	Phototherapy for jaundice, 393
natural killer cells and, 101	for scabies, 161	4th pharyngeal pouch, 621	Phrenic nerve, 663
Performance anxiety, 567	Permissive action	Pharyngitis	Phyllodes tumor, 649
Perfusion, and ventilation, 669	catecholamine responsiveness, 235	adenovirus, 164	Physical abuse (child), 556
Perfusion-limited gas exchange, 668	Pernicious anemia, 372	diphtheria, 139	Physician-assisted suicide, 268
Perfusion pressure regulation, 297	autoantibody, 115	mononucleosis, 165	Physician-patient relationship, 268
Periarteriolar lymphatic sheath (PALS), 98	B <sub>12</sub> deficiency, 69, <b>420</b> Peroneus brevis, 453	prophylaxis (rheumatic fever), 198 Streptococcus pyogenes, 136	Physiologic dead space, 664 Physiologic neonatal jaundice, <b>393</b>
Pericardial effusion, 684	Peroneus longus, 453	unvaccinated children, 186	Physiology
Pericarditis	Peroxisome	Pharyngoesophageal false	cardiovascular, 284–298
acute, 313	metabolic processes, 47	diverticulum, 384	endocrine, 328-336
fibrinous, 305	Persistent cervical sinus, 619	Pharynx, 662	gastrointestinal, 371-375
jugular venous pulse in, 287	Persistent depressive disorder	blood supply and innervation of,	hematologic/oncologic, 410
Kussmaul sign in, 316	(dysthymia), 561	364 Pl	neurological, 493–515
picornaviruses, 167 postinfarction, 305, 307	Persistent thyroglossal duct, 326	Phenacetin, 606 Phenelzine, 575	renal, 581-592 reproductive, 629-636
pulsus paradoxus in, 310	Persistent truncus arteriosus, 281, 298 Personality, <b>565</b>	Phenobarbital, 546	respiratory, 664–669
renal failure, 603	Personality disorders, 565	epilepsy, 544	USMLE Step 1 preparation for,
rheumatoid arthritis, 466	Cluster A, 565	as weak acid, 233	276
Pericardium	Cluster B, 565	Phenotypic mixing, 162	Physostigmine
anatomy of, 283	Cluster C, 565, 566	Phenoxybenzamine, 244	anticholinergic toxicity treatment,
calcification in, 211	Pertussis, 126	for pheochromocytomas, 350	248
Perineal straddle injury, 627	Pertussis toxin, 132, 143	Phentolamine, 244	anticholinesterase, 240
Perinephric abscesses, 600 Perineurium, 495	Pes cavus Friedreich ataxia, 531	Phenylalanine classification of, 81	glaucoma, 552 Pia mater, 496
Periodic acid-Schiff stain, 125	Petechiae	tyrosine catabolism, 83	Pica, 567
glycogen storage diseases, 87	aplastic anemia, 421	Phenylephrine, 242, <b>686</b>	Pick disease, 520
Periorbital edema	Peutz-Jeghers syndrome, 220, <b>387</b>	Phenylketones, 84	bodies, 520
thyroid disease and, 340	PEX genes, 47	Phenylketonuria	Pickwickian syndrome, 679
Trichinella spiralis, 161	Peyer patches, 362, <b>374</b>	tyrosine in, <b>84</b>	Picornaviruses, 163, 168
Peripartum mood disturbances, <b>562</b>	IgA antibody production, 105	Phenytoin P. 450	characteristics, 167
Peripheral blood smear, 416	Salmonella/Shigella invasion, 144	cytochrome P-450 and, 252	genomes, 163
basophilic stippling, 419	Peyronie disease, 651	epilepsy, 544 folate deficiency caused by, 420	Pierre Robin sequence, 620 Pigmented skin disorders, <b>476</b>
postsplenectomy, 98, 423 Rouleaux formation, 431	PGI <sub>2</sub> , 485 P-glycoprotein, <b>227</b>	gingival hyperplasia, 250	Pigmented skin disorders, <b>476</b> Pigment-producing bacteria, <b>128</b>
schistocytes, 423	Phage	megaloblastic anemia, 250	Pigment stones, 396
Schüffner stippling, 157	bacterial transduction, 130	peripheral neuropathy, 251	Pill-rolling tremor, 519
		- * * * * * * * * * * * * * * * * * * *	-

FAS1\_2019\_21\_Index\_749-806.indd 788 11/21/19 12:27 PM

Pilocarpine, <b>240</b> , 552
D:1 .: 520
Pilocytic astrocytoma, 528
Pilus, 124
Pimozide, 572
Pindolol, 245, 319
Pineal gland, 504
Pinealoma, 528
Pinworms, 159
Pioglitazone, 353
Piperacillin
* -
characteristics of, 188
Pseudomonas aeruginosa, 143
Piroxicam, 486
Pisiform bone, 449
Pitting edema, 309
Pituitary adenoma, 339, 527
Pituitary apoplexy, 339
Pituitary drugs, 354
Pituitary gland, <b>327</b>
Pituitary prolactinomas, 328
Pituitary tumors
diabetes insipidus, 338
MEN 1 and, 351
Pityriasis rosea, 482
Pityrosporum spp, 152
pKa, 233
PKD genes
renal cyst disorders and, 604
Placebo, 256
Placenta
estrogen production, 630
fetal component, <b>617</b>
hormone secretion by, 633
maternal component, 617
progesterone production, 630
Placenta accreta/increta/percreta, 640
Placental aromatase deficiency, 639
Placental insufficiency
oligohydramnios and, 641
Potter sequence, 578
preeclampsia, 643
DI
Placenta previa, 640
Plague 149
Plague, 149
Plague, 149 Plantar aponeurosis, 461
Plague, 149 Plantar aponeurosis, 461 Plantar fasciitis, 461
Plague, 149 Plantar aponeurosis, 461 Plantar fasciitis, 461
Plague, 149 Plantar aponeurosis, 461 Plantar fasciitis, 461 Plantar flexion, 453
Plague, 149 Plantar aponeurosis, 461 Plantar fasciitis, 461 Plantar flexion, 453 Plantaris, 453
Plague, 149 Plantar aponeurosis, 461 Plantar fasciitis, 461 Plantar flexion, 453 Plantaris, 453 Plantar reflex, 510
Plague, 149 Plantar aponeurosis, 461 Plantar fasciitis, 461 Plantar flexion, 453 Plantaris, 453 Plantar reflex, 510 Plaques (skin), 475
Plague, 149 Plantar aponeurosis, 461 Plantar fasciitis, 461 Plantar flexion, 453 Plantaris, 453 Plantar reflex, 510
Plague, 149 Plantar aponeurosis, 461 Plantar fasciitis, 461 Plantar flexion, 453 Plantaris, 453 Plantar reflex, 510 Plaques (skin), 475 actinic keratosis, 482
Plague, 149 Plantar aponeurosis, 461 Plantar fasciitis, 461 Plantar flexion, 453 Plantaris, 453 Plantar reflex, 510 Plaques (skin), 475 actinic keratosis, 482 basal cell carcinoma, 484
Plague, 149 Plantar aponeurosis, 461 Plantar fasciitis, 461 Plantar flexion, 453 Plantaris, 453 Plantar reflex, 510 Plaques (skin), 475 actinic keratosis, 482 basal cell carcinoma, 484 hairy leukoplakia, 479
Plague, 149 Plantar aponeurosis, 461 Plantar fasciitis, 461 Plantar flexion, 453 Plantaris, 453 Plantar reflex, 510 Plaques (skin), 475 actinic keratosis, 482 basal cell carcinoma, 484 hairy leukoplakia, 479 lichen planus, 482
Plague, 149 Plantar aponeurosis, 461 Plantar fasciitis, 461 Plantar flexion, 453 Plantaris, 453 Plantar reflex, 510 Plaques (skin), 475 actinic keratosis, 482 basal cell carcinoma, 484 hairy leukoplakia, 479 lichen planus, 482
Plague, 149 Plantar aponeurosis, 461 Plantar fasciitis, 461 Plantar flexion, 453 Plantaris, 453 Plantar reflex, 510 Plaques (skin), 475 actinic keratosis, 482 basal cell carcinoma, 484 hairy leukoplakia, 479 lichen planus, 482 pityriasis rosea, 482
Plague, 149 Plantar aponeurosis, 461 Plantar fasciitis, 461 Plantar flexion, 453 Plantaris, 453 Plantar reflex, 510 Plaques (skin), 475 actinic keratosis, 482 basal cell carcinoma, 484 hairy leukoplakia, 479 lichen planus, 482 pityriasis rosea, 482 psoriasis, 477
Plague, 149 Plantar aponeurosis, 461 Plantar fasciitis, 461 Plantar flexion, 453 Plantar reflex, 510 Plaques (skin), 475 actinic keratosis, 482 basal cell carcinoma, 484 hairy leukoplakia, 479 lichen planus, 482 pityriasis rosea, 482 psoriasis, 477 seborrheic dermatitis, 476
Plague, 149 Plantar aponeurosis, 461 Plantar fasciitis, 461 Plantar flexion, 453 Plantaris, 453 Plantaris, 510 Plaques (skin), 475 actinic keratosis, 482 basal cell carcinoma, 484 hairy leukoplakia, 479 lichen planus, 482 pityriasis rosea, 482 psoriasis, 477 seborrheic dermatitis, 476 squamous cell carcinoma, 484
Plague, 149 Plantar aponeurosis, 461 Plantar fasciitis, 461 Plantar flexion, 453 Plantar reflex, 510 Plaques (skin), 475 actinic keratosis, 482 basal cell carcinoma, 484 hairy leukoplakia, 479 lichen planus, 482 pityriasis rosea, 482 psoriasis, 477 seborrheic dermatitis, 476
Plague, 149 Plantar aponeurosis, 461 Plantar fasciitis, 461 Plantar flexion, 453 Plantaris, 453 Plantar reflex, 510 Plaques (skin), 475 actinic keratosis, 482 basal cell carcinoma, 484 hairy leukoplakia, 479 lichen planus, 482 pityriasis rosea, 482 psoriasis, 477 seborrheic dermatitis, 476 squamous cell carcinoma, 484 Plasma cell dyscrasias, 431
Plague, 149 Plantar aponeurosis, 461 Plantar fasciitis, 461 Plantar flexion, 453 Plantar reflex, 510 Plaques (skin), 475 actinic keratosis, 482 basal cell carcinoma, 484 hairy leukoplakia, 479 lichen planus, 482 pityriasis rosea, 482 psoriasis, 477 seborrheic dermatitis, 476 squamous cell carcinoma, 484 Plasma cell dyscrasias, 431 Plasma cells, 409
Plague, 149 Plantar aponeurosis, 461 Plantar fasciitis, 461 Plantar flexion, 453 Plantar reflex, 510 Plaques (skin), 475 actinic keratosis, 482 basal cell carcinoma, 484 hairy leukoplakia, 479 lichen planus, 482 pityriasis rosea, 482 psoriasis, 477 seborrheic dermatitis, 476 squamous cell carcinoma, 484 Plasma cell dyscrasias, 431 Plasma cells, 409 Plasmalogens, 47
Plague, 149 Plantar aponeurosis, 461 Plantar fasciitis, 461 Plantar flexion, 453 Plantar reflex, 510 Plaques (skin), 475     actinic keratosis, 482     basal cell carcinoma, 484     hairy leukoplakia, 479     lichen planus, 482     pityriasis rosea, 482     psoriasis, 477     seborrheic dermatitis, 476     squamous cell carcinoma, 484 Plasma cell dyscrasias, 431 Plasma cells, 409 Plasmalogens, 47 Plasma membrane
Plague, 149 Plantar aponeurosis, 461 Plantar fasciitis, 461 Plantar flexion, 453 Plantar reflex, 510 Plaques (skin), 475 actinic keratosis, 482 basal cell carcinoma, 484 hairy leukoplakia, 479 lichen planus, 482 pityriasis rosea, 482 psoriasis, 477 seborrheic dermatitis, 476 squamous cell carcinoma, 484 Plasma cell dyscrasias, 431 Plasma cells, 409 Plasmalogens, 47
Plague, 149 Plantar aponeurosis, 461 Plantar fasciitis, 461 Plantar flexion, 453 Plantar reflex, 510 Plaques (skin), 475     actinic keratosis, 482     basal cell carcinoma, 484     hairy leukoplakia, 479     lichen planus, 482     pityriasis rosea, 482     psoriasis, 477     seborrheic dermatitis, 476     squamous cell carcinoma, 484 Plasma cell dyscrasias, 431 Plasma cells, 409 Plasmalogens, 47 Plasma membrane     sodium-potassium pump, 49
Plague, 149 Plantar aponeurosis, 461 Plantar fasciitis, 461 Plantar flexion, 453 Plantar reflex, 510 Plaques (skin), 475     actinic keratosis, 482     basal cell carcinoma, 484     hairy leukoplakia, 479     lichen planus, 482     pityriasis rosea, 482     psoriasis, 477     seborrheic dermatitis, 476     squamous cell carcinoma, 484 Plasma cell dyscrasias, 431 Plasma cells, 409 Plasmalogens, 47 Plasma membrane     sodium-potassium pump, 49     structure of, 49
Plague, 149 Plantar aponeurosis, 461 Plantar fasciitis, 461 Plantar fasciitis, 461 Plantar flexion, 453 Plantaris, 453 Plantar reflex, 510 Plaques (skin), 475 actinic keratosis, 482 basal cell carcinoma, 484 hairy leukoplakia, 479 lichen planus, 482 pityriasis rosea, 482 psoriasis, 477 seborrheic dermatitis, 476 squamous cell carcinoma, 484 Plasma cell dyscrasias, 431 Plasma cells, 409 Plasma membrane sodium-potassium pump, 49 structure of, 49 Plasma osmolality
Plague, 149 Plantar aponeurosis, 461 Plantar fasciitis, 461 Plantar flexion, 453 Plantaris, 453 Plantar reflex, 510 Plaques (skin), 475 actinic keratosis, 482 basal cell carcinoma, 484 hairy leukoplakia, 479 lichen planus, 482 pityriasis rosea, 482 psoriasis, 477 seborrheic dermatitis, 476 squamous cell carcinoma, 484 Plasma cell dyscrasias, 431 Plasma cells, 409 Plasmalogens, 47 Plasma membrane sodium-potassium pump, 49 structure of, 49 Plasma osmolality DI treatment, 338
Plague, 149 Plantar aponeurosis, 461 Plantar fasciitis, 461 Plantar fasciitis, 461 Plantar flexion, 453 Plantaris, 453 Plantar reflex, 510 Plaques (skin), 475 actinic keratosis, 482 basal cell carcinoma, 484 hairy leukoplakia, 479 lichen planus, 482 pityriasis rosea, 482 psoriasis, 477 seborrheic dermatitis, 476 squamous cell carcinoma, 484 Plasma cell dyscrasias, 431 Plasma cells, 409 Plasma membrane sodium-potassium pump, 49 structure of, 49 Plasma osmolality DI treatment, 338 Plasmapheresis, 524, 596
Plague, 149 Plantar aponeurosis, 461 Plantar fasciitis, 461 Plantar fasciitis, 461 Plantar flexion, 453 Plantaris, 453 Plantar reflex, 510 Plaques (skin), 475 actinic keratosis, 482 basal cell carcinoma, 484 hairy leukoplakia, 479 lichen planus, 482 pityriasis rosea, 482 psoriasis, 477 seborrheic dermatitis, 476 squamous cell carcinoma, 484 Plasma cell dyscrasias, 431 Plasma cells, 409 Plasma membrane sodium-potassium pump, 49 structure of, 49 Plasma osmolality DI treatment, 338 Plasmapheresis, 524, 596
Plague, 149 Plantar aponeurosis, 461 Plantar fasciitis, 461 Plantar flexion, 453 Plantar reflex, 510 Plaques (skin), 475 actinic keratosis, 482 basal cell carcinoma, 484 hairy leukoplakia, 479 lichen planus, 482 pityriasis rosea, 482 psoriasis, 477 seborrheic dermatitis, 476 squamous cell carcinoma, 484 Plasma cell dyscrasias, 431 Plasma cells, 409 Plasma membrane sodium-potassium pump, 49 structure of, 49 Plasma osmolality DI treatment, 338 Plasmapheresis, 524, 596 Plasma protein concentration, 583
Plague, 149 Plantar aponeurosis, 461 Plantar fasciitis, 461 Plantar flexion, 453 Plantar reflex, 510 Plaques (skin), 475 actinic keratosis, 482 basal cell carcinoma, 484 hairy leukoplakia, 479 lichen planus, 482 pityriasis rosea, 482 psoriasis, 477 seborrheic dermatitis, 476 squamous cell carcinoma, 484 Plasma cell dyscrasias, 431 Plasma cells, 409 Plasmalogens, 47 Plasma membrane sodium-potassium pump, 49 structure of, 49 Plasma osmolality DI treatment, 338 Plasmapheresis, 524, 596 Plasma protein concentration, 583 Plasma volume measurement, 581
Plague, 149 Plantar aponeurosis, 461 Plantar fasciitis, 461 Plantar flexion, 453 Plantar reflex, 510 Plaques (skin), 475     actinic keratosis, 482     basal cell carcinoma, 484     hairy leukoplakia, 479     lichen planus, 482     pityriasis rosea, 482     psoriasis, 477     seborrheic dermatitis, 476     squamous cell carcinoma, 484 Plasma cell dyscrasias, 431 Plasma cells, 409 Plasmalogens, 47 Plasma membrane     sodium-potassium pump, 49     structure of, 49 Plasma osmolality     DI treatment, 338 Plasmapheresis, 524, 596 Plasma protein concentration, 583 Plasma volume measurement, 581 Plasminogen, 437
Plague, 149 Plantar aponeurosis, 461 Plantar fasciitis, 461 Plantar flexion, 453 Plantar reflex, 510 Plaques (skin), 475     actinic keratosis, 482     basal cell carcinoma, 484     hairy leukoplakia, 479     lichen planus, 482     pityriasis rosea, 482     psoriasis, 477     seborrheic dermatitis, 476     squamous cell carcinoma, 484 Plasma cell dyscrasias, 431 Plasma cells, 409 Plasmalogens, 47 Plasma membrane     sodium-potassium pump, 49     structure of, 49 Plasma osmolality     DI treatment, 338 Plasmapheresis, 524, 596 Plasma rotein concentration, 583 Plasma volume measurement, 581 Plasminogen, 437 Plasmodium spp
Plague, 149 Plantar aponeurosis, 461 Plantar fasciitis, 461 Plantar flexion, 453 Plantar reflex, 510 Plaques (skin), 475     actinic keratosis, 482     basal cell carcinoma, 484     hairy leukoplakia, 479     lichen planus, 482     pityriasis rosea, 482     psoriasis, 477     seborrheic dermatitis, 476     squamous cell carcinoma, 484 Plasma cell dyscrasias, 431 Plasma cells, 409 Plasmalogens, 47 Plasma membrane     sodium-potassium pump, 49     structure of, 49 Plasma osmolality     DI treatment, 338 Plasmapheresis, 524, 596 Plasma protein concentration, 583 Plasma volume measurement, 581 Plasminogen, 437
Plague, 149 Plantar aponeurosis, 461 Plantar fasciitis, 461 Plantar fasciitis, 461 Plantar flexion, 453 Plantaris, 453 Plantar reflex, 510 Plaques (skin), 475     actinic keratosis, 482     basal cell carcinoma, 484     hairy leukoplakia, 479     lichen planus, 482     pityriasis rosea, 482     psoriasis, 477     seborrheic dermatitis, 476     squamous cell carcinoma, 484 Plasma cell dyscrasias, 431 Plasma cells, 409 Plasma membrane     sodium-potassium pump, 49     structure of, 49 Plasma osmolality     DI treatment, 338 Plasmapheresis, 524, 596 Plasma protein concentration, 583 Plasma volume measurement, 581 Plasminogen, 437 Plasmodium spp     chloroquine, 200
Plague, 149 Plantar aponeurosis, 461 Plantar fasciitis, 461 Plantar fasciitis, 461 Plantar flexion, 453 Plantaris, 453 Plantar reflex, 510 Plaques (skin), 475 actinic keratosis, 482 basal cell carcinoma, 484 hairy leukoplakia, 479 lichen planus, 482 pityriasis rosea, 482 psoriasis, 477 seborrheic dermatitis, 476 squamous cell carcinoma, 484 Plasma cell dyscrasias, 431 Plasma cells, 409 Plasmalogens, 47 Plasma membrane sodium-potassium pump, 49 structure of, 49 Plasma osmolality DI treatment, 338 Plasmapheresis, 524, 596 Plasma protein concentration, 583 Plasma volume measurement, 581 Plasminogen, 437 Plasmodium spp chloroquine, 200 Plasmodium falciparum, 157, 200
Plague, 149 Plantar aponeurosis, 461 Plantar fasciitis, 461 Plantar fasciitis, 461 Plantar flexion, 453 Plantaris, 453 Plantar reflex, 510 Plaques (skin), 475 actinic keratosis, 482 basal cell carcinoma, 484 hairy leukoplakia, 479 lichen planus, 482 pityriasis rosea, 482 psoriasis, 477 seborrheic dermatitis, 476 squamous cell carcinoma, 484 Plasma cell dyscrasias, 431 Plasma cells, 409 Plasmalogens, 47 Plasma membrane sodium-potassium pump, 49 structure of, 49 Plasma osmolality DI treatment, 338 Plasmapheresis, 524, 596 Plasma protein concentration, 583 Plasma volume measurement, 581 Plasminogen, 437 Plasmodium spp chloroquine, 200 Plasmodium falciparum, 157, 200 Plasmodium malariae, 157
Plague, 149 Plantar aponeurosis, 461 Plantar fasciitis, 461 Plantar fasciitis, 461 Plantar flexion, 453 Plantaris, 453 Plantar reflex, 510 Plaques (skin), 475     actinic keratosis, 482     basal cell carcinoma, 484     hairy leukoplakia, 479     lichen planus, 482     pityriasis rosea, 482     psoriasis, 477     seborrheic dermatitis, 476     squamous cell carcinoma, 484 Plasma cell dyscrasias, 431 Plasma cells, 409 Plasmalogens, 47 Plasma membrane     sodium-potassium pump, 49     structure of, 49 Plasma osmolality     DI treatment, 338 Plasmapheresis, 524, 596 Plasma protein concentration, 583 Plasma volume measurement, 581 Plasminogen, 437 Plasmodium spp     chloroquine, 200 Plasmodium falciparum, 157, 200 Plasmodium malariae, 157 Plasmodium malariae, 157
Plague, 149 Plantar aponeurosis, 461 Plantar fasciitis, 461 Plantar fasciitis, 461 Plantar flexion, 453 Plantaris, 453 Plantar reflex, 510 Plaques (skin), 475 actinic keratosis, 482 basal cell carcinoma, 484 hairy leukoplakia, 479 lichen planus, 482 pityriasis rosea, 482 psoriasis, 477 seborrheic dermatitis, 476 squamous cell carcinoma, 484 Plasma cell dyscrasias, 431 Plasma cells, 409 Plasmalogens, 47 Plasma membrane sodium-potassium pump, 49 structure of, 49 Plasma osmolality DI treatment, 338 Plasmapheresis, 524, 596 Plasma protein concentration, 583 Plasma volume measurement, 581 Plasminogen, 437 Plasmodium spp chloroquine, 200 Plasmodium falciparum, 157, 200 Plasmodium malariae, 157
Plague, 149 Plantar aponeurosis, 461 Plantar fasciitis, 461 Plantar fasciitis, 461 Plantar flexion, 453 Plantar reflex, 510 Plaques (skin), 475 actinic keratosis, 482 basal cell carcinoma, 484 hairy leukoplakia, 479 lichen planus, 482 pityriasis rosea, 482 psoriasis, 477 seborrheic dermatitis, 476 squamous cell carcinoma, 484 Plasma cell dyscrasias, 431 Plasma cells, 409 Plasmalogens, 47 Plasma membrane sodium-potassium pump, 49 structure of, 49 Plasma osmolality DI treatment, 338 Plasmapheresis, 524, 596 Plasma protein concentration, 583 Plasma volume measurement, 581 Plasminogen, 437 Plasmodium spp chloroquine, 200 Plasmodium falciparum, 157, 200 Plasmodium malariae, 157 Plasmodium ovale, 157 Plasmodium vivax, 157
Plague, 149 Plantar aponeurosis, 461 Plantar fasciitis, 461 Plantar fasciitis, 461 Plantar flexion, 453 Plantaris, 453 Plantar reflex, 510 Plaques (skin), 475     actinic keratosis, 482     basal cell carcinoma, 484     hairy leukoplakia, 479     lichen planus, 482     pityriasis rosea, 482     psoriasis, 477     seborrheic dermatitis, 476     squamous cell carcinoma, 484 Plasma cell dyscrasias, 431 Plasma cells, 409 Plasmalogens, 47 Plasma membrane     sodium-potassium pump, 49     structure of, 49 Plasma osmolality     DI treatment, 338 Plasmapheresis, 524, 596 Plasma protein concentration, 583 Plasma volume measurement, 581 Plasminogen, 437 Plasmodium spp     chloroquine, 200 Plasmodium falciparum, 157, 200 Plasmodium malariae, 157 Plasmodium malariae, 157

Platelet-derived growth factor
(PDGF)
in wound healing, 216
signaling pathways for, 337
Platelet disorders, 426, <b>427</b>
transfusion for, 429
Platysma muscle, 620
Pleiotropy, 56 Pleomorphic adenomas, 376
Pleural effusion, <b>681</b>
asbestosis, 677
lung cancer, 684
mesothelioma, 678
physical findings, 680
Pleuritis, 466
Pleuroperitoneal membrane, 370
Plicae circulares, 362 Plummer-Vinson syndrome, 377, 418
Pneumatosis intestinalis, 386
Pneumococcal vaccine, 127
Pneumoconioses, 675, <b>677</b>
Pneumocystis jirovecii, <b>154</b>
dapsone, 194
fluorescent antibody stain, 125
HIV-positive adults, 177
immunocompromised patients, 179
prophylaxis, 198 silver stain for, 125
TMP-SMX, 194
Pneumocytes, 661
Pneumomediastinum, 672
Pneumonia, <b>683</b>
acute respiratory distress syndrome,
678
adenovirus, 164 chlamydiae, 148
coccidioidomycosis, 151
common causes, <b>179</b>
Haemophilus influenzae, 142
measles-associated death, 170
Pneumocystis jirovecii, 154
PPI adverse effects, 399
Q fever, 150 readmissions with, 272
Staphylococcus aureus, 135
Streptococcus pneumoniae, 136
Streptococcus agalactiae, 137
VZV, 165
Pneumoperitoneum, 380
Pneumothorax, 680, <b>682</b>
Podocytes glomerular filtration barrier and,
<b>581</b> , 595
Poikilocytosis, 407
Point of service plan, 271
bol gene, 175
Poliomyelitis, <b>531</b>
restrictive lung disease, 675
Poliovirus, 531 immunodeficient patients, 118
medical importance, 167
picornavirus, 168
unvaccinated children, 186
Polyadenylation signal, 41
Polyangiitis, microscopic
autoantibody, 115
Polyarteritis nodosa, 173, <b>314</b>
Polyarthralgias
gonococcal arthritis, 468 rubella, 182
Polycystic disease (kidney), 604
Polycystic disease (kidney), 60 i Polycystic ovarian syndrome (PCOS),
645
anovulation, 645
antiandrogens, 658
clomiphene, 656

Polycythemia, 434 blood oxygen in, 666 Eisenmenger syndrome, 299 ESR in, 214 paraneoplastic syndromes, 228 Polycythemia vera, 433 Budd-Chiari syndrome and, 392 hepatocellular carcinoma, 392 Polydactyly, 63 Polydipsia, 346 Polyhydramnios, 491, 641 esophageal atresia and, 359 Polymerase chain reaction (PCR), 52 Polymorphic ventricular tachycardia, 294 Polymyalgia rheumatica, 470 ÉSŘ in, 214 giant cell arteritis and, 314 Polymyositis autoantibody, 115 Polymyositis/dermatomyositis, 471 Polymyxin B, 143, **193**, 198 Polymyxins, 198 mechanism and use, 193 Polyneuritis, 66 Polyneuropathy, 425 familial amyloid, 212 Polyomaviruses characteristics of, 164 DNA viruses, 163 genome, 163 naked viruses, 163 Polyostotic fibrous dysplasia, 57 Polyposis syndromes, 387 Polyps adenomatous, 387 APC gene, 387 colonic, 387 hyperplastic, 387 inflammatory pseudopolyps, 387 KRAS gene, 387 mucosal, 387 nasal (cystic fibrosis), 60 neoplastic transformation of, 387 non-neoplastic, 387 serrated, 387 submucosal, 387 uterine, 650 Polysaccharide capsule antigens carrier proteins with, 127 Polvuria diabetes insipidus, 338 diabetes mellitus, 346 hyperparathyroidism, 345 lithium, 574 Pompe disease, 87 Pons cranial nerve nuclei of, 505 development of, 490 Pontiac fever, 143 Pontine syndrome, 514 "Pope's blessing" (median nerve injury), 451 Popliteal artery, 455 atherosclerosis in, 302 Popliteal fossa, 455 Popliteus, 453 Porcelain gallbladder, 396, 397 Porphobilinogen deaminase, 425 Porphyria, 425, 546 Porphyria cutanea tarda, 425 Portal hypertension ARPKD, 604 cirrhosis and, 389 pulmonary arterial hypertension,

Schistosoma spp, 161 serum markers for, 390 varices and, 365 Portal triad, 361, 367 Portal vein, 361, 367 in fetal circulation, 282 Portosystemic anastomoses, 365 Positive predictive value (PPV), 257, 259 Positive punishment (aversive stimulus), 554 Positive reinforcement, 554 Positive skew distribution, 262 Posterior cerebral artery, 502, 515 Posterior circulation strokes, 514 Posterior circumflex artery, 455 Posterior communicating artery in saccular aneurysm, 516 Posterior cruciate ligament (PCL) injury, 454 Posterior descending artery (PDA), Posterior drawer sign, 454 Posterior fossa malformations, 492 Posterior hypothalamus, 498 Posterior inferior cerebellar artery stroke effects, 514 Posterior malleolus, 455 Posterior pituitary gland, 327 Posterior tibial artery, 455 Posterior urethral valves, 579 Postherpetic neuralgia, 165 Postinfectious encephalomyelitis, 524 Postoperative ileus, 240 Postpartum hemorrhage, 641 Postpartum mood disturbances, 562 Postpartum psychosis, 562 Postpartum thyroiditis, 341 Postprandial pain, 363 Postrenal azotemia, 601 Poststreptococcal glomerulonephritis (acute), 596 Post-traumatic stress disorder (PTSD) acute stress disorder, 564 diagnostic criteria/treatment, 564 dissociative identity disorder, 558 drug therapy for, 572 prazosin for, 244 SSRIs for, 575 venlafaxine, 575 Postural hypotension midodrine for, 242 trazodone, 576 Postviral infections, 179 Potassium amphotericin B, 199 in cardiac muscle, 292 diabetic ketoacidosis, 347 shifts in, 590 torsades de pointes and, 294 Potassium channel blockers, 323 Potassium channels myocardial action potential, 292 opioid effect, 551 Potassium chloride, 249 Potassium iodide Sporothrix schenckii, 154 for thyroid storm, 342 Potassium-sparing diuretics, 609 Potency of drugs vs efficacy, 233 Potentiation of drugs, 235 Pott disease, 180

FAS1\_2019\_21\_Index\_749-806.indd 789 11/21/19 12:27 PM

INDEX

Potter sequence (syndrome)
ARPKD, 604
oligohydramnios and, <b>578</b> , 641
pulmonary hypoplasia, 660
Poxvirus, 164, 479
PPD test
for tuberculosis, 140
PPSV23 (pneumococcal
polysaccharide vaccine),
127
PR3-ANCA/c-ANCA autoantibody,
115
Practice tests, 21
Prader-Willi syndrome
chromosome association, 64
ghrelin in, <b>336</b> , 371
Pramlintide, 249, 353
Prasugrel, 411, 437
Praziquantel
antihelminthic therapy, 200
tapeworms, 160
trematodes, 160
Prazosin, 244
Precision vs accuracy, 259
Precocious puberty
adrenal steroids and, 335
leuprolide, 656
McCune-Albright syndrome, 57
pinealoma, 528
types, <b>637</b>
Precontemplation stage, substance
addiction, 568
Predictive value, 257
Prednisolone
for thyroid storm, 342
Preeclampsia, 643
hydatidiform moles, 642
Preferred provider organization plan,
271
Prefrontal cortex, 501
Pregnancy
advanced maternal age, 63
advanced maternal age, 63 aliskiren contraindication, 610
aliskiren contraindication, 610
aliskiren contraindication, 610 amniotic fluid abnormalities, 641
aliskiren contraindication, 610 amniotic fluid abnormalities, 641 anemia caused by, 418
aliskiren contraindication, 610 amniotic fluid abnormalities, 641 anemia caused by, 418 carpal tunnel syndrome in, 459
aliskiren contraindication, 610 amniotic fluid abnormalities, 641 anemia caused by, 418 carpal tunnel syndrome in, 459 choriocarcinomas and, 642
aliskiren contraindication, 610 amniotic fluid abnormalities, 641 anemia caused by, 418 carpal tunnel syndrome in, 459 choriocarcinomas and, 642 contraindicated antimicrobials, 204
aliskiren contraindication, 610 amniotic fluid abnormalities, 641 anemia caused by, 418 carpal tunnel syndrome in, 459 choriocarcinomas and, 642 contraindicated antimicrobials, 204 ESR in, 214
aliskiren contraindication, 610 amniotic fluid abnormalities, 641 anemia caused by, 418 carpal tunnel syndrome in, 459 choriocarcinomas and, 642 contraindicated antimicrobials, 204 ESR in, 214 estrogen in, 630
aliskiren contraindication, 610 amniotic fluid abnormalities, 641 anemia caused by, 418 carpal tunnel syndrome in, 459 choriocarcinomas and, 642 contraindicated antimicrobials, 204 ESR in, 214 estrogen in, 630 ethical situations, 268–269
aliskiren contraindication, 610 amniotic fluid abnormalities, 641 anemia caused by, 418 carpal tunnel syndrome in, 459 choriocarcinomas and, 642 contraindicated antimicrobials, 204 ESR in, 214 estrogen in, 630 ethical situations, 268–269 fetal circulation, 282
aliskiren contraindication, 610 amniotic fluid abnormalities, 641 anemia caused by, 418 carpal tunnel syndrome in, 459 choriocarcinomas and, 642 contraindicated antimicrobials, 204 ESR in, 214 estrogen in, 630 ethical situations, 268–269 fetal circulation, 282 fetal respiration, 660
aliskiren contraindication, 610 amniotic fluid abnormalities, 641 anemia caused by, 418 carpal tunnel syndrome in, 459 choriocarcinomas and, 642 contraindicated antimicrobials, 204 ESR in, 214 estrogen in, 630 ethical situations, 268–269 fetal circulation, 282 fetal respiration, 660 folate deficiency caused by, 420
aliskiren contraindication, 610 amniotic fluid abnormalities, 641 anemia caused by, 418 carpal tunnel syndrome in, 459 choriocarcinomas and, 642 contraindicated antimicrobials, 204 ESR in, 214 estrogen in, 630 ethical situations, 268–269 fetal circulation, 282 fetal respiration, 660 folate deficiency caused by, 420 folic acid supplementation, 68
aliskiren contraindication, 610 amniotic fluid abnormalities, 641 anemia caused by, 418 carpal tunnel syndrome in, 459 choriocarcinomas and, 642 contraindicated antimicrobials, 204 ESR in, 214 estrogen in, 630 ethical situations, 268–269 fetal circulation, 282 fetal respiration, 660 folate deficiency caused by, 420 folic acid supplementation, 68 heparin in, 436
aliskiren contraindication, 610 amniotic fluid abnormalities, 641 anemia caused by, 418 carpal tunnel syndrome in, 459 choriocarcinomas and, 642 contraindicated antimicrobials, 204 ESR in, 214 estrogen in, 630 ethical situations, 268–269 fetal circulation, 282 fetal respiration, 660 folate deficiency caused by, 420 folic acid supplementation, 68 heparin in, 436 hypertension and treatment in,
aliskiren contraindication, 610 amniotic fluid abnormalities, 641 anemia caused by, 418 carpal tunnel syndrome in, 459 choriocarcinomas and, 642 contraindicated antimicrobials, 204 ESR in, 214 estrogen in, 630 ethical situations, 268–269 fetal circulation, 282 fetal respiration, 660 folate deficiency caused by, 420 folic acid supplementation, 68 heparin in, 436 hypertension and treatment in, 243, 316, 643
aliskiren contraindication, 610 amniotic fluid abnormalities, 641 anemia caused by, 418 carpal tunnel syndrome in, 459 choriocarcinomas and, 642 contraindicated antimicrobials, 204 ESR in, 214 estrogen in, 630 ethical situations, 268–269 fetal circulation, 282 fetal respiration, 660 folate deficiency caused by, 420 folic acid supplementation, 68 heparin in, 436 hypertension and treatment in, 243, 316, 643 hypothyroidism in, 341
aliskiren contraindication, 610 amniotic fluid abnormalities, 641 anemia caused by, 418 carpal tunnel syndrome in, 459 choriocarcinomas and, 642 contraindicated antimicrobials, 204 ESR in, 214 estrogen in, 630 ethical situations, 268–269 fetal circulation, 282 fetal respiration, 660 folate deficiency caused by, 420 folic acid supplementation, 68 heparin in, 436 hypertension and treatment in, 243, 316, 643 hypothyroidism in, 341
aliskiren contraindication, 610 amniotic fluid abnormalities, 641 anemia caused by, 418 carpal tunnel syndrome in, 459 choriocarcinomas and, 642 contraindicated antimicrobials, 204 ESR in, 214 estrogen in, 630 ethical situations, 268–269 fetal circulation, 282 fetal respiration, 660 folate deficiency caused by, 420 folic acid supplementation, 68 heparin in, 436 hypertension and treatment in, 243, 316, 643 hypothyroidism in, 341 insulin in, 334 Listeria monocytogenes in, 139
aliskiren contraindication, 610 amniotic fluid abnormalities, 641 anemia caused by, 418 carpal tunnel syndrome in, 459 choriocarcinomas and, 642 contraindicated antimicrobials, 204 ESR in, 214 estrogen in, 630 ethical situations, 268–269 fetal circulation, 282 fetal respiration, 660 folate deficiency caused by, 420 folic acid supplementation, 68 heparin in, 436 hypertension and treatment in, 243, 316, 643 hypothyroidism in, 341 insulin in, 334 Listeria monocytogenes in, 139
aliskiren contraindication, 610 amniotic fluid abnormalities, 641 anemia caused by, 418 carpal tunnel syndrome in, 459 choriocarcinomas and, 642 contraindicated antimicrobials, 204 ESR in, 214 estrogen in, 630 ethical situations, 268–269 fetal circulation, 282 fetal respiration, 660 folate deficiency caused by, 420 folic acid supplementation, 68 heparin in, 436 hypertension and treatment in, 243, 316, 643 hypothyroidism in, 341 insulin in, 334 Listeria monocytogenes in, 139 lithium in, 298, 300
aliskiren contraindication, 610 amniotic fluid abnormalities, 641 anemia caused by, 418 carpal tunnel syndrome in, 459 choriocarcinomas and, 642 contraindicated antimicrobials, 204 ESR in, 214 estrogen in, 630 ethical situations, 268–269 fetal circulation, 282 fetal respiration, 660 folate deficiency caused by, 420 folic acid supplementation, 68 heparin in, 436 hypertension and treatment in, 243, 316, 643 hypothyroidism in, 341 insulin in, 334 Listeria monocytogenes in, 139 lithium in, 298, 300 maternal complications, 272
aliskiren contraindication, 610 amniotic fluid abnormalities, 641 anemia caused by, 418 carpal tunnel syndrome in, 459 choriocarcinomas and, 642 contraindicated antimicrobials, 204 ESR in, 214 estrogen in, 630 ethical situations, 268–269 fetal circulation, 282 fetal respiration, 660 folate deficiency caused by, 420 folic acid supplementation, 68 heparin in, 436 hypertension and treatment in, 243, 316, 643 hypothyroidism in, 341 insulin in, 334 Listeria monocytogenes in, 139 lithium in, 298, 300 maternal complications, 272 maternal phenylketonuria, 84
aliskiren contraindication, 610 amniotic fluid abnormalities, 641 anemia caused by, 418 carpal tunnel syndrome in, 459 choriocarcinomas and, 642 contraindicated antimicrobials, 204 ESR in, 214 estrogen in, 630 ethical situations, 268–269 fetal circulation, 282 fetal respiration, 660 folate deficiency caused by, 420 folic acid supplementation, 68 heparin in, 436 hypertension and treatment in, 243, 316, 643 hypothyroidism in, 341 insulin in, 334 Listeria monocytogenes in, 139 lithium in, 298, 300 maternal complications, 272 maternal phenylketonuria, 84 opiate use during, 615
aliskiren contraindication, 610 amniotic fluid abnormalities, 641 anemia caused by, 418 carpal tunnel syndrome in, 459 choriocarcinomas and, 642 contraindicated antimicrobials, 204 ESR in, 214 estrogen in, 630 ethical situations, 268–269 fetal circulation, 282 fetal respiration, 660 folate deficiency caused by, 420 folic acid supplementation, 68 heparin in, 436 hypertension and treatment in, 243, 316, 643 hypothyroidism in, 341 insulin in, 334 Listeria monocytogenes in, 139 lithium in, 298, 300 maternal complications, 272 maternal phenylketonuria, 84 opiate use during, 615 parental consent and, 265
aliskiren contraindication, 610 amniotic fluid abnormalities, 641 anemia caused by, 418 carpal tunnel syndrome in, 459 choriocarcinomas and, 642 contraindicated antimicrobials, 204 ESR in, 214 estrogen in, 630 ethical situations, 268–269 fetal circulation, 282 fetal respiration, 660 folate deficiency caused by, 420 folic acid supplementation, 68 heparin in, 436 hypertension and treatment in, 243, 316, 643 hypothyroidism in, 341 insulin in, 334 Listeria monocytogenes in, 139 lithium in, 298, 300 maternal complications, 272 maternal phenylketonuria, 84 opiate use during, 615 parental consent and, 265 physiologic adaptations in, <b>633</b>
aliskiren contraindication, 610 amniotic fluid abnormalities, 641 anemia caused by, 418 carpal tunnel syndrome in, 459 choriocarcinomas and, 642 contraindicated antimicrobials, 204 ESR in, 214 estrogen in, 630 ethical situations, 268–269 fetal circulation, 282 fetal respiration, 660 folate deficiency caused by, 420 folic acid supplementation, 68 heparin in, 436 hypertension and treatment in, 243, 316, 643 hypothyroidism in, 341 insulin in, 334 Listeria monocytogenes in, 139 lithium in, 298, 300 maternal complications, 272 maternal phenylketonuria, 84 opiate use during, 615 parental consent and, 265 physiologic adaptations in, 633 pituitary infarcts with, 339
aliskiren contraindication, 610 amniotic fluid abnormalities, 641 anemia caused by, 418 carpal tunnel syndrome in, 459 choriocarcinomas and, 642 contraindicated antimicrobials, 204 ESR in, 214 estrogen in, 630 ethical situations, 268–269 fetal circulation, 282 fetal respiration, 660 folate deficiency caused by, 420 folic acid supplementation, 68 heparin in, 436 hypertension and treatment in, 243, 316, 643 hypothyroidism in, 341 insulin in, 334 Listeria monocytogenes in, 139 lithium in, 298, 300 maternal complications, 272 maternal phenylketonuria, 84 opiate use during, 615 parental consent and, 265 physiologic adaptations in, 633 pituitary infarcts with, 339 posterior urethral valve diagnosis,
aliskiren contraindication, 610 amniotic fluid abnormalities, 641 anemia caused by, 418 carpal tunnel syndrome in, 459 choriocarcinomas and, 642 contraindicated antimicrobials, 204 ESR in, 214 estrogen in, 630 ethical situations, 268–269 fetal circulation, 282 fetal respiration, 660 folate deficiency caused by, 420 folic acid supplementation, 68 heparin in, 436 hypertension and treatment in, 243, 316, 643 hypothyroidism in, 341 insulin in, 334 Listeria monocytogenes in, 139 lithium in, 298, 300 maternal complications, 272 maternal phenylketonuria, 84 opiate use during, 615 parental consent and, 265 physiologic adaptations in, 633 pituitary infarcts with, 339 posterior urethral valve diagnosis, 579
aliskiren contraindication, 610 amniotic fluid abnormalities, 641 anemia caused by, 418 carpal tunnel syndrome in, 459 choriocarcinomas and, 642 contraindicated antimicrobials, 204 ESR in, 214 estrogen in, 630 ethical situations, 268–269 fetal circulation, 282 fetal respiration, 660 folate deficiency caused by, 420 folic acid supplementation, 68 heparin in, 436 hypertension and treatment in, 243, 316, 643 hypothyroidism in, 341 insulin in, 334 Listeria monocytogenes in, 139 lithium in, 298, 300 maternal complications, 272 maternal phenylketonuria, 84 opiate use during, 615 parental consent and, 265 physiologic adaptations in, 633 pituitary infarcts with, 339 posterior urethral valve diagnosis, 579 progesterone in, 630
aliskiren contraindication, 610 amniotic fluid abnormalities, 641 anemia caused by, 418 carpal tunnel syndrome in, 459 choriocarcinomas and, 642 contraindicated antimicrobials, 204 ESR in, 214 estrogen in, 630 ethical situations, 268–269 fetal circulation, 282 fetal respiration, 660 folate deficiency caused by, 420 folic acid supplementation, 68 heparin in, 436 hypertension and treatment in, 243, 316, 643 hypothyroidism in, 341 insulin in, 334 Listeria monocytogenes in, 139 lithium in, 298, 300 maternal complications, 272 maternal phenylketonuria, 84 opiate use during, 615 parental consent and, 265 physiologic adaptations in, 633 pituitary infarcts with, 339 posterior urethral valve diagnosis, 579 progesterone in, 630 prolactin and, 330
aliskiren contraindication, 610 amniotic fluid abnormalities, 641 anemia caused by, 418 carpal tunnel syndrome in, 459 choriocarcinomas and, 642 contraindicated antimicrobials, 204 ESR in, 214 estrogen in, 630 ethical situations, 268–269 fetal circulation, 282 fetal respiration, 660 folate deficiency caused by, 420 folic acid supplementation, 68 heparin in, 436 hypertension and treatment in, 243, 316, 643 hypothyroidism in, 341 insulin in, 334 Listeria monocytogenes in, 139 lithium in, 298, 300 maternal complications, 272 maternal phenylketonuria, 84 opiate use during, 615 parental consent and, 265 physiologic adaptations in, 633 pituitary infarcts with, 339 posterior urethral valve diagnosis, 579 progesterone in, 630 prolactin and, 330 pyelonephritis, 600
aliskiren contraindication, 610 amniotic fluid abnormalities, 641 anemia caused by, 418 carpal tunnel syndrome in, 459 choriocarcinomas and, 642 contraindicated antimicrobials, 204 ESR in, 214 estrogen in, 630 ethical situations, 268–269 fetal circulation, 282 fetal respiration, 660 folate deficiency caused by, 420 folic acid supplementation, 68 heparin in, 436 hypertension and treatment in, 243, 316, 643 hypothyroidism in, 341 insulin in, 334 Listeria monocytogenes in, 139 lithium in, 298, 300 maternal complications, 272 maternal phenylketonuria, 84 opiate use during, 615 parental consent and, 265 physiologic adaptations in, 633 pituitary infarcts with, 339 posterior urethral valve diagnosis, 579 progesterone in, 630 pyelonephritis, 600 pyogenic granulomas and, 478
aliskiren contraindication, 610 amniotic fluid abnormalities, 641 anemia caused by, 418 carpal tunnel syndrome in, 459 choriocarcinomas and, 642 contraindicated antimicrobials, 204 ESR in, 214 estrogen in, 630 ethical situations, 268–269 fetal circulation, 282 fetal respiration, 660 folate deficiency caused by, 420 folic acid supplementation, 68 heparin in, 436 hypertension and treatment in, 243, 316, 643 hypothyroidism in, 341 insulin in, 334 Listeria monocytogenes in, 139 lithium in, 298, 300 maternal complications, 272 maternal phenylketonuria, 84 opiate use during, 615 parental consent and, 265 physiologic adaptations in, 633 pituitary infarcts with, 339 posterior urethral valve diagnosis, 579 progesterone in, 630 prolactin and, 330 pyelonephritis, 600

stillbirth, 182
Streptococcus agalactiae in, 137
syphilis in, 147 TBG in, 331
termination of, 657
TORCH infections, 182
Turner syndrome and, 638 twinning in, 616
urinary tract infections, 181
venous sinus thrombosis in, 503 vitamin B <sub>9</sub> deficiency, 68
Pregnancy complications, <b>640–641</b>
Prehn sign, 654
Preload in cardiac output, 284 Premature ejaculation, 575
Premature labor and delivery
cryptorchidism and, 651 low birth weight with, 635
murmur in prematurity, 291
Premature ovarian failure, 636, 645 Premotor cortex, 501
Preoptic nucleus, 498
Prepatellar bursitis, 460
Preprocollagen, 51 Preproinsulin, 334
Prerenal azotemia, 601
Presbycusis, 270, 533 Presbyopia, <b>535</b>
Preschool age development, 635
Presenilin, 520
Pressure-volume loops, <b>287</b> Presynaptic α2-autoreceptor, 239
Pretectal nuclei, 539
Preterm birth common cause of death, 272
Pretest probability, 257
Prevalence diagnostic test evaluation, 257
incidence vs, <b>259</b>
observational studies, 256
Prevotella spp, 179 Priapism, 651
sickle cell anemia, 422
trazodone and, 576 Primaquine, 157
hemolysis in G6PD deficiency, 250
Primary adrenal insufficiency, 349 Primary amyloidosis, 212
Primary bacterial peritonitis, 390
Primary biliary cholangitis, 395
Primary central nervous system lymphoma, 430
Primary ciliary dyskinesia, 49
Primary disease prevention, 270 Primary glomerular disease, 594
Primary hemostasis, 411
Primary hyperaldosteronism, 349 hypertension with, 300
markers in, 591
Primary hyperparathyroidism, 345,
464 Primary hypertension, 316
Primary hypogonadism, 639
Primary ovarian insufficiency, <b>645</b> Primary polycythemia, 433
Primary sclerosing cholangitis, 395
ulcerative colitis, 382
Primary spontaneous pneumothorax, 682
Primase
replication initiation by, 38
FIIIIIIdolle, 519
Primidone, 519 Primitive atrium, 281
Primitive atrium, 281 Primitive pulmonary vein, 281 Primitive reflexes, <b>510</b>

D 201
Primitive ventricle, 281 Pringle maneuver, 361
PR interval, 293, 295
antiarrhythmic effects, 323, 324
prolonged, 295
shortened, 294 Prinzmetal angina
calcium channel blockers for, 318
ischemic manifestations, 304
propranolol adverse effects, 323
Prions, <b>178</b> Privacy and confidentiality, 267
Probenecid, 252
cidofovir with, 202
gout, 487
Procainamide, 322 Procaine, 550
Procarbazine, 251, <b>441</b>
Procedure bias, 260
Process improvement model, 273
quality measurement, 273 Processus vaginalis, 624
Procoagulation, 413
Progesterone
lactation and, 636
menstrual cycle, 632 ovulation, 632
signaling pathways for, 337
source and function of, 630
Progestins, <b>657</b> Progressive multifocal
leukoencephalopathy
(PML), 494, <b>524</b>
HIV-positive adults, 177
polyomaviruses, 164 rituximab, 443
Proguanil, 200
Projection, 555
Prokaryotes
DNA replication in, 38 mRNA start codons, 44
RNA polymerases in, 42
Prolactin, 330
circadian rhythm, 497
function of, 328 lactation and, 636
secretion of, 327
signaling pathways for, 337
tuberoinfundibular pathway, 499
Prolactin-inhibiting factor, 328 Prolactinomas
dopamine agonists for, 330
Proliferative glomerular disorders,
594 D
Prometaphase, 46 Promoters (gene expression), 41
Promyelocytic leukemia, 66
Pronephros, 578
Proopiomelanocortin, 327
Propafenone, 322 Proper hepatic artery, 361
Prophase, 46
Prophylaxis
antimicrobial, 197, 198
antimycobacterial drugs for, 196 HIV/AIDS patients, <b>198</b>
in HIV/AIDS patients, 198
Pneumocystis jirovecii, 154
rabies postexposure, 171 for RSV, 169
Trichomonas vaginalis, 158
Propionyl-CoA carboxylase
metabolic pathways, 74
vitamin B <sub>7</sub> and, 68 Propofol, 550
- 10P0101, //0

Propranolol, 245, 323, 342
essential tremor, 519
Proprioception Friedreich ataxia, 531
Propylthiouracil
agranulocytosis, 250
aplastic anemia, 250 thionamides, 354
for thyroid storm, 342
Prostacyclin analogues, 686 Prostaglandin analogs, 254
Prostaglandins
aspirin effects, 486
cortisol effect on, 336 glaucoma treatment, 552
kidney functions, 589
Prostate cancer adenocarcinomas, <b>654</b>
incidence/mortality of, 222
leuprolide for, 656
metastases of, 223 Prostate gland
lymphatic drainage of, 624
with urethral injury, 627
Prostate-specific antigen (PSA), 227, 654
Prostatic acid phosphatase (PAP), 654
Prostatic adenocarcinoma, 654 Prostatitis, <b>654</b>
gonorrhea, 184
Prosthetic devices
Staphylococcus epidermidis, 135 Prosthetic heart valves, 423
Protamine sulfate, 248, 436
Protease inhibitors
fat redistribution, 250 HIV therapy, 203
hyperglycemia, 249
naming convention for, 253 Proteases, 373
Proteasome, <b>48</b>
Protein A, 129
Proteinases, 406 Protein C/S deficiency, 428
Protein-energy malnutrition, 71
Protein kinase A fructose bisphosphatase-2 and, 76
Protein metabolism
amino acids, 81
Proteins free radical effect on, 210
Protein synthesis
elongation, 45 inhibitors, <b>191</b> , 253
initiation of, 44, <b>45</b>
insulin and, 334
metabolic site, 72 posttranslational modification, 45
sequence of, 45
termination, 45
trimming, 45 Proteinuria
ACE inhibitors for, 610
angiotensin II receptor blockers, 610
diabetes mellitus, 346
nephritic syndrome, 595
nephrotic syndrome, 595, 597 preeclampsia, 643
renal papillary necrosis and, 602
serum sickness, 113 Proteolysis
cortisol and, 336
Proteolytic processing, in collagen
synthesis, 50

FAS1\_2019\_21\_Index\_749-806.indd 790 11/21/19 12:27 PM

Proteus spp	vancomycin for, 190	Pterygoid muscles, 507	Punishment, 554
struvite stones with, 127	watery diarrhea, 179	PTH-related peptide (PTHrP), 332	Pupil
urease-positive, 127	Pseudomembranous pharyngitis	PTHrP (parathyroid hormone-related	Argyll Robertson, 147
xanthogranulomatous	diphtheria, 139	protein), 228	CN III palsy, 541
pyelonephritis, 600 Proteus mirabilis	Pseudomonas spp aeruginosa, <b>143</b>	Ptosis	control, 507, <b>539</b>
cephalosporins, 189	biofilm production, 128	CN III damage, 541 Horner syndrome, 540	light reflex, 539 pupillary light reflex, 539
penicillins for, 188	ceftazidime, 189	myasthenia gravis, 472	syphilis, 147, 184
urinary tract infections, 181, 600	culture requirements for, 126	saccular aneurysm, 516	Pure motor stroke, 514
Prothrombin	cystic fibrosis, 60, 179	Puberty	Pure red cell aplasia, 228
complex concentrate transfusion,	encapsulated, 127	GnRH and, 328	thymoma and, 98
429	epididymitis and orchitis, 654	Kallmann syndrome and, 639	Purines, 194
warfarin effect on, 436	exotoxin production, 132	precocious, 57, 335	de novo synthesis, 36, 73
Prothrombin gene mutation, 428 Prothrombin time, 390	fluoroquinolones, 195 immunodeficient patients, 118	Tanner stages, 637 Pubic tubercle, 370	Lesch-Nyhan syndrome, 37
Protofilament, 48	multidrug-resistant, 198	Public health sciences, 256–273	salvage deficiencies, <b>37</b>
Proton pump inhibitors, 254, <b>399</b>	nosocomial infection, 179, 185	Pudendal nerve, 366, 453	structure of, 35 Purkinje cells
Beers criteria, 247	osteomyelitis, 180	Pulmonary anthrax, 137	cerebellum, 499
for Helicobacter pylori, 146	penicillins for, 188	Pulmonary arterial hypertension	of cerebellum, 210
gastrin and, 371	pigment production, 128	(PAH), 679	in paraneoplastic cerebellar
Protozoa	pyocyanin of, 109	Pulmonary artery, 619	degeneration, 228
CNS infections, <b>156</b>	tricuspid valve endocarditis, 311 UTIs, 181	fetal circulation, 282	Purkinje fibers, 293
GI infections, <b>155</b> hematologic infections, <b>157</b>	Pseudo-Pelger-Huet anomaly, 432	Pulmonary artery stenosis, 300 Pulmonary capillary wedge pressure	Purpura
miscellaneous, <b>158</b>	Pseudopseudohypoparathyroidism,	(PCWP), 297, 668	aplastic anemia, 421
watery diarrhea, 179	344	Pulmonary circulation, <b>668</b>	Pustular psoriasis, 475 Pustules, 475
Proximal convoluted tubules	Pseudotumor cerebri, 521	Pulmonary edema, 309	acne, 477
(PCT)	drug reactions and, 251	consolidation in, 680	pseudofolliculitis barbae, 477
in ATN, 602	vitamin A toxicity, 66	LV failure, 307	rosacea, 477
defects in, 586	Pseudovirion, 162	mannitol, 607	Putamen, 500
diuretics and, 609	Psittacosis, 149 Psoriasis, 477	nitrates for, 318 opioids for, 551	neurodegenerative disorders, 520
dopamine secretion by, 589 glucose clearance and, 584	arthritis and, 469	preeclampsia and, 643	Pyelonephritis, <b>600</b>
ischemia susceptibility, 210	cyclosporine, 120	Pulmonary embolism, <b>672</b>	kidney stones, 598
relative concentrations in, 587	etanercept for, 487	chronic thromboembolism, 679	urinary tract infections, 181, 600
renal cell carcinoma and, 605	hyperkeratosis/parakeratosis, 475	direct factor Xa inhibitors for,	WBC casts in, 594 Pygmalion effect, 260
Proximal interphalangeal (PIP) joints,	infliximab/adalimumab for, 487	437	Pyloric sphincter, 373
451	methotrexate for, 440	heparin for, 436	Pyloric stenosis, 359
Proximal renal tubular acidosis	skin lesions, 475	tamoxifen/raloxifene and, 443	Pyloromyotomy, 359
(type 2), 593 PRPP (glutamine-phosphoribosyl-	therapeutic antibodies, 122 Psoriatic arthritis, 469	thrombolytics for, 437 ventilation/perfusion with, 669	Pyoderma gangrenosum
pyrophosphate)	HLA-B27 and, 100	Pulmonary fibrosis	inflammatory bowel disease, 382
amidotransferase, 73	leflunomide for, 486	amiodarone and, 323	Pyogenic granulomas, 478
Pruritus	psoriasis and, 477	bleomycin, 439	Pyramidal cells, 210
anal, 159	Psychiatric emergencies	busulfan, 441	Pyramidalis muscle, 369 Pyramidal tract demyelination,
atopic dermatitis, 477	acute dystonia, 569	diffusion in, 668	multiple sclerosis, 523
biliary tract disease, 395	delirium tremens, 569	drug reaction and, 251	Pyrantel pamoate, 200
chloroquine, 200 cutaneous mycoses, 152	hypertensive crisis, 569 lithium toxicity, <b>569</b>	methotrexate, 440 restrictive lung disease, 675	Pyrazinamide, <b>197</b>
ectoparasites, 161	neuroleptic malignant syndrome,	Pulmonary hypertension, <b>679</b>	gout, 250
histamine receptors and, 238	569	cor pulmonale, 668	hepatitis, 249
hyperchylomicronemia, 94	serotonin syndrome, 569	drug therapy, <b>686</b>	Mycobacterium tuberculosis, 196
lichen planus, 482	tricyclic antidepressant overdose,	Schistosoma, 160	Pyridostigmine, 240
pseudofolliculitis barbae, 477	569	Pulmonary hypoplasia, 660	myasthenia gravis treatment, 472 Pyridoxal phosphate, 67
urticaria, 477	Psychiatry, 554–576	Pulmonary infections	Pyridoxine, 67
Prussian blue stain, 677 Psammoma bodies, 211, <b>227</b>	pathology, 556–570 pharmacology, 572–576	in immunocompromised patients, 139	Pyrimethamine, 200
mesotheliomas, 678	psychology, 554–555	Pulmonary Langerhans cell	effect on purine synthesis, 36
papillary thyroid carcinoma, 343	Psychoactive drug intoxication/	histiocytosis, 675	Pyrimidine dimers, 40
Pseudoappendicitis	withdrawal, <b>570–571</b>	Pulmonary surfactant	Pyrimidines
Yersinia enterocolitica, 144	Psychological child abuse, 556	club cells, 660, 661	de novo synthesis, 36
Pseudocysts, 397	Psychology, 554–555	NRDS, 661	structure of, 35
Pseudoephedrine, <b>686</b>	Psychosis, <b>559</b>	Pulmonary vascular resistance (PVR),	Pyrimidine synthesis, 486 Pyruvate carboxylase, 77, 78
Pseudofolliculitis barbae, 477 Pseudofractures, 463	corticosteroids, 120 diabetic ketoacidosis, 347	<b>668</b> Pulmonic stenosis	metabolic pathways, 74
Pseudoglandular stage	drug therapy for, 573	wide splitting in, 289	vitamin B <sub>7</sub> and, 68
(development), 660	LSD and, 571	Pulmonic valves, 281	Pyruvate dehydrogenase
Pseudogout, 467	major depressive disorder with, 561	"Pulseless disease," 314	complex, <b>76</b>
Pseudoĥermaphrodites, 639	PCP and, 571	Pulse pressure	deficiency, 77
Pseudohypoparathyroidism, 344	postpartum, 562	equation for, 285	metabolic pathways, 74
Pseudomembranous colitis	Psychotherapy, <b>572</b>	Pulsus paradoxus, 310	vitamin B <sub>1</sub> and, 66
clindamycin, 192 Clostridium difficile, 138	oppositional defiant disorder, 557 Psychotic disorders	croup, 170 "Punched out" bone lesions (X-ray),	Pyruvate kinase, 74 deficiency, 422
drug reaction and, 249	readmissions with, 272	431	Pyruvate metabolism, <b>77</b>
penicillins, 188	PTEN gene, 224	Punched-out ulcers, 377	Pyuria, 601
	=		

FAS1\_2019\_21\_Index\_749-806.indd 791 11/21/19 12:27 PM

INDEX

Q	Rapidly progressive	Red cell casts, 315	recombinant cytokines, 121
Q fever	glomerulonephritis	Red-green color blindness, 197	therapeutic antibodies, 122
	(RPGN), 596	Red hemorrhagic infarct, 210	Renal clearance, <b>582</b>
rickettsial disease, 150	Rasagiline, <b>549</b>	Red hepatization, 683	Renal cortex
transmission, 149			
QRS complex, 293	Rasburicase, <b>444</b>	Red nucleus (midbrain), 511–552	atrophy of, 599
QT interval	RAS gene, 343	Redox reactions	Renal disorders/failure
atypical antipsychotic effect on, 573	Rashes	free radical injury and, 210	consequences of, <b>603</b>
Class IA antiarrhythmic effects, 322	"blueberry muffin," 169	vitamin B <sub>2</sub> and, 67	diabetes mellitus, 346
	carbapenems, 190	Red pulp (spleen), 98	diffuse cortical necrosis, 602
congenital long QT syndrome, 294	childhood, 183	Red rashes of childhood, <b>183</b>	ESR in, 214
drug-induced long, 294	cytomegalovirus, 182	Reduced filling (cardiac cycle), 287	Fabry disease, 88
ECG, 293	desquamating, 314	Redundant/degenerate genetic code,	features of, 591
ondansetron effect on, 400		redundant/degenerate genetic code,	_ 1
in torsades de pointes, 294	fluoroquinolones, 195	2/ D 10: 1 11 420	gout and, 467
Quadrantanopia, 542	heliotrope, 228	Reed-Sternberg cells, 429	in utero, 578
Quadriceps, 452	macrolides, 193	Refeeding syndrome, anorexia	markers for, 591
Quality measurements, <b>273</b>	palms and soles, 150	nervosa, 567	myoclonus in, 519
Quality measurements, 273	penicillinase-sensitive penicillins,	Referred pain	NSAIDs, 589
Quantifying risk, 258	188	cholecystitis, 396	preeclampsia and, 643
Quaternary amines, 204	rickettsial infections, 150	from diaphragm, 663	renal cyst disorders, <b>604</b>
Quaternary disease prevention, 270	rubella, 169, 182	Reflex bradycardia, 588	tetracycline use in, 192
Quetiapine, 573			
Quiescent (stable) cells, 46	syphilis, 147, 184	Reflexes	waxy casts in, 594
Quinidine, 157, 200, 322	unvaccinated children, 186	clinical, 510	Wilson disease, 395
cinchonism, 251	Rathke pouch, 327, 528	cranial nerve, 507	Renal/genitourinary drug reactions,
	tumor, 613	motor neuron sign, 529	251
Quinine, 200	Rationalization, 555	primitive, 510	Renal hypoxia, 666
Quinolone	Raynaud phenomenon, <b>472</b>	Reflex tachycardia, 244	Renal ischemia, 486
Legionella pneumophila, 143	Buerger disease, 314	Refractive errors (vision), <b>535</b>	Renal medulla
Quinupristin, 198	calcium channel blockers for, 318	Refractory hypertension, 658	hydronephrosis, 599
R	scleroderma and, 473	Refsum disease, 47	Renal oncocytoma, 605
Rabies, <b>171</b>	Razor bumps, 477	Refusing care	Renal osteodystrophy, 345, <b>603</b>
active and passive immunity, 110	RBC casts (urine), 594	minors, 269	Renal papillary necrosis, 602
	RBC inclusions, 416–444	Regadenoson, 304	pyelonephritis and, 600
rhabdovirus, 167	RBC morphology (pathologic), 414	Regan-Lowe medium, 126	sickle cell anemia, 422
viral receptors, 166	Rb gene, 224	Regional specification (brain), 490	Renal plasma flow, 582
Rachischisis, 491	Reabsorption/secretion rate	Registering for exam, 5–6	glomerular dynamics and, 583
Rachitic rosary, 463	calculation, 584	Regression, 555	Renal sympathetic discharge, 588
Radial head subluxation, 461	Reaction formation, 555	Regulation of cell cycle	
Radial nerve, 447			Renal toxicity
neurovascular pairing, 455	Reactive arthritis, 469	Cyclin-dependent kinases (CDKs),	ganciclovir, 202
Radiation exposure	Campylobacter jejuni, 145	46	Renal tubular acidosis (RTA), <b>593</b>
	chlamydia, 148, 184	p53, 46	Renal tubular defects, 585, <b>586</b>
acute myelogenous leukemia and,	HLA-B27 and, 100	Tumor suppressors, 46	Renal vascular smooth muscle, 238
432	Reactive attachment disorder, 556	Regulation of gene expression, 41	Renin, 588
aplastic anemia, 421	Readmission recurrences, 272	Regulatory T cells, <b>102</b>	ACE inhibitor effect on, 610
apoptosis caused by, 208	Reassortment (viral), 162	cell surface proteins, 110	aliskiren effect on, 610
as carcinogen, 225	Recall bias in studies, 260	Regurgitation	in hyperaldosteronism, 349
free radical injury caused by, 210			
hypopituitarism, 339	Receiving operating characteristic	in GERD, 377	renal disorders and, 591
Radiation therapy	curve, <b>260</b>	Reheated rice syndrome, 138	sympathetic receptors and, 238
	Receptor binding, 234	Reichert cartilage, 620	Renin-angiotensin-aldosterone
acute pericarditis and, 313	Receptor fusion proteins	Reid index, 674	system, 327, 588
angiosarcomas, 478	naming conventions for, 254	Reinforcement, 554	Renovascular disease, <b>604</b>
lymphopenia, 424	Receptor-mediated endocytosis, 47	Relapse stage, substance addiction, 568	Renovascular hypertension, 349
neutropenia, 424	Receptors (viral), 166	Relapsing fever	Reoviruses
osteosarcoma and, 465	Receptor tyrosine kinase	animal transmission, 149	characteristics, 167
pancreatic cancer, 398	hormone messenger, 337	lice, 161	genome, 163
papillary thyroid carcinoma risk,	as oncogene product, 224	Relationship with patients, 268	naked viruses, 163
343	Recessive inheritance, 59	Relative risk reduction (RRR), 258	segmented, 168
readmissions with, 272			
	Recklinghausen disease, 525	Relative risk (RR), 256, <b>258</b> , 263	Repaglinide, 353
Radiculopathy	Recombinant cytokines, 121	Reliability, 259	Reperfusion injury, 210
lumbosacral, 455	Recombination (viral), 162	Remodeling (tissue), 216	Reperfusion therapy, 307
Radon	Recruiting study participants, 260	REM sleep, 497	Replication fork, 38
as carcinogen, 225	Rectal sparing, 382	Renal agenesis	Reportable diseases
Ragged red muscle fibers, 59	Rectosigmoid junction	bilateral, 578	confidentiality exceptions, 267
Rales, 309	blood supply to, 363	unilateral, 579	Repression, 555
Raloxifene, 443, 656	Rectum	Renal artery, 580	Repressor proteins
Raltegravir, 203	blood supply and innervation, 364	stenosis, 610	lactose effects on, 40
Ramelteon, <b>547</b>			
	familial adenomatous polyposis,	Renal blood flow (RBF), 363, 580	Reproductive/endocrine drug
Ramipril, 610	387	acute injury and, 602	reactions, 249
Ranitidine, 399			Reproductive hormones, 655
	Hirschsprung disease, 384	NSAID effects on, 589	
RANKL (RANK ligand), 332, 459		renal plasma flow and, 582	Reproductive system, 612–653
Ranolazine	Hirschsprung disease, 384		
	Hirschsprung disease, 384 ischemia susceptibility, 210	renal plasma flow and, 582	Reproductive system, 612–653
Ranolazine mechanism and clinical use, <b>319</b>	Hirschsprung disease, 384 ischemia susceptibility, 210 portosystemic anastomosis, 365 Rectus abdominis muscle, 369	renal plasma flow and, 582 Renal cell carcinoma, <b>605</b> bevacizumab for, 442	Reproductive system, 612–653 anatomy, 624–627 embryology, 612–623
Ranolazine mechanism and clinical use, <b>319</b> Raphe nucleus, 495	Hirschsprung disease, 384 ischemia susceptibility, 210 portosystemic anastomosis, 365 Rectus abdominis muscle, 369 Recurrent branch (median nerve),	renal plasma flow and, 582 Renal cell carcinoma, <b>605</b> bevacizumab for, 442 carcinogens for, 225	Reproductive system, 612–653 anatomy, 624–627 embryology, 612–623 pathology, 638–652
Ranolazine mechanism and clinical use, <b>319</b> Raphe nucleus, 495 Rapid automated broth cultures, 126	Hirschsprung disease, 384 ischemia susceptibility, 210 portosystemic anastomosis, 365 Rectus abdominis muscle, 369 Recurrent branch (median nerve), 447	renal plasma flow and, 582 Renal cell carcinoma, <b>605</b> bevacizumab for, 442 carcinogens for, 225 chromosome association, 64	Reproductive system, 612–653 anatomy, 624–627 embryology, 612–623 pathology, 638–652 pharmacology, 655–658
Ranolazine mechanism and clinical use, <b>319</b> Raphe nucleus, 495 Rapid automated broth cultures, 126 Rapid-eye movement (REM) sleep,	Hirschsprung disease, 384 ischemia susceptibility, 210 portosystemic anastomosis, 365 Rectus abdominis muscle, 369 Recurrent branch (median nerve), 447 Recurrent laryngeal nerve	renal plasma flow and, 582 Renal cell carcinoma, <b>605</b> bevacizumab for, 442 carcinogens for, 225 chromosome association, 64 hypercalcemia and, 228	Reproductive system, 612–653 anatomy, 624–627 embryology, 612–623 pathology, 638–652 pharmacology, 655–658 physiology, 629–636
Ranolazine mechanism and clinical use, <b>319</b> Raphe nucleus, 495 Rapid automated broth cultures, 126	Hirschsprung disease, 384 ischemia susceptibility, 210 portosystemic anastomosis, 365 Rectus abdominis muscle, 369 Recurrent branch (median nerve), 447	renal plasma flow and, 582 Renal cell carcinoma, <b>605</b> bevacizumab for, 442 carcinogens for, 225 chromosome association, 64	Reproductive system, 612–653 anatomy, 624–627 embryology, 612–623 pathology, 638–652 pharmacology, 655–658

FAS1\_2019\_21\_Index\_749-806.indd 792 11/21/19 12:27 PM

Rescheduling exam, 6	Retinal vein occlusion, 537	Ribavirin, 204	Rivastigmine, 240, 549
Reserpine	Retinitis	contraindicated in pregnancy, 204	RNA
Parkinson-like syndrome, 251	AIDS, 165	purine synthesis, 36	capping, 41
Residual volume (RV), 664	cidofovir, 202	Riboflavin, 67	interference, 56
Resistance in vessels, 286 Respiration	foscarnet, 202 Retinitis pigmentosa, <b>538</b>	Ribose, 79 Ribosomes, 46	processing (eukaryotes), <b>41</b> RNA polymerases
exercise response, 670	Retinoblastoma	Rice-water diarrhea	types and functions of, <b>42</b>
high altitude response, 670	chromosome association, 64	organisms causing, 179	RNA viruses, <b>167</b>
in diabetic acidosis, 347	heterozygosity loss, 56	Vibrio cholerae, 146	genome, <b>163</b>
Kussmaul, 347	Retinoblastomas	Richter transformation, 432 Rickets, 463	Robertsonian translocation, <b>64</b>
Respiratory acidosis, 592 Respiratory alkalosis, 592	osteosarcomas, 465 Retinoids, 477	hypophosphatemic, 591, 593	Rocker-bottom feet, 63 "Rocket tails," 139
high altitude, 670	Retinopathy	lab values in, 464	Rocky Mountain spotted fever, 150
Respiratory burst, 109	Alport syndrome, 596	vitamin D and, 70	animal transmission, 149
free radical injury and, 210	chloroquine, 200	Rickettsia	chloramphenicol, 192
Respiratory depression anesthetics, 550	diabetes mellitus, 346 hypertension, 300	Gram stain, 125 Rickettsial diseases, <b>150</b>	Romaña sign, 158 Romano-Ward syndrome, 294
barbiturates, 546, 570	of prematurity, 210, 661	Rickettsia prowazekii, 150	Romberg sign, 147, 530
benzodiazepines, 544, 570	sorbitol, 81	transmission of, 149, 161	Romiplostim (TPO analog), 121
epilepsy drugs, 544	Retrograde amnesia, 558	Rickettsia rickettsii, 150	Root cause analysis, 274
inhaled anesthetics, 550	Retroperitoneal fibrosis, 599	animal transmission, 149	Rooting reflex, 510
opioids, 551, 570 psychoactive drug intoxication, 570	Retroperitoneal structures, <b>360</b> Retrospective studies, 260	chloramphenicol, 192 <i>Rickettsia</i> spp	Ropivacaine, 550 Rosacea, 477
tricyclic antidepressants, 575	Retroviruses	intracellular organism, 127	Rose gardener's disease, 154
Respiratory drug reactions, 251	characteristics, 167	tetracyclines, 192	Rosenthal fibers, 528
Respiratory syncytial virus (RSV)	genomes, 163	Rickettsia typhi, 149, 150	Roseola
paramyxovirus, 167, 169 pneumonia, 179, 683	Rett syndrome, 61, <b>62</b>	Riedel thyroiditis, 341	HHV-6/HHV-7, 165 rash, 183
prophylaxis, 122	Reverse transcriptase, 175 Telomerase, 38	Rifabutin, 196 Rifampin, 196	Rosiglitazone, 353
Respiratory system, 660–683	Reverse transcriptase polymerase	cytochrome P-450 and, 252	Rotator cuff muscles, <b>446</b>
anatomy, 662–663	chain reaction, 52	Hansen disease, 141	Rotavirus, 168
change in elderly, <b>665</b>	Reye syndrome, <b>390</b>	hepatitis, 249	diarrhea, 167
embryology, 660 pathology, 671–681	Reynolds pentad, 397 Rhabdomyolysis	Mycobacterium leprae, 196 Mycobacterium tuberculosis, 196	Rotenone, 78 Roth spots, 311
pharmacology, 686–687	daptomycin, 195	as prophylaxis, 198	Rotor syndrome, 393, 394
physiology, 664–669	Rhabdomyomas, 316	prophylaxis with Haemophilus	Rough endoplasmic reticulum, 46
Respiratory tract infections	nomenclature for, 220	influenzae for contacts, 142	Rouleaux formation, 431
C3 deficiency, 107	Rhabdomyosarcomas	protease inhibitors and, 203	Round ligament of uterus, 625
Respiratory tree, <b>662</b> Respiratory zone, 662	dactinomycin for, 439 nomenclature for, 220	RNA polymerase inhibition, 42 Rifamycins, <b>196</b>	Rovsing sign, 383 Rubella, <b>169</b>
Resting tremor, 519	variant, 644	Rifaximin, 391	cardiac defect association, 300
Restless legs syndrome, 519	Rhabdoviruses	Rift Valley fever, 167	cataracts, 535
Restricting type of anorexia nervosa,	characteristics, 167	Right anterior cardinal vein, 281	heart murmur with, 291
567 Restrictive cardiomyopathy, 308	negative-stranded, 168 Rhagades, 147	Right bundle branch, 293 Right bundle branch block, 289	rash, 183 TORCH infection, 182
hemochromatosis, 395	Rh blood classification, 405	Right common cardinal vein, 281	unvaccinated children, 186
Restrictive lung diseases, 675	newborn hemolysis, 405	Right coronary artery (RCA)	Rubeola (measles) virus, 170
ankylosing spondylitis, 469	Rheumatic fever, <b>312</b>	coronary circulation, 283	Ruffini corpuscles, 494
flow volume loops, 673	chorea with, 519 heart murmur with, 291	occlusions of, 305	Ryanodine receptor, 456 RYR1 gene, 550
sarcoidosis, 6/6 Reteplase (rPA), 437	myocarditis with, 313	Right heart failure, 309 Right horn of sinus venosus, 281	KIKI gene, 770
Rete testis, 652	Streptococcus pyogenes, 136	Right lower quadrant (RLQ) pain, 384	S
RET gene, 224	streptolysin O, 133	Right marginal artery, 283	S-100, 227
carcinoma risks with, 343	type II hypersensitivity, 112	Right-to-left shunts, 298 Right upper quadrant (RUQ) pain, 397	Saber shins
Hirschsprung disease, 384 Reticular activating system, 511	Rheumatoid arthritis, 457, 466 autoantibody, 115	Right ventricular hypertrophy (RVH)	congenital syphilis, 147 syphilis, 182
Reticular fibrous framework (spleen),	azathioprine for, 440	high altitude, 670	Sabin poliovirus vaccine, 167
98	carpal tunnel syndrome and,	pulmonary hypertension, 679	Sabouraud agar, 126
Reticulate bodies, 148	459	Riluzole, 549	Saccular aneurysms, 516
Reticulin, 50 Reticulocyte index (RI), <b>417</b>	celecoxib for, 486 etanercept for, 487	Ringed sideroblasts, 416 ring-enhancing lesions (MRI)	Ehlers-Danlos syndrome, 51 renal cyst disorders and, 604
Reticulocytes, 407	HLA-DR4 and, 100	Toxoplasma gondii, 156	Saccular (development stage), 660
in aplastic anemia, 421	immunosuppressants, 120	Ringworm	Sacrococcygeal teratomas, 652
intravascular hemolysis, 421	infliximab/adalimumab for, 487	griseofulvin, 200	Sacubitril
Retina chronic hyperglycemia, 537	leflunomide for, 486 methotrexate for, 440	tinea corporis, 152 Risedronate, 486	mechanism and clinical use, <b>319</b> Saddle embolus, 672
embryologic derivation of, 613	rituximab for, 443	Risk assessment, 258	Saddle nose
Retinal hemorrhage	Rheumatoid factor, 115	Risk quantification, 258	syphilis, 182
hypertensive emergency, 300	Rhinitis	Risperidone, 573	Safety culture, <b>273</b>
Retinal pathology degeneration, 536	phenylephrine for, 242	Ristocetin, 411	Salicylates toxicity treatment for, 248
degeneration, 550 detachment, <b>537</b>	Rhinophyma, 477 Rhinosinusitis, <b>671</b>	risus sardonicus tetanospasmin, 138	as weak acids, 233
hemorrhage, 537	Rhinovirus	Ritonavir	Salivary gland tumors, <b>376</b>
retinitis, 536	picornavirus, 167, <b>168</b>	HIV therapy, 203	Salivary stimulation, 240
vein occlusion, <b>537</b>	receptors for, 166	Rituximab, 122, <b>443</b>	Salmeterol, 242, 687
visual field defects, 542	Rhizopus spp, 153	Rivaroxaban, 437	Salmonella, 118

FAS1\_2019\_21\_Index\_749-806.indd 793 11/21/19 12:27 PM

794 INDEX

Salmonella spp animal transmission, 149 bloody diarrhea, 179 encapsulated bacteria, 127 food poisoning, 178 intracellular organism, 127 Shigella spp vs, **144** osteomyelitis, 180 penicillins for, 188 reactive arthritis, 469 TMP-SMX for, 194 Salmonella typhi, 144 Salpingitis ectopic pregnancy and, 641 Sampling bias, 260 "sand"(orange) in diaper, 37 Sandflies (disease vectors), 158 Sandfly fever, 167 SA node, 292 Saponification, 209 Saprophyticus urease-positive, 127 Saguinavir, 203 Sarcoidosis erythema nodosum, 482 restrictive lung disease, 676 Sarcoma botryoides, 644 Sarcomas metastases of, 223 methotrexate for, 440 nomenclature of, 220 Sarcoplasmic reticulum, 456 Sargramostim (GM-CSF), 121 SARS (sudden acute respiratory syndrome), 167 Satiety/hunger regulation, 498 Saturday night palsy, 447 "Saw-tooth" crypt pattern, 387 Saxagliptin, 353 SBLA cancer syndrome, 224 Scabies, 161, 200 Scalded skin syndrome Staphylococcus aureus, 135 toxic shock syndrome toxin, 133 Scales (skin), 475 basal cell carcinoma, 484 pityriasis rosea, 482 psoriasis, 477 seborrheic dermatitis, 476 Scaphoid bone, 449 Scar formation, 218 Scarlet fever presentation, 136 rash with, 183 Streptococcus pyogenes, 136 S cells, 371 Schatzki rings, 377 Schaumann bodies, 676 Schilling test, 420 Schistocytes, 414 in extrinsic hemolytic anemias, 423 HELLP syndrome, 643 in intravascular hemolysis, 421 in microangiopathic anemia, 423 Schistosoma haematobium bladder cancer, 226 disease association, 161 squamous cell carcinoma of bladder, 606 Schistosoma spp, 160, 161 Schistosomiasis portal hypertension, 389 pulmonary arterial hypertension, 679 Schizoaffective disorder, 560 Schizoid personality disorder, 565

Schizophrenia, 572 atypical antipsychotics for, 573 diagnostic criteria, 560-576 neurotransmitters for, 495 readmissions with, 272 Schizophrenia spectrum disorders, 560 Schizophreniform disorder, 560 Schizotypal personality, 560, 565 Schüffner stippling in blood smear, 157 Schwann cells, 494 Guillain-Barré syndrome, 524 origin of, 490 Schwannomas, 494, 527 Sciatic nerve, 452 SCID (severe combined immunodeficiency), 37, 117 adenosine deaminase deficiency, lymphopenia caused by, 424 thymic shadow in, 98 Sclerae alkaptonuria, 84 osteogenesis imperfecta, 51 Scleritis, 466 Sclerodactyly, 473 Scleroderma, 473 Scleroderma (diffuse) autoantibody, 115 Sclerodermal esophageal dysmotility, Sclerosing adenosis, 649 Sclerosing cholangitis, 393, 395 ulcerative colitis association, 382 Scombroid poisoning, 247 Scopolamine, 241 Scoring of USMLE Step 1 exam, 7, 8–9 Scorpion sting, 397 Scotoma, 542 Scrotal hematoma, 627 Scrotum, 627 lymphatic drainage of, 624 masses in, 652 Scurvy collagen synthesis and, 50 vitamin C deficiency, 69 Seafood toxins, 247 Seal-like barking cough, 170 Seborrheic dermatitis, 476 Sebum, 477 Secobarbital, 546 Secondary adrenal insufficiency, 349 Secondary amyloidosis, 212 Secondary biliary cholangitis, 395 Secondary disease prevention, 270 Secondary glomerular disease, 594 Secondary hyperaldosteronism, 349 Secondary hyperparathyroidism, 345, Secondary polycythemia, 433 Secondary spontaneous pneumothorax, 682 Second-degree AV block, 295 Second messengers G-protein linked, 238 Second-wind phenomenon, 87 regulatory substances, 371 secretory cell location, 373 somatostatinomas and, 351

Secretion rate calculation, 584

Segmented viruses, 168

Secretory (exported) protein synthesis,

Seizures anti-NMDA receptor encephalitis, 228 barbiturates for, 546 benzodiazepine withdrawal, 546, 570 β-blockers, 245 brain injury with recurring, **517** bupropion, 576 clozapine use and, 573 cytomegalovirus, 182 drug reaction and, 251 with eclampsia, 643 electrolyte disturbances, 591 enflurane, 251 foscarnet, 202 during heat stroke, 517 herpesviruses and, 164, 165, 183 high fever, 165 imipenem/cilastatin, 251 isoniazid, 197 medium-chain acyl-CoA dehydrogenase deficiency, meropenem, 190 nitrosourea toxicity, 441 parasite infestation and, 161 PCP, 571 phenylketonuria, 84 psychoactive drug intoxication/ withdrawal, 570–571 Rett syndrome, 62 Sturge-Weber syndrome, 525 Taenia solium, 160, 161 tramadol and, 552 types of, 517 venous sinus thrombosis, 503 visceral larva migrans, 159 vitamin B<sub>6</sub> deficiency, 67 Zellweger syndrome, 47 Selection bias, 260 Selective estrogen receptor modulators (SERMs), 443, 462, **656** Selective IgA deficiency, 116 Selective media, 126 Selective mutism, 557 Selectivity β-blockers, 245 Selegiline, 548, **549**, 575 Selenium sulfide tinea versicolor, 152 Self-fulfilling prophecies, 260 Self-image of patient, 268 Self-mutilation Lesch-Nyhan syndrome, 37 Semimembranosus, 451, 452 Seminal vesicles, 622 Seminiferous tubules, 626, 628, 629 Seminoma, 653 Semitendinosus, 451, 452 Sensitivity (diagnostic tests), 257 Sensorineural hearing loss, 533 Sensory cortex, 514 topographic representation, 502 Sensory innervation derivation of, 620 lower extremity, 452, 453 tongue, 493 upper extremity nerve injury, 447 Sensory loss conversion disorder and, 566 stroke effects, 514 Sensory modalities/pathways receptors for, **494** spinal tracts in, 509 thalamus in, 498 Separation anxiety disorder, 557

Separation anxiety (infants), 635 Sepsis ARDS, 678 immunodeficient patients, 118 lymphopenia with, 424 neutropenia with, 424 shock with, 310 Streptococcus agalactiae, 137 Septate uterus, 623 Septation of heart chambers, 280 Septic arthritis, 468 gonococci, 142 Staphylococcus aureus, 135 Septicemia Listeria monocytogenes, 139 readmissions with, 272 Waterhouse-Friderichsen syndrome, 349 Septic shock diffuse cortical necrosis (renal), 602 macrophages and, 407 norepinephrine for, 242 Septum primum, 280 Septum secundum, 280 Sequence (morphogenesis error), 613 Serine, 224 Serologic markers hepatitis, 174 Seronegative spondyloarthritis, **469** Serosa, 362 Serotonergic drugs, 574 Serotonin changes with disease, 495 vitamin B<sub>6</sub> and, 67 Serotonin syndrome, 400, 547, 552, atypical antidepressants, 576 dextromethorphan, 686 MAOIs, 575 MDMÁ, 571 oxazolidinones, 193 Serous cystadenocarcinoma, 227, 646 Serous cystadenoma, 646 Serpentine cord, 140 Serrated colon polyps, 387 Serratia marcescens, 128 treatment of, 189 in immunodeficiency, 128 UTIs, 181 Serratia spp immunodeficient patients, 118 Serratus anterior muscle, 448 Sertoli cells secretions of, 622, 628 sexual determination, 622 tumors of, 653 Sertoli-Leydig cell tumor, 647 Sertraline, 575 Serum amyloid A, 213 Serum markers (liver pathology), 390 Serum osmolarity antidiuretic hormone regulation of, 329 Serum protein electrophoresis (SPEP) in plasma cell dyscrasias, 431 Serum tumor markers, 226 Sevelamer, 355 17α-hydroxylase, 335 17-hydroxyprogesterone, 335 Sevoflurane, 550 Sex chromosome disorders, 638 Sex cord stromal tumors, 647 Sex development disorders phenotypic and gonadal disagreement in, 639 physical characteristics, 639

FAS1\_2019\_21\_Index\_749-806.indd 794 11/21/19 12:27 PM

INDEX

Con homeono hindina alabulia
Sex hormone–binding globulin
(SHBG), 337
Sex hormone disorder diagnosis, 639 Sex pilus (bacterial genetics), 130
Sex steroid replacement, 339
Sexual abuse, 556, 558
Sexual behavior
hypothalamus regulation of, 498
Sexual differentiation, <b>622</b> , 636
Sexual dysfunction
β-blockers and, 245, 323
cimetidine, 399
differential diagnosis of, <b>567</b>
Lambert-Eaton myasthenic
syndrome, 472
Peyronie disease and, 651
tuberoinfundibular pathway, 499
Sexually transmitted infections (STIs)
clinical features, <b>184</b>
parental consent with, 265
Sézary syndrome, 430
Shawl and face rash, 471
Sheehan syndrome, 339
Sheep (disease vectors), 160
Shiga-like toxin (SLT), 145
cytokine release and, 132
Shiga toxin, 130, 132, 144
Shigella boydii, 144
Shigella dysenteriae, 144
Shigella flexneri, 144
Shigella sonnei, 144
Shigella spp
bloody diarrhea, 179
penicillinase-sensitive penicillins
for, 188
reactive arthritis, 469
TMP-SMX, 194
vs Salmonella spp, 144
Shingles, 165
Shin splints, 461
Shock, 310
dopamine for, 242
Ebola, 171
endotoxins, 131
in pulmonary anthrax, 137
norepinephrine for, 242
Waterhouse-Friderichsen syndrome
and, 349
short-chain fatty acids
in anaerobic organisms, 127
SIADH, 338
drug raction and, 249
markers in, 591
paraneoplastic syndrome, 228
Sialadenitis, 376
Sialolithiasis, <b>376</b>
Sialyl Lewis <sup>x</sup> , 215
Sibling studies, 256
Sickle cell disease, <b>422</b> , 651
ESR in, 214
osteonecrosis and, 463
postsplenectomy state in, 98
Streptococcus pneumoniae, 136
Sickle cells, 415
Sideroblastic anemia
causes and treatment, 419
lead poisoning, 419
vitamin B <sub>6</sub> deficiency, 67
Sigmoid colon, 383
Sigmoid sinus, 503
Sigmoid volvulus, 386
Signaling pathways
endocrine hormones, <b>337</b>
steroid hormones, <b>337</b>
Signal recognition particle (SRP), 47
Signet ring cells, 379

Sign of Leser-Trélat, 228
Sildenafil, 651
Silencer (gene expression), 41 Silicosis, 677
Silver stain, 125, 143
Simeprevir, 204
Simple partial seizures, 517 Simple pneumothorax, 680
Simple renal cysts, 604
Single nucleotide (point) mutation, 39
Single nucleotide polymorphisms (SNPs), 54
Single nucleotide substitutions, 39
Single-stranded binding proteins, 38 Sinusitis
brain abscesses, 180
C3 deficiency and, 107 Kartagener syndrome, 49
Streptococcus pneumoniae, 136
Wegener granulomatosis, 315 Sinus venosus, 281
Sirolimus
immunosuppressant, 120
Sister Mary Joseph nodules, 379 Sitagliptin, 353
Situs inversus, 49
6-mercaptopurine, 440 azathioprine, 120
for ulcerative colitis, 382
purine synthesis, 36
targets of, 438 Sjögren syndrome, <b>468</b>
autoantibody, 115
pilocarpine for, 240 rheumatoid arthritis, 466
Skeletal muscles
ACh receptors in, 236
blood flow regulation in, 297 glycogen metabolism in, 86
somatic nerve, supply of, 236
Skewed distributions, 262 Skin
blood flow regulation in, 297
collagen in, 50 normal flora of, 135
pigmentation, 56
wrinkles of aging, 52
Skin anatomy, 473–483 layers of, <b>473</b>
microscopic terms, 475
morphology, 475 Skin cancer, <b>484</b>
albinism and, 476
Lynch syndrome and, 388 Skin drug reactions, 250
Skin flora, 178
Skin lesions
autoimmune disorders, 480 bulla, 475
burns, 483
café-au-lait spots, 57 cancer, 222
common disorders, <b>477</b>
crust, 475 dermatitis herpetiformis, 381
erythema multiforme, 151
Gottron papules, 228
hyperlipidemia signs, 300, <b>301</b> hyperpigmentation, 395
inflammatory bowel disease, 382
Kaposi sarcoma, 165 kwashiorkor, 71
macule, 475
papule 475

papule, 475 patch, 475

petechiae, 407	
pigmentation disorders, 475, <b>476</b>	
plaque, 475	
pustule, 475 scale, 475	
scaling, 152	
scaly, 66	
seborrheic keratoses, 228 splinter hemorrhages, 311	
striae, 348	
T-cell lymphoma, 430	
telangiectasia, 316, 473	
ulcers, 158 vascular tumors, 478	
vasculitides, 314	
verrucous, 151 vesicle, 475	
wheal, 475	
Skip lesions, 382	
Skull thickening, 463	
Slapped cheek rash, 183 Sleep	
ghrelin/leptin production, 336	
Sleep disturbance	
apnea, <b>679</b> benzodiazepines and, 570	
β-blockers, 245	
delirium and, 558	
generalized anxiety disorder, 563 in geriatric patients, 270	
hypnagogic hallucinations, 559	
hypnopompic, 559	
paralysis, 568 paroxysmal nocturnal dyspnea,	
309	
pulsus paradoxus in, 310	
sleep terror disorder, 567, <b>568</b> varenicline, 576	
Sleep physiology, 497	
stages in, 497	
Sleepwalking sleep stages and, 497	
SLE (systemic lupus erythematosus),	,
470	
antiphospholipid syndrome and, 470	
autoantibodies, 115	
DPGN, 596	
HLA subtypes, 100 kidney disease with, 596	
Raynaud phenomenon, 472	
Sliding hiatal hernia, 370	
Slime (S) layer, 124 Slipped capital femoral epiphysis,	
461	
osteonecrosis, 463	
Slow acetylators, 232 Small bowel disease, 374	
Small cell carcinoma of lung, <b>684</b>	
carcinogens for, 225	
immunohistochemical stains for, 227	
oat cell carcinoma, 684	
paraneoplastic syndromes, 228	
Lambert-Eaton myasthenic syndrome, 472	
topotecan for, 442	
Small interfering RNA (siRNA) <b>56</b>	
Small intestine, 371	١
Small lymphocytic lymphoma (SLL) 432	1,
Small molecule inhibitors	
naming conventions for, 254	
Smallpox, 164 Small-vessel vasculitis	

presentation and pathology, 314

Smoking abdominal aortic aneurysms and, atherosclerosis and, 302 Buerger disease and, 314 bupropion for cessation, 576 carcinogenicity of, 225 cataracts, 535 colorectal cancer and, 388 emphysema, 674 esophageal cancer and, 378 head and neck cancer, 671 hormonal contraception, 657 Legionnaires' disease, 143 lung cancer, 684 pancreatic cancer and, 398 renal cell carcinoma, 605 saccular aneurysms, 516 squamous cell carcinoma of bladder, 606 stomach cancer and, 379 teratogenic effects, 614 transitional cell carcinoma, 606 varenicline for cessation, 576 Smooth brain, 491 Smooth endoplasmic reticulum, 46 Smooth muscle BMPR2 gene, 679 contraction of, 457 glomus tumors, 478 respiratory tree, 662 tumor nomenclature in, 220 Smooth muscle (vascular) in arteriolosclerosis, 301 atherosclerosis and, 302 calcium channel blocker action, Smudge cells, 432 SNARE proteins in neurotransmission, 138 SNc (substantia nigra pars compacta), SNRIs (serotonin-norepinephrine reuptake inhibitors ) clinical use, 572 major depressive disorder, 561 mechanism and clinical use, 575 Snuffles, 147 "Soap bubble" appearance/lesions giant cell tumor, 464 Cryptococcus neoformans, 153 Social anxiety disorder, 563 drug therapy for, 572 SSRIs for, 575 venlafaxine for, 575 Social engagement infant deprivation effects, 556 Sodium channel blockers, **322** Sodium channels cystic fibrosis, 60 epilepsy drug effects, 544 local anesthetic effects, 550 pacemaker action potential and, 292 permethrin, 200 Sodium-glucose co-transporters (SGLT), 334, 353, 373, 584 Sodium oxybate (GHB) narcolepsy treatment, 568 Sodium-potassium channels, 236 Sodium-potassium pump, 49 Sodium stibogluconate, 158, 200 Sofosbuvir, 204 Solifenacin, 241 Solitary functioning kidney, 579 Solitary nucleus of medulla, 296

FAS1\_2019\_21\_Index\_749-806.indd 795 11/21/19 12:27 PM

796 INDEX

Somatic hypermutation, 101	Spirochetes, 146	SSRIs (selective serotonin reuptake	Statins
Somatic mosaicism	Spironolactone, <b>609</b> , 658	inhibitors), <b>575</b>	for acute coronary syndromes, 307
Sturge-Weber syndrome, 525	for heart failure, 309	anxiety disorders, 562	hepatitis, 249
Somatic mosaicism, 57	Splay (glucose clearance), 584	atypical depression, 561	myopathy, 250
Somatic nerves male sexual response, 627	Spleen bacterial clearance by, 127	clinical use, 572 major depressive disorder, 561	Statistical distribution, <b>262</b> Statistical hypotheses, <b>262</b>
Somatic symptom disorder, <b>566</b>	blood supply and innervation of,	mechanism and clinical use, 575	confidence interval, 263
Somatic symptoms	364	obsessive-compulsive disorder, 563	correct result, 263
characteristics of, 566	embryology, 360	panic disorder, 563	incorrect results, 263
conversion disorder, 566	in gastrointestinal anatomy, 361	phobias, 563	test for, 264
illness anxiety disorder, 566	ischemia susceptibility, 210	postpartum depression, 562	Status epilepticus, 517
somatic symptom disorder, 566	structure and function, <b>98</b>	SIADH caused by, 249	treatment, 544
Somatomedin, 329	thrombocytes in, 407	Stable angina, 304	Stavudine, 203
Somatosensory cortex (primary), 501	Splenectomy, 422	Stable (quiescent) cells, 46	Steady state, 231
thalamic relays to, 498	peripheral blood smear after, 423	Stab wounds and winged scapula, 448	Steatohepatitis, 389
Somatostatin	Splenic artery, 364	Staghorn calculi, 598	Steatorrhea
function of, 328	Splenic flexure	Stains (bacterial), 125	chronic pancreatitis, 397
glucagon and, 333	blood supply to, 363	Standard deviation	cystic fibrosis, 60
hypothalamic/pituitary drugs, 354	Splenomegaly	dispersion, 262	malabsorption syndromes and, 38
production of, 329	anemia, 157	variability, 259	octreotide effect, 400
regulatory substances, 371	cirrhosis, 389	Standard error of the mean, 262	Steatosis (hepatic), 390, <b>391</b>
secretory cell locations, 373	hairy cell leukemia, 432	Stapedial artery, 619	Steeple sign (x-ray), 170
Somatostatinoma, 351	hereditary spherocytosis, 422	Stapedius muscle, 620	Stellate cells, 367
pancreatic cell tumor, 351 Somatotropin, 329	malaria, 157 myelofibrosis, 433	Stapes (ossicles), 533, 620	Stellate ganglion, 685 Stem cells
Sorbitol metabolism, <b>81</b>	rheumatoid arthritis, 466	Staphylococcal scalded skin syndrome, 479	in aplastic anemia, 421
Sotalol, 323	visceral leishmaniasis, 158	Staphylococcal toxic shock syndrome	bone marrow, 108
Southern blot, 53	Splenorenal ligament, 361	(TSS), 135	CD34 protein, 110
Southwestern blot, 53	Splicing of pre-mRNA, <b>42</b>	Staphylococcus aureus, 135	myelodysplastic syndromes and,
Space of Disse, 367	alternative splicing, 43	bacterial endocarditis, 311	431, 432
Spaghetti and meatballs appearance,	Splinter hemorrhages, 311	β-hemolytic nature of, 135	Steppage gait, 453
152	Splitting, 555	brain abscesses, 180	Sterilization/disinfection methods,
Spasmolytics, <b>551</b>	Splitting of heart sounds, 288, 289	cephalosporins, 189	204
Spastic paralysis	Spondyloarthritis (seronegative), 469	cystic fibrosis, <b>60</b> , 179	Steroid hormone signaling pathways
tetanospasmin, 138	Spongiosis, 475	dapsone, 195	337
Spastic paresis, 529	Spontaneous abortion	exotoxin production, 133	Steroids
Special senses	antiphospholipid syndrome, 470	food poisoning, 178	acute pancreatitis, 397
ophthalmology, 534–543	Listeria monocytogenes, 139	immunocompromised patients, 179	adrenal insufficiency, 349
otology, 533–534	syphilis, 182	influenza, 169	berylliosis, 677
Specificity equation, 257	vitamin A excess, 614	IV drug use, 179	CRH levels in, 328
Specific learning disorder, 557	Spontaneous bacterial peritonitis,	nosocomial infection, 179, <b>185</b>	multiple sclerosis, 523
Spermatic cord, 369 Spermatocele, 652	389, <b>390</b> Spontaneous pneumothorax, 682	osteomyelitis and, 180 penicillins for, 188	synthesis of, 46, 72 TBG and, 331
Spermatocytes, 628	Sporadic porphyria cutanea tarda,	pigment production, 128	Stevens-Johnson syndrome, 194, <b>481</b>
Spermatogenesis, 628	173	pneumonia, 683	544
cryptorchidism and, 651	Spore-forming bacteria, <b>129</b> , 138	postviral infection, 179	atypical variant of, 150
process of, <b>629</b>	Spores, 124	prophylaxis for, 198	drug reaction and, 250
prolactin effect on, 330	Sporothrix schenckii, <b>154</b>	septic arthritis, 468	sulfa drug allergies, 252
Spermatogonia, 628	Sporotrichosis, 154	skin infections, 479	Stimulants
Spermiogenesis, 629	Sprain (ankle), 455	Staphylococcus epidermidis, 135	for ADHD, 557
Sphenomandibular ligament, 620	Sprue	gram-positive testing, 134	intoxication and withdrawal, 570
Sphenoparietal sinus, 503	fat-soluble vitamin deficiencies	in vivo biofilm production, 128	laxative, 401
Spherocytosis, 415	and, 65	normal flora, 178	St. John's wort, 252
autoimmune hemolytic anemia, 415	vitamin B <sub>12</sub> deficiency, 69	nosocomial infection, 185	St. Louis encephalitis, 167
extrinsic hemolytic anemia, 423	"Spur cells," 414	osteomyelitis, 180	Stomach
hereditary, 421, 422	Sputum	urease-positive, 127	basal electric rhythm, 362
Sphincter of Oddi, <b>368</b> , 371	currant jelly, 145	vancomycin for, 190	blood supply to, 364
Sphingolipidoses, 88	Klebsiella spp, 186	Staphylococcus gallolyticus, 137	cholecystokinin effect on, 371
Sphingomyelin, 88	Streptococcus pneumoniae, 136	Staphylococcus pyogenes	in gastrointestinal anatomy, 361
Sphingomyelinase, 88 Spina bifida	rusty, 136 Squalene epoxidase, 199	skin infections, 479 Staphylococcus saprophyticus, <b>136</b>	histology of, 362 regulatory substances, 371
neural tube defect, 491	Squamous cell carcinoma, 484	gram-positive testing, 134	sclerosis of, 473
Spinal cord	anus and cervix, 177	urinary tract infections, 600	secretin effect on, 371
embryologic derivation, 613	bladder, 160, <b>606</b>	UTIs, 181	Stone bone, 463
lesions of, <b>530</b>	carcinogens in, 225	Staphylococcus spp	Straight sinus, 503
lower extent of, <b>507</b>	cervix, 645	antibiotic tests for, 134	Stranger anxiety (infants), 635
nerve nuclei of, 505	esophagus, 378	facultative anaerobic metabolism,	Strategies
nerves of, <b>507</b>	head and neck, 671	127	clinical vignette, 23
tracts of, <b>508</b> , 509	hypercalcemia and, 228	Starling curves, 285, 297	test-taking, 22–23
Spinal cord syndromes	lungs, 684	Starling forces, 297	Strawberry cervix, <b>181</b> , 184
multiple sclerosis, 523	pectinate line and, 366	"Starry sky" appearance of B cells,	Strawberry hemangiomas, 478
Spinal muscular atrophy, 530	penis, 651	430	Strawberry tongue, 136
splicing of pre-mRNA in, 42	of skin, 482	Start and stop codons, 44	Kawasaki, 314
Spinothalamic tract, 509	Squamous epithelium, 662	Startle myoclonus, 521	scarlet fever, 136
thalamic relay for, 498	SRY gene, 622	Starvation phases, 91	Streak gonads, 622

FAS1\_2019\_21\_Index\_749-806.indd 796 11/21/19 12:27 PM

Streptococcus agalactiae (group B	Studies	Suicide	Surgical procedures
strep), <b>137</b>	error types, 256	deaths from, 272	readmissions with, 272
β-hemolytic nature of, 135	Studying for USMLE Step 1 exam	physician-assisted, 268	Surrogate decision-maker, 266
encapsulated bacteria, 127	timeline for, 16–19	risk factors for, 562	Suvorexant, <b>547</b>
gram-positive testing, 134	Sturge-Weber syndrome, 525	Sulbactam, 189	Swallowing
in neonates, 182	Stylohyoid ligament, 620	Sulfadiazine, 194	tongue movement in, 493
		,	Swan-Ganz catheter, 297
prophylaxis for, 198	Stylohyoid muscle, 620	Toxoplasma gondii, 156	
Streptococcus bovis, 137	Styloid process, 620	Sulfa drugs, 252	Swarming, 181
Streptococcus mutans	Stylopharyngeus, 620	megaloblastic, 250	Sweat glands, 236
biofilm production, 128	Subacute combined degeneration	rash, 250	embryologic derivation, 613
normal flora, 178	(SCD), 69, 530	Sulfamethoxazole (SMX), 194	pilocarpine effects, 240
Streptococcus pneumoniae, <b>136</b>	Subacute endocarditis	Sulfapyridine, 400	Swiss cheese model, 273
chloramphenicol, 192	enterococci, 137	Sulfasalazine, 252, <b>400</b> , 466	Sydenham chorea, 312, <b>519</b>
cystic fibrosis, 179	Staphylococcus gallolyticus, 137	Sulfatides, 140	Sylvian fissure, 501
encapsulated bacteria, 127	Subacute granulomatous thyroiditis,	Sulfisoxazole, 194	Sympathetic nervous system
gram-positive testing, 134	341	Sulfonamides	denervation of face, 540
IgA protease and, 129	Subarachnoid hemorrhage, 513, 518	cytochrome P-450 and, 252	male sexual response, 627
influenza, 169	aneurysms, 516	hemolysis in G6PD deficiency, 250	receptor targets, 236
IV drug use and, 179	nimodipine for, 318	hypothyroidism, 249	venous return and, 286
meningitis, 179, 180	Subarachnoid space, 507	mechanism and use, <b>194</b>	Sympatholytic drugs, <b>243</b>
penicillin G/V for, 187	Subclavian arteries, 619	Nocardia spp, 139	Sympathomimetics
pneumonia, 179, <b>683</b>	Subcutaneous fat	photosensitivity, 250	direct, 242
postviral infection, 179	erythema nodosum in, 482	pregnancy contraindication, 204	indirect, 242
transformation in, 130	skin layers, 473	trimethoprim, 194	Syncope
α-hemolysis, 135	Subcutis, 473	vitamin B <sub>9</sub> deficiency, 68	during exercise, 308
Streptococcus pyogenes (group A	Subdural hematomas, 513	Sulfonylureas, 353	pulsus parvus et tardus, 291
strep), 130, 133, <b>136</b>	Subendocardium, 210	disulfiram-like reaction, 251	Synctiotrophoblasts, 617, 633
β-hemolysis, 135	Sublimation, 555	insulin and, 334	β-hCG and, 226
lab testing, 134	Sublingual gland	Sulfur granules, 128, 139	hCG secretion by, 633
in renal disease, 596	stones in, 376	Sumatriptan, 547	Syndrome of apparent
M protein and, 129	Submandibular gland	cluster headaches, 518	mineralocorticoid excess,
rash, 183	stones in, 376	coronary vasospasm with, 248	586
treatment of, 187, 192	Submucosa, 362	Sunburn, 482	markers in, 591
Streptococcus pyogenes toxic shock—	Submucosal polyps, 387	Sunburst pattern (X-ray), 465	Syndrome of inappropriate
like syndrome	Subscapularis muscle, 446	Superficial inguinal nodes, 624	antidiuretic hormone
skin infection with, 135	Substance abuse	Superior colliculi, 504	secretion (SIADH), <b>338</b>
Streptococcus sanguinis, 128	adult T-cell lymphoma and, 430	Superior gluteal nerve, 453	Synergism
Streptococcus spp	Candida albicans, 153	Superior mesenteric artery (SMA),	Aspirin and, 235
antibiotic tests for, 134	delirium with, 558	364	of drugs, 235
facultative anaerobic metabolism,	dissociative identity disorder and, 558	syndrome, 363	Syphilis, <b>147</b>
127	parental consent, 265	Superior oblique muscle, 540	fluorescent antibody stain for, 125
septic arthritis, 468	torsades de pointes in, 294	Superior olive (nucleus), 498	STI, 184
Streptogramins, 198	tricuspid valve endocarditis and,	Superior ophthalmic vein, 503	syphilitic heart disease, 312
Streptokinase, 437	311	Superior rectal vein, 365	tabes dorsalis, 530
Streptolysin O, 133	Substance P, 551	Superior rectus muscle, 540	testing for, 148
Streptomycin, 191, <b>197</b>	Substance P antagonist, 401	Superior sagittal sinus, 503	thoracic aortic aneurysms and, 302
Stress incontinence, 599	Substance use disorder, <b>568</b>	Superior sulcus tumor, 685	TORCH infection, 182
Stress-related disorders, 564	addiction, stages of change in	Superior vena cava	Syringomyelia, <b>492</b>
		embryologic development of, 281	spinal cord lesions, 530
Striated muscle, 220	overcoming, 568		
Striatum, <b>500</b> , 514	Substantia nigra pars compacta	in fetal circulation, 282	Syrinx, 492
String sign (x-ray), 382	(SNc), 500	Superior vena cava syndrome, 98, <b>685</b>	Systemic amyloidosis, 212
Stroke, 512	Subthalamic nucleus, 500	lung cancer, 684	Systemic juvenile idiopathic arthritis,
ADP receptor inhibitors for, 437	lesions in, 511	Pancoast tumor, 685	468
atrial fibrillation and, 295	Subunit vaccines, 111	Superoxide dismutase, 109	Systemic lupus erythematosus (SLE),
central post-stroke pain syndrome,	Succimer	free radical elimination by, 210	470
515	heavy metal toxicity, 248	Supination	Systemic mycoses, <b>151</b>
direct factor Xa inhibitors for, 437	lead poisoning, 419	Erb palsy, 448	Systemic primary carnitine
eclampsia, 643	Succinate dehydrogenase, 67, 78	forearm, 447	deficiency, 89
effects of, 514–515	Succinylcholine, 551, 590	Supportive therapy, 572	Systemic sclerosis, 473
homocystinuria, 84	Succinyl-CoA	Suppression, 555	Systemic senile amyloidosis, 212
hypertension, 300	gluconeogenesis, 78	Suprachiasmatic nucleus (SCN),	Systolic ejection, 287
hypertensive emergency and, 300	TCA cycle, 77	497–498	Systolic murmur, 308
sickle cell anemia, 422	Sucking reflex, 510	sleep physiology and, 497	0,00000
syphilis, 147	Sucralfate, 399	Supracondylar fracture, 447	T
thrombolytics for, 437	Sudden death	Supraoptic nucleus, 498	T3 (liothyronine), 354
Stroke volume, 284	cardiac death, 304, 313	Suprascipular nerve, 446	T4 (levothyroxine), 354
equation for, 285	cocaine use, 571	Supraspinatus muscle, <b>446</b> , 448	Tabes dorsalis, <b>147</b> , 184
Strongyloides spp, 158, 159	cor pulmonale, 679	Supraventricular tachycardia	spinal cord lesions, 530
Structural quality measurement,	with myocarditis, 313	adenosine for diagnosing, 324	Tachyarrhythmia
273	sleep apnea, 679	β-blockers for, 245, 323	isoproterenol for evaluating, 242
Struvite stones	Sudden infant death syndrome	calcium channel blockers for, 324	thyroid storm, 342
with Proteus spp, 127	(SIDS), 635	Suramin, 200	Tachycardia
ST segment, 293	Suicidal patients, 268	Surface F protein, 169	β-blockers, 245
ST-segment elevation MI (STEMI)	confidentiality exceptions and, 267	Surfactant (pulmonary), 661	drug-induced, 318
diagnosis of, 304	elderly, 270	Surgical neck of humerus, 455	MDMA, 571

FAS1\_2019\_21\_Index\_749-806.indd 797 11/21/19 12:27 PM

798 INDEX

Tachycardia (continued) metronidazole, 195 with myocarditis, 313 PCP, 571 phenoxybenzamine, 244 reflex, 244 stimulants and, 570 supraventricular, 245 thyroid hormones, 354 Wolff-Parkinson-White syndrome, Tachyphylaxis, 235 Tacrolimus hyperglycemia, 249 immunosuppression, 120 Tactile hallucinations, 559 cocaine, 571 Taenia solium, 160, 161 Takayasu arteritis, 314 Tamm-Horsfall mucoprotein, 594 Tamoxifen, 443, 656 hot flashes with, 249 Tamsulosin, 244, 658 Tanner stages (sexual development),
637 Tardive dyskinesia antipsychotic drugs and, 573 metoclopramide adverse effect, nigrostriatal pathway, 499 Target cells, 415 postsplenectomy, 98 Tarsal tunnel syndrome, 453 cranial nerve lesions and, 532 loss with stroke, 514 thalamic relay for, 498 TATA box, 41 Taxanes, 441 Tav-Sachs disease İysosomal storage disease, 88 Tazobactam, 189 TCA cycle, 77 hyperammonemia, 82 metabolic site, 72 pyruvate metabolism, 77 rate-determining enzyme for, 73 TCA toxicity treatment of, 233 T cells, 127, 409 activation, **103** adaptive immunity, 99 anergy, 110 cell surface proteins, 110 corticosteroid effects, 120 cytokine production, 101, 108 cytotoxic, 102 delayed (type IV) hypersensitivity, differentiation and maturation, 98, **102** disorders of, 116, 117 functions, 101 leflunomide effects, 486 lymph nodes, 96 macrophage interaction, 102 major functions of, 101 neoplasms, 430 polysaccharide antigens and, 127 regulatory, 102 sirolimus effect, 120 spleen, 98 thymus, 98 untreated HIV, 176 Tea-colored urine, 425 "Teardrop" RBCs, 414, 433

Tearing stimulation, 240 Teenagers common causes of death, 272 congenital syphilis, 147 dentinogenesis imperfecta, 51 discoloration, 192, 204, 250, 614 Gardner syndrome, 387 osteogenesis imperfecta, 51 Sjögren syndrome and, 468 Telangiectasias basal cell carcinomas, 484 hereditary hemorrhagic, 316 Telencephalon, 490 Tellurite agar, 126 Telomerase action of, 38 Telophase, 46 Temazepam, 546 Temperature receptors, 494 Temperature regulation, 498 Temperature sensation cape-like distribution loss, 492, 530 loss with strokes, 514 Temporal arteritis, 314 Temporalis muscle, 507 Temporal lobe, **501**, 514 Temporal lobe encephalitis, 164 Tendinopathy (rotator cuff), 446 Tendinous xanthomas, 301 familial hypercholesterolemia, 94 Tendonitis drug reaction and, 250 fluoroquinolones, 195 Tendons collagen in, 50 Tenecteplase (TNK-tPA), 437 Teniposide, 442 Tennis elbow, 459 "Tennis rackets" (Birbeck) granules, Tenofovir, 203 Tenosynovitis, 468 Tension headaches, 518 Tension pneumothorax, 680, 682 Tensor fascia latae muscle, 453 Tensor tympani muscle, 620 Tensor veli palatini muscle, 620 ACE inhibitors, 610 aminoglycosides, 191 angiotensin II receptor blockers, 610 in fetal development, 612 fetal effects of, 614 griseofulvin, 200, 204 leflunomide, 486 lithium as, 574 methimazole as, 354 propylthiouracil in pregnancy, 354 ribavirin, 204 vitamin A, 66 warfarin as, 436 Teratoma immature, 647 mature cystic, 647 testicular, 653 Terazosin, 244 Terbinafine, **199** Terbutaline, 242

Teres minor, 446

Teriparatide, 462, 487

Terminal bronchioles, 660

Terminal complement deficiencies (C5–C9), 107

Terminal deoxynucleotidyl transferase (TdŤ), 104 Tertiary adrenal insufficiency, 349 Tertiary disease prevention, 270 Tertiary hyperparathyroidism, 345 Tesamorelin, 328 descent of, 624 lymphatic drainage of, 624 progesterone production, 630 Testicular atrophy alcoholism, 571 muscular dystrophy, 61 Testicular cancer, 439, 442, **653** Testicular torsion, 651 Testicular tumors germ cell, 652-653 non-germ cell tumors, 653 Testing agencies, 24 Testis-determining factor, 622 Testosterone, 636, 658 androgen insensitivity syndrome, 639 Leydig cell secretion, 628 Sertoli cells, 628 SHBG effect on, 337 signaling pathways for, 337 spermatogenesis, 628 Testosterone-secreting tumors, 639 Testosterone synthesis, 199 Test-taking strategy, 22–23 Tetanospasmin, 132 blocks release of GABA, 138 Tetanus exotoxins, 131 Tetanus toxin, 110 hypocalcemia, 591 hypoparathyroidism, 344 Tetrabenazine Huntington disease, 549 Tourette syndrome, 572 Tetracaine, 550 Tetracyclines, 192 esophagitis, 249 Fanconi syndrome, 251 photosensitivity, 250 protein synthesis inhibition, 191 pseudotumor cerebri and, 521 teratogenicity, 204, 614 tooth discoloration, 250 Tetrahydrobiopterin (bh4) in phenylketonuria, 84 Tetrahydrofolic acid (THF), 68, 194 Tetralogy of Fallot, 298 22q11 syndromes, 300 fetal alcohol syndrome, 300 outflow tract formation, 281 Tetrodotoxin, 247 in wound healing, 216 neural development, 490 regulatory T cells, 102 Thalamus development of, 490 limbic system and, 498

Theophylline, 687 therapeutic index of, 234 Therapeutic antibodies, 121, **122** Therapeutic index (TI), 234 Therapeutic window, 234 Thermogenin, 78 Theta rhythm (EEG), 497 Thiamine, 66 Thiazide diuretics, 609 in gout, 250 in heart failure, 309 in hypertension, 316 Thiazides, 609 Thionamides, **354** Thiopental, 546, 550 Thioridazine, 573 Third-degree (complete) AV block, 3rd pharyngeal pouch, 621 3rd pharyngeal arch, 620 Thirst hypothalamus and, 498 30S inhibitors, 191 Thoracic aortic aneurysm, 300, 302 Thoracic outlet syndrome, 448, 684 Threadworms, 159 Threonine, 81 Threonine kinase, 224 Thrombi atherosclerosis, 302 mural, 305, 307 post-MI, 305 Thrombin, 436 Thromboangiitis obliterans, 314 Thrombocytes (platelets), 407 disorders, 426-427 function tests of, 426 heparin adverse effects, 436 leukemias, 432 liver markers, 390 mixed coagulation disorders, 428 thrombolytics and, 437 transfusion of, 421, 429 in wound healing, 216 Thrombocythemia (essential), 433 Thrombocytopenia, 407 Class IA antiarrhythmics, 322 cytarabine, 440 drug reaction and, 250 Escherichia coli, 145 ganciclovir, 202 glycoprotein IIb/IIIa inhibitors, 438 heparin adverse effects, 436 oxazolidinones, 193 protease inhibitors, 203 recombinant cytokines, 121 sulfa drug allergies, 252 TORCH infections, 182 transfusion for, 429 Wiskott-Aldrich syndrome, 117 Thrombocytosis postsplenectomy, 98 Thromboembolic event atrial fibrillation, 295 Thrombogenesis, 411 Thrombolytic drugs, 413, 437 Thrombophlebitis pancreatic cancer, 398 Thrombopoietin, 121 signaling pathways, 337 Thrombosis celecoxib, 486 contraceptive and hormone replacement, 250 essential thrombocythemia, 433 homocystinuria, 84

FAS1\_2019\_21\_Index\_749-806.indd 798 11/21/19 12:27 PM

neuropathic pain, 515 Thalassemia, 418

target cells in, 415

teratogenicity, 614

Thayer-Martin agar, 126

Theca-lutein cysts, 642, 646

Thenar muscles, 447, 448, 450

Thalidomide

Thecoma, 647

Thrombotic stroke, 512
Thrush, 117
Candida albicans, 153
hairy leukoplakia vs, 479
HIV-positive adults, 177
nystatin, 199
"Thumbprint" sign (imaging) colonic ischemia, 386
"Thumb sign" (X-ray) flu, 142
Thymic aplasia, 116
chromosome association, 64
lymphopenia with, 424
Thymic cortex
T cell selection in, 102
Thymic hyperplasia
myasthenia gravis association, 472
Thymic shadow, 117 Thymidine, 194
Thymidine kinase, 201
Thymidylate, 36
Thymoma
disease associations with, 98
myasthenia gravis and, 228, 472
paraneoplastic syndromes, 228
Thymus
benign neoplasm, <b>98</b>
fetal development, 326
pharyngeal pouch derivation, 621 T cell differentiation, 102
T cell origination in, 409
Thymus-dependent antigens, 105
Thymus-independent antigens, 105
Thyroglossal duct cyst, 326
Thyroid adenomas, 342
Thyroid cancer, 343
amyloidosis in, 212
carcinogens in, 225
metastases to, 223 Psammoma bodies in, 227
Thyroid cartilage, 620
Thyroid development, 326
pharmacal pauch derivation 621
pharyngeal pouch derivation, 621
Thyroidectomy, 343
Thyroidectomy, 343 Thyroid hormones, <b>331</b>
Thyroidectomy, 343 Thyroid hormones, <b>331</b> signaling pathways for, 337
Thyroidectomy, 343 Thyroid hormones, <b>331</b> signaling pathways for, 337 in toxic multinodular goiter, 342
Thyroidectomy, 343 Thyroid hormones, <b>331</b> signaling pathways for, 337 in toxic multinodular goiter, 342 Thyroiditis, 341
Thyroidectomy, 343 Thyroid hormones, <b>331</b> signaling pathways for, 337 in toxic multinodular goiter, 342 Thyroiditis, 341 Thyroidization of kidney, 600
Thyroidectomy, 343 Thyroid hormones, <b>331</b> signaling pathways for, 337 in toxic multinodular goiter, 342 Thyroiditis, 341 Thyroidization of kidney, 600 Thyroid peroxidase, 331
Thyroidectomy, 343 Thyroid hormones, <b>331</b> signaling pathways for, 337 in toxic multinodular goiter, 342 Thyroiditis, 341 Thyroidization of kidney, 600 Thyroid peroxidase, 331 Thyroid-regulating hormone (TRH) signaling pathways for, 337
Thyroidectomy, 343 Thyroid hormones, <b>331</b> signaling pathways for, 337 in toxic multinodular goiter, 342 Thyroiditis, 341 Thyroidization of kidney, 600 Thyroid peroxidase, 331 Thyroid-regulating hormone (TRH) signaling pathways for, 337 Thyroid-stimulating hormone (TSH)
Thyroidectomy, 343 Thyroid hormones, <b>331</b> signaling pathways for, 337 in toxic multinodular goiter, 342 Thyroiditis, 341 Thyroidization of kidney, 600 Thyroid peroxidase, 331 Thyroid-regulating hormone (TRH) signaling pathways for, 337 Thyroid-stimulating hormone (TSH) Graves disease and, 342
Thyroidectomy, 343 Thyroid hormones, <b>331</b> signaling pathways for, 337 in toxic multinodular goiter, 342 Thyroiditis, 341 Thyroidization of kidney, 600 Thyroid peroxidase, 331 Thyroid-regulating hormone (TRH) signaling pathways for, 337 Thyroid-stimulating hormone (TSH) Graves disease and, 342 secretion of, 327
Thyroidectomy, 343 Thyroid hormones, <b>331</b> signaling pathways for, 337 in toxic multinodular goiter, 342 Thyroiditis, 341 Thyroidization of kidney, 600 Thyroid peroxidase, 331 Thyroid-regulating hormone (TRH) signaling pathways for, 337 Thyroid-stimulating hormone (TSH) Graves disease and, 342 secretion of, 327 signaling pathways of, 337
Thyroidectomy, 343 Thyroid hormones, <b>331</b> signaling pathways for, 337 in toxic multinodular goiter, 342 Thyroiditis, 341 Thyroidization of kidney, 600 Thyroid peroxidase, 331 Thyroid-regulating hormone (TRH) signaling pathways for, 337 Thyroid-stimulating hormone (TSH) Graves disease and, 342 secretion of, 327 signaling pathways of, 337 Thyroid-stimulating immunoglobulin
Thyroidectomy, 343 Thyroid hormones, <b>331</b> signaling pathways for, 337 in toxic multinodular goiter, 342 Thyroiditis, 341 Thyroidization of kidney, 600 Thyroid peroxidase, 331 Thyroid-regulating hormone (TRH) signaling pathways for, 337 Thyroid-stimulating hormone (TSH) Graves disease and, 342 secretion of, 327 signaling pathways of, 337 Thyroid-stimulating immunoglobulin (TSI), 331
Thyroidectomy, 343 Thyroid hormones, <b>331</b> signaling pathways for, 337 in toxic multinodular goiter, 342 Thyroiditis, 341 Thyroidization of kidney, 600 Thyroid peroxidase, 331 Thyroid-regulating hormone (TRH) signaling pathways for, 337 Thyroid-stimulating hormone (TSH) Graves disease and, 342 secretion of, 327 signaling pathways of, 337 Thyroid-stimulating immunoglobulin (TSI), 331 Thyroid storm, 342
Thyroidectomy, 343 Thyroid hormones, <b>331</b> signaling pathways for, 337 in toxic multinodular goiter, 342 Thyroiditis, 341 Thyroiditis, 341 Thyroid-regulating hormone (TRH) signaling pathways for, 337 Thyroid-stimulating hormone (TSH) Graves disease and, 342 secretion of, 327 signaling pathways of, 337 Thyroid-stimulating immunoglobulin (TSI), 331 Thyroid storm, 342 Thyrotoxicosis, 331 Thyrotoxicosis, 331 Thyrotoxicosis, 331 Thyrotoxicosis, 331
Thyroidectomy, 343 Thyroid hormones, <b>331</b> signaling pathways for, 337 in toxic multinodular goiter, 342 Thyroiditis, 341 Thyroiditis, 341 Thyroid-regulating hormone (TRH) signaling pathways for, 337 Thyroid-stimulating hormone (TSH) Graves disease and, 342 secretion of, 327 signaling pathways of, 337 Thyroid-stimulating immunoglobulin (TSI), 331 Thyroid-stimulating immunoglobulin (TSI), 331 Thyroid storm, 342 Thyrotoxicosis, 331 Thyrotopin-releasing hormone (TRH), <b>328</b> , 330
Thyroidectomy, 343 Thyroid hormones, <b>331</b> signaling pathways for, 337 in toxic multinodular goiter, 342 Thyroiditis, 341 Thyroiditis, 341 Thyroid-regulating hormone (TRH) signaling pathways for, 337 Thyroid-stimulating hormone (TSH) Graves disease and, 342 secretion of, 327 signaling pathways of, 337 Thyroid-stimulating immunoglobulin (TSI), 331 Thyroid-stimulating immunoglobulin (TSI), 331 Thyroid storm, 342 Thyrotoxicosis, 331 Thyrotoxicosis, 331 Thyrotopin-releasing hormone (TRH), <b>328</b> , 330 Thyroxine, 339
Thyroidectomy, 343 Thyroid hormones, <b>331</b> signaling pathways for, 337 in toxic multinodular goiter, 342 Thyroiditis, 341 Thyroiditis, 341 Thyroid-regulating hormone (TRH) signaling pathways for, 337 Thyroid-regulating hormone (TSH) Graves disease and, 342 secretion of, 327 signaling pathways of, 337 Thyroid-stimulating immunoglobulin (TSI), 331 Thyroid storm, 342 Thyroid storm, 342 Thyrotoxicosis, 331 Thyrotoxicosis, 331 Thyrotoxicosis, 331 Thyrotoxicosis, 339 Thyroxine, 339 Thyroxine, 339 Thyroxine-binding globulin (TBG),
Thyroidectomy, 343 Thyroid hormones, <b>331</b> signaling pathways for, 337 in toxic multinodular goiter, 342 Thyroiditis, 341 Thyroiditis, 341 Thyroid-regulating hormone (TRH) signaling pathways for, 337 Thyroid-stimulating hormone (TSH) Graves disease and, 342 secretion of, 327 signaling pathways of, 337 Thyroid-stimulating immunoglobulin (TSI), 331 Thyroid storm, 342 Thyrotoxicosis, 331 Thyrotropin-releasing hormone (TRH), <b>328</b> , 330 Thyroxine, 339 Thyroxine-binding globulin (TBG),
Thyroidectomy, 343 Thyroid hormones, <b>331</b> signaling pathways for, 337 in toxic multinodular goiter, 342 Thyroiditis, 341 Thyroiditis, 341 Thyroid-regulating hormone (TRH) signaling pathways for, 337 Thyroid-stimulating hormone (TSH) Graves disease and, 342 secretion of, 327 signaling pathways of, 337 Thyroid-stimulating immunoglobulin (TSI), 331 Thyroid storm, 342 Thyroid storm, 342 Thyrotoxicosis, 331 Thyrotropin-releasing hormone (TRH), <b>328</b> , 330 Thyroxine, 339 Thyroxine-binding globulin (TBG), 331 TIBC (total iron-binding capacity)
Thyroidectomy, 343 Thyroid hormones, 331 signaling pathways for, 337 in toxic multinodular goiter, 342 Thyroiditis, 341 Thyroiditis, 341 Thyroid-regulating hormone (TRH) signaling pathways for, 337 Thyroid-stimulating hormone (TSH) Graves disease and, 342 secretion of, 327 signaling pathways of, 337 Thyroid-stimulating immunoglobulin (TSI), 331 Thyroid-stimulating immunoglobulin (TSI), 331 Thyrotoxicosis, 331 Thyrotoxicosis, 331 Thyrotropin-releasing hormone (TRH), 328, 330 Thyroxine, 339 Thyroxine-binding globulin (TBG), 331 TIBC (total iron-binding capacity) anemia of chronic disease, 421 lab values in anemia, 419
Thyroidectomy, 343 Thyroid hormones, <b>331</b> signaling pathways for, 337 in toxic multinodular goiter, 342 Thyroiditis, 341 Thyroiditis, 341 Thyroid-regulating hormone (TRH) signaling pathways for, 337 Thyroid-stimulating hormone (TSH) Graves disease and, 342 secretion of, 327 signaling pathways of, 337 Thyroid-stimulating immunoglobulin (TSI), 331 Thyroid-stimulating immunoglobulin (TSI), 331 Thyrotoxicosis, 331 Thyrotoxicosis, 331 Thyrotropin-releasing hormone (TRH), <b>328</b> , 330 Thyroxine, 339 Thyroxine-binding globulin (TBG), 331 TIBC (total iron-binding capacity) anemia of chronic disease, 421 lab values in anemia, 419 microcytic anemia, 418
Thyroidectomy, 343 Thyroid hormones, <b>331</b> signaling pathways for, 337 in toxic multinodular goiter, 342 Thyroiditis, 341 Thyroiditis, 341 Thyroid-regulating hormone (TRH) signaling pathways for, 337 Thyroid-stimulating hormone (TSH) Graves disease and, 342 secretion of, 327 signaling pathways of, 337 Thyroid-stimulating immunoglobulin (TSI), 331 Thyroid-stimulating immunoglobulin (TSI), 331 Thyrotoxicosis, 331 Thyrotoxicosis, 331 Thyrotropin-releasing hormone (TRH), <b>328</b> , 330 Thyroxine, 339 Thyroxine-binding globulin (TBG), 331 TIBC (total iron-binding capacity) anemia of chronic disease, 421 lab values in anemia, 419 microcytic anemia, 418 Tibialis anterior, 453
Thyroidectomy, 343 Thyroid hormones, 331 signaling pathways for, 337 in toxic multinodular goiter, 342 Thyroiditis, 341 Thyroiditis, 341 Thyroid-regulating hormone (TRH) signaling pathways for, 337 Thyroid-regulating hormone (TSH) Graves disease and, 342 secretion of, 327 signaling pathways of, 337 Thyroid-stimulating immunoglobulin (TSI), 331 Thyroid-stimulating immunoglobulin (TSI), 331 Thyroid-stimulating immunoglobulin (TSI), 331 Thyroid-stimulating immunoglobulin (TRH), 328, 330 Thyrotoxicosis, 331 Thyrotropin-releasing hormone (TRH), 328, 330 Thyroxine, 339 Thyroxine-binding globulin (TBG), 331 TIBC (total iron-binding capacity) anemia of chronic disease, 421 lab values in anemia, 419 microcytic anemia, 418 Tibialis anterior, 453 Tibial nerve, 452–453
Thyroidectomy, 343 Thyroid hormones, <b>331</b> signaling pathways for, 337 in toxic multinodular goiter, 342 Thyroiditis, 341 Thyroidization of kidney, 600 Thyroid peroxidase, 331 Thyroid-regulating hormone (TRH) signaling pathways for, 337 Thyroid-stimulating hormone (TSH) Graves disease and, 342 secretion of, 327 signaling pathways of, 337 Thyroid-stimulating immunoglobulin (TSI), 331 Thyroid-stimulating immunoglobulin (TSI), 331 Thyrotoxicosis, 331 Thyrotropin-releasing hormone (TRH), <b>328</b> , 330 Thyroxine, 339 Thyroxine-binding globulin (TBG), 331 TIBC (total iron-binding capacity) anemia of chronic disease, 421 lab values in anemia, 419 microcytic anemia, 418 Tibialis anterior, 453 Tibial nerve, 452–453 neurovascular pairing, 455
Thyroidectomy, 343 Thyroid hormones, 331 signaling pathways for, 337 in toxic multinodular goiter, 342 Thyroiditis, 341 Thyroiditis, 341 Thyroid-regulating hormone (TRH) signaling pathways for, 337 Thyroid-regulating hormone (TSH) Graves disease and, 342 secretion of, 327 signaling pathways of, 337 Thyroid-stimulating immunoglobulin (TSI), 331 Thyroid-stimulating immunoglobulin (TSI), 331 Thyroid-stimulating immunoglobulin (TSI), 331 Thyroid-stimulating immunoglobulin (TRH), 328, 330 Thyrotoxicosis, 331 Thyrotropin-releasing hormone (TRH), 328, 330 Thyroxine, 339 Thyroxine-binding globulin (TBG), 331 TIBC (total iron-binding capacity) anemia of chronic disease, 421 lab values in anemia, 419 microcytic anemia, 418 Tibialis anterior, 453 Tibial nerve, 452–453
Thyroidectomy, 343 Thyroid hormones, <b>331</b> signaling pathways for, 337 in toxic multinodular goiter, 342 Thyroiditis, 341 Thyroidization of kidney, 600 Thyroid peroxidase, 331 Thyroid-regulating hormone (TRH) signaling pathways for, 337 Thyroid-stimulating hormone (TSH) Graves disease and, 342 secretion of, 327 signaling pathways of, 337 Thyroid-stimulating immunoglobulin (TSI), 331 Thyroid-stimulating immunoglobulin (TSI), 331 Thyroid storm, 342 Thyrotoxicosis, 331 Thyrotropin-releasing hormone (TRH), <b>328</b> , 330 Thyroxine, 339 Thyroxine-binding globulin (TBG), 331 TIBC (total iron-binding capacity) anemia of chronic disease, 421 lab values in anemia, 419 microcytic anemia, 418 Tibialis anterior, 453 Tibial nerve, 452–453 neurovascular pairing, 455 Ticagrelor, 437

Ticks (disease vectors), 149–150

Ticlopidine, 411, <b>437</b>
Tics (Tourette syndrome), 557
Tidal volume (TV), 664 Tigecycline, <b>192</b>
Tight junctions, <b>474</b> , 496
Timolol, 245, 323, <b>552</b>
Tinea, <b>152</b> , 200
Tinea capitis, 152 Tinea corporis, 152
Tinea cruris, 152
Tinea pedis, 152
Tinea unguium, 152
Tinea versicolor, 152
Tinel sign, 459 Tinnitus
streptomycin, 197
Tiotropium, 241, <b>687</b>
Tirofiban, 411, <b>438</b>
Tissue factor activation, 133 Tissue plasminogen activator (tPA)
for ischemic stroke, 512
Tizanidine, 243, <b>551</b>
TMP-SMX, 194
for Pneumocystis jirovecii, 154
prophylaxis, 198 TNF-α, 108, 133, 208
TNF-α inhibitors, 487
TNF (tumor necrosis factor), 227
Tobramycin, 191
Tocolytics, 657 Toddler development, 635
Togaviruses
characteristics of, 167
genomes of, 163
rubella as, 169 Toll-like receptors (TLRs), 99
Tolterodine, 241
Tolvaptan, 354
Tongue
development, 493 as ectopic thyroid tissue, 326
glossoptosis, 620
pharyngeal arch derivation, 620
Tonic-clonic seizures, 517
drug therapy for, 544 Tonic seizures, 517
Tonsils
agammaglobulinemia, 116
immune system organ, 96
pharyngeal pouch derivation, 621 Tooth abnormalities
opalescent teeth, 51
Tophus formation, 467
Topiramate
epilepsy, 544 migraine headaches, 518
pseudotumor cerebri, 521
Topoisomerases, 195
Topotecan, 442
TORCH infections, 169, <b>182</b> cataracts, 535
neonatal manifestations, 182
Torsades de pointes, 294
adenosine for, 324
Class IA antiarrhythmics, 322 drug reaction and, 248
hypomagnesemia, 591
ibutilide, 323
sotalol, 323
Torsemide, 608
Torticollis, 519 Torus (buckle) fracture, 462
Total anomalous pulmonary venous
return (TAPVR), 298

Total peripheral resistance (TPR),
286 Tourette syndrome, 557
drug therapy for, 572 obsessive-compulsive disorder and,
563 sympatholytic drugs for, 243
Toxic dose, 234 Toxicities and side effects of drugs,
120, 248–253 Toxic megacolon
Clostridium difficile, 138 Tovio multipodular goiter, 342
Toxic multinodular goiter, 342 Toxic shock-like syndrome, 136
Toxic shock syndrome, 133
exotoxin A, 133 presentation, 135
Staphylococcus aureus, 135
toxin, 133
Toxins
myocarditis with, 313 seafood (ingested), 247
Toxins (bacterial)
anthrax, 137 endotoxins, 132
enterotoxins, 132
erythrogenic, 136
exfoliative, <b>133</b> , 135 exotoxins, 132–133
features of, 131
lysogenic phage encoding, 130
toxin-mediated disease, 135 Toxocara canis, 159
Toxocara spp, 158
Toxoid, 111
Toxoplasma gondii, 156 HIV-positive adults, 177
TORCH infection, 182
Toxoplasma spp, 180
Toxoplasmosis primary central nervous system
lymphoma vs, 430
prophylaxis, 194, <b>198</b>
pyrimethamine, 200 TP53 gene, 224
Trabecula
spleen, 98 Trachea
bifurcation of, 663
fetal development, 326
respiratory tree, 662 Tracheal deviation, 680, <b>682</b>
Tracheoesophageal fistula (TEF)/
anomalies, 359
Traction apophysitis, 461 Tractus solitarius, 506
Tramadol, 552
seizures, 251
"Tram-track" appearance, 596 Transcortical aphasia, 516
Transcription factor, 224
Transduction (bacterial genetics), 130 Transference, 554
Transferrin, 213
free radical elimination by, 210
indirect measure of, 419 lab values in anemia, 419
Transformation (bacterial genetics),
130
Transformation zone (cervix) dysplasia, 645
histology of, 626
Transfusion reaction, 114
Transient arthritis in Lyme disease, 146
Transient ischemic attack (TIA), 512

Transitional cell carcinomas, 225 Transition metals and free radical injuries, 210 Transjugular intrahepatic portosystemic shunt (TIPS), 365 Transketolase metabolic pathways, 74 vitamin B<sub>1</sub> and, 66 Translocation Down syndrome, 63 fluorescence in situ hybridization, in protein synthesis, 45 Robertsonian, 64 Transmural inflammation fistulas, Transpeptidases, 187 Transplants immunosuppressants in, 120 rejection, 101, **119** t(8;14), 430, 434 t(9;22) (Philadelphia), 434 t(14;18), 430, **434** t(15;17), 434 Transposition (bacterial genetics), Transposition of great vessels, 298 embryologic development, 281 maternal diabetes and, 300 Transposon in bacterial genetics, 131 Transsexualism, 567 Transversalis fascia, 369 Transverse sinus, 503 Transversion mutation, 39 Transversus abdominis, 369, 452 Transvestism, 567 Tr antigens, 228 Tranyleypromine, 575 Trapezium bone, 449 Trapezoid bone, 449 TRAP (tartrate-resistant acid phosphatase), 227, 342 Trastuzumab, 122, 444–443 Trauma pneumothorax, 682 psychiatric disorders due to, 564 Traumatic aortic rupture, 303 Traumatic pneumothorax, 682 Travelers' diarrhea, 145 Trazodone, 576, 651 Treacher Collins syndrome, 620 "tree bark" appearance (aorta), 312 Trematodes, 160 Tremor, 519 immunosuppressants, 120 Trench fever, 161 Trendelenburg sign, 453 Treponema, 146 Gram stain, 125 Treponema pallidum penicillin G/V for, 187 STI, 184 Triamterene, 609 Triazolam, 546 Triceps reflex, 510 Triceps surae, 453 Trichinella spiralis, 159, 161 Trichinosis, 159  $Trichomonas\ {\rm spp}$ vaginitis, 181 Trichomonas vaginalis, 158, 181, 184 Trichomoniasis, 184 Trichophyton spp, 152

return (TAPVR), 298 Total lung capacity (TLC), 664

Total parenteral nutrition (TPN), 396

INDEX

Trichotillomania, 563	Truncal ataxia, 499	Type IV hypersensitivity reactions	Unvaccinated children, 186
Trichuris, 158	Truncus arteriosus	contact dermatitis, 477	Upper extremity nerves, 447
Tricuspid atresia, 281, 298	22q11 syndromes, 300	Typhoid fever, 144	Upper motor neuron lesion
Tricuspid regurgitation, 287	Trypanosoma brucei, <b>156</b> , 200	Typhus, 150	facial nerve, 532
Ebstein anomaly and, 298	Trypanosoma cruzi, 158	transmission of, <b>149</b> , 161	Urachal cysts, 618
heart murmurs with, 291	achalasia and, 376	Tyramine, 244	Urachus, 282, <b>618</b>
Tricuspid valve endocarditis, 311 Tricyclic antidepressants (TCAs)	nifurtimox for, 200 Trypsin, 373	Tyramine-induced hypertensive crisis procarbazine, 441	Urea cycle, 82 metabolic site, 72
antimuscarinic reaction, 251	Trypsingen, 373	Tyrosinase, 476	ornithine transcarbamylase
mechanism and clinical use, 575	Tryptase, 408	Tyrosine	deficiency and, 83
naming convention for, 253	Tryptophan, 81	in phenylketonuria, 84	rate-determining enzyme for, 73
torsades de pointes, 248	TSC1/TSC2 genes, 224	Tyrosine kinase	Ureaplasma spp, 125, 127
toxicity of, 569	Tsetse flies (disease vectors), 156	endocrine hormone messenger, 337	Urease, 181
toxicity treatment, 248	TSST-1 superantigen, 135	insulin and, 334	Urease-positive organisms, 127
as weak bases, 233 Trientine, 395	<i>t</i> -tests, 264 T-tubule membrane, 456	as oncogene product, 224 Tzanck test, 166	Uremia acute pericarditis, 313
Trifluoperazine, 573	Tuberculosis, 140	,	renal failure, 603
Trigeminal nerve (CN V), 506	Addison disease, 349	U	Ureter, 625
lesion of, 532	corticosteroids and, 336	Ubiquitination, 45	bifid, 579
neuralgia, 518	erythema nodosum, 482	Ubiquitin-proteasome system, 48	constrictions in, 583
pharyngeal arch derivation, 620	isoniazid, 197	UDP-glucuronosyltransferase	course of, <b>581</b>
thalamic relay for, 498 tongue, 493	necrosis and, 209 silicosis, 677	physiologic neonatal jaundice, 393 Ulcerative colitis, 382	embryology, 578 gynecological exam damage to, 581
Triglycerides	Tuberin protein, 224, <b>525</b>	autoantibody, 115	obstruction of, 579, <b>599</b>
hypertriglyceridemia, 94	Tuberoinfundibular pathway, 499	spondyloarthritis, 469	Ureteric bud, 579
insulin and, 334	Tuberous sclerosis	sulfasalazine for, 400	Ureteropelvic junction
Von Gierke disease, 87	chromosome abnormalities, 525	Ulcers (gastrointestinal)	development of, 578
Trihexyphenidyl, 241	tumor suppressor genes and, 224	bismuth/sucralfate for, 399	Urethra
acute dystonia treatment, 241 Trimethoprim, 187, <b>194</b>	Tubular necrosis, 594, <b>602</b>	complications of, 380	BPH, 654 injury to, 627
folate deficiency with, 420	Tubulointerstitial inflammation WBC casts in, 594	Crohn disease, 382 Curling, 379	posterior valves in, 579
mechanism and use, 194	Tubulointerstitial nephritis, 601	Cushing, 379	Urethritis
pyrimidine synthesis and, 36	Tularemia, 149	esophageal, 377	chlamydia, 148, <b>184</b>
teratogenicity, 614	Tumor grade vs stage, 220	Helicobacter pylori, 146	Chlamydia trachomatis, 149
Trimming (protein synthesis), 45	Tumor lysis syndrome, 434–435	palatal/tongue, 151	gonorrhea, 184
Trinucleotide repeat expansion	Tumor markers (serum), <b>226</b>	peptic, 379	reactive arthritis, 469
diseases, <b>62</b> Friedreich ataxia, 62	acute lymphoblastic leukemia, 432	Žollinger-Ellison syndrome, 352 Ulcers (skin)	Urge incontinence, 599 drug therapy for, 241
Huntington disease, 62	colorectal cancer, 388	Raynaud syndrome, 472	Uric acid
myotonic dystrophy, 62	pancreatic adenocarcinomas, 398	Ulipristal, 657	Lesch-Nyhan syndrome, 37
Triose kinase, 80	Tumors	Ulnar claw, 447, 451	Von Gierke disease, 87
Triple-blinded studies, 256	benign vs malignant, 220	Ulnar nerve, <b>447</b> , 459	Uric acid (kidney stones), 598
Triptans, 547	grade vs stage, 220	Ulnar nerve injury, 449	Urinalysis
angina and, 304	immunohistochemical stains for,	Ultrasonography	in renal disease, 601
for migraine headaches, 518 Triquetrum bone, 449	227 nomenclature of, 220	fetal cardiac activity on, 612 kidney disease/disorder diagnoses,	reducing sugar, 80 Urinary incontinence
Trismus (lockjaw)	Tumor suppressor genes, 46, <b>224</b>	579	drug therapy for, 241
tetanospasmin, 138	Tunica albuginea, 651	renal cysts on, 604	ephedrine for, 242
Trisomies, autosomal, 63	Tunica vaginalis, 624	Umbilical artery, 282, <b>618</b>	hydrocephalus, 522
Trisomy 13 (Patau syndrome), 63, 64	Turcot syndrome, 387	Umbilical cord, 618	mechanisms and associations of,
disease associations with, 491	Turner syndrome, 638	Umbilical hernia	599
hCG in, 633 Trisomy 18 (Edwards syndrome),	cardiac defect association, 300 coarctation of aorta and, 299	congenital, 358 Umbilical vein, 618	urgency incontinence, 237
<b>63</b> , 64	T wave (ECG), 293	blood in, 282	Urinary retention, 237 atropine, 241
disease associations with, 535	21-hydroxylase, 335	postnatal derivative of, 282	bethanechol for, 240
hCG in, 633	22q11 deletion syndromes, 116, 300	Umbilicus	delirium, 558
Trisomy 21 (Down syndrome), 62,	Twin concordance studies, 256	portosystemic anastomosis, 365	neostigmine for, 240
<b>63</b> , 64	Twinning, 616	UMP synthase, 420	post-void residual, 599
disease associations with, 226, 299–	Thromboxane A <sub>2</sub> (TXA), 411, 486	Unambiguous genetic code, 37	treatment of, 237
300, 384, 395, 432, 535 tRNA	aspirin effects, 486 thrombogenesis, 411	Uncal herniation, 529 Uncinate process, 360	Urinary tract infections (UTIs), 181 antimicrobial prophylaxis for, 198
structure, 44	Tympanic membrane, 533	Unconjugated bilirubin, 375	BPH, 654
Trochlea, 540	Type I errors (hypothesis testing), 263	Unconjugated (indirect)	cystitis, 600
Trochlear nerve (CN IV), 506	Type I hypersensitivity, 105, <b>112</b> , 408	hyperbilirubinemia, 393	duplex collecting system and, 579
ocular motility, 540	Type II errors in hypothesis testing,	Uncoupling agents, 78	enterococci, 137
palsy of, 541	263	Undifferentiated thyroid carcinomas,	epididymitis and orchitis with, 654
Tropheryma whipplei, 125, <b>381</b>	Type II hypersensitivity, 112	343	Klebsiella, 145
Tropical sprue, 381 Tropicamide, 241	organ transplants, 119 Type II hypersensitivity reactions	Undulant fever, 149 "Unhappy triad" (knee injuries), 460	pyelonephritis, 600 Staphylococcus saprophyticus, 136
Troponins, 304, 306, 456	rheumatic fever, 312	Unilateral renal agenesis, 579	sulfa drugs for, 252
Trousseau sign, <b>344</b> , 591	Type III hypersensitivity reactions,	Uniparental disomy, 57	sulfonamides for, 194
Trousseau syndrome	113	Universal electron acceptors, 75	TMP-SMX for, 194
pancreatic cancer, 398	organ transplants, 119	Universal genetic code, 37	Urinary tract obstruction, 599
paraneoplastic syndrome, 228	Type IV hypersensitivity	Unnecessary procedure requests,	Urine
True-negative rate, 257 True-positive rate, 257	DRESS syndrome, 250 graft-versus-host disease, 119	268–269 Unstable angina, 304	Bence Jones proteinuria, 431 casts in, 594
riue-positive rate, 27/	State versus-most disease, 117	Chotable angilla, 701	Casto 111, 771

FAS1\_2019\_21\_Index\_749-806.indd 800 11/21/19 12:27 PM

**DEX** 801

diuretic effects on, 609	Vagal nuclei, 506	Vasculitides, 314–315	Ventricular fibrillation
leaks with urethral injury, 627	Vagina	Vasculitis	ECG tracing, 295
osmolality in acute injury, 601	anatomy of, 626	focal necrotizing, 315	torsades de pointes, 294
pregnancy test, 633	drainage of, 624	immunoglobulin A, 315	Ventricular filling
renal tubular acidosis, 593	epithelial histology of, 626	intraparenchymal hemorrhage,	early diastole, 287
Urine acidification, 233	genital embryology, 622	513	ECG and, 293
Urine alkalization, 233	Vaginal bleeding	large-vessel, 314	Ventricular free wall rupture, 307
Urine pH and drug elimination, 233	cervical cancer, 645	leukoclastic, 173	Ventricular myocytes, 296
Urobilinogen	Vaginal candidiasis	medium-vessel, 314	Ventricular noncompliance, 287
extravascular hemolysis, 421 intravascular hemolysis, 421	nystatin, 199 Vaginal infections, <b>181</b>	methotrexate for, 440 small-vessel, 314	Ventricular septal defect (VSD), 299
Urogenital fold, 624	Vaginal tumors, <b>644</b>	Vasculopathy	congenital rubella, 300
Urosepsis, 600	Vaginismus, 567	noninflammatory, 473	cri-du-chat syndrome, 64
Urothelial carcinoma (bladder), 606	Vaginitis	Vas deferens, 626	Down syndrome, 300
Urticaria, 475, <b>477</b>	Trichomonas spp, <b>158</b> , 181	Vasoactive intestinal polypeptide	fetal alcohol syndrome, 300
ethosuximide, 544	trichomoniasis, 184	(VIP), 371	heart murmurs, 291
scombroid poisoning, 247	Vagus nerve (CN X), 506	Vasoconstriction, 589	outflow tract formation, 281
serum sickness, 113	baroreceptors/chemoreceptors	Vasoconstrictors, 550	Ventricular system, 504
sulfa drug allergies, 252	and, 296	Vasodilation	Ventriculomegaly, 520, <b>522</b>
as type I hypersensitivity, 112	cardiac glycoside effects, 321	sympathetic receptors, 238	Ventromedial nucleus
USMLE Step 1 exam	Curling ulcers and, 379	Vasodilators	(hypothalamus), 498
check-in process, 7	diaphragm innervation, 663	afterload effects, 284	Verapamil, 308, <b>318</b> , 319, 321, 518
clinical vignette strategies, 23	gastrointestinal regulation	aortic dissections, 303	Verrucae, 477
content areas covered in, 3	substances and, 371	atrial natriuretic peptide as, 296	Vertebral compression fractures,
goal-setting for, 12	lesions of, 532	coronary steal syndrome, 304	462
leaving exam early, 8	pharyngeal arch derivation,	nitrates as, 318	Vertebral landmarks
overview of, 2	620 structures innervated, 373	Vasogenic edema, 496	diaphragm, 663
passing rates for, 10 practice exams for, 11, <b>21–22</b>	tongue, 493	Vasopressin, 329 receptors, 238	Vertigo, 534
registering for, 5–6	Valacyclovir, <b>201</b>	Vasopressors, 286	posterior circulation stroke, 514 streptomycin, 197
rescheduling, 6	Validity, 259	V(D)J recombination, 99	Vesicles (skin), 475
score notifications for, 7	Valine Valine	VDRL false positives, 148	varicella zoster virus, 479
scoring of, 8–9	classification of, 81	Vector-borne illnesses, 150	Vesicourachal diverticulum, 618
testing agencies, 24	maple syrup urine disease, 84	Veganism and B <sub>12</sub> deficiency, 420	Vesicoureteral reflux, 579
testing locations, 6	Valproic acid	Vegetative state	hydronephrosis, 599
test-taking strategies, 22–23	cytochrome P-450, 252	axonal injury and, 515	pyelonephritis, 600
time budgeting during, 7–8	epilepsy, 544	VEGF (vascular endothelial growth	Vesicular monoamine transporter
types of questions on, 8	hepatic necrosis, 249	factor), 216	(VMAT), 549
Ustekinumab, 122	migraine headaches, 518	Velocardiofacial syndrome, 116	Vesicular tinea pedis, 152
Uterine conditions	pancreatitis, 249	Vemurafenib, <b>444</b> , 484	Vesicular trafficking proteins, 47
non-neoplastic, 648	Valsartan, 610	Venlafaxine, 575	Vestibular schwannomas, 527
Uterine (Müllerian duct) anomalies,	Valvular disease	clinical use, 572	Vestibulocochlear nerve (CN VIII),
622–623	pressure-volume loops, 288	panic disorder, 563	506
Uterine neoplasms, 648	Valvular dysfunction, 310	phobias, 563	VHL gene, 224
Uterovaginal agenesis, 639 Uterus	Vancomycin, 190 Clostridium difficile, 138	PTSD, 564	Vibrio cholerae, 146
anomalies of, 623	cutaneous flushing, 248	Venodilators, 284 Venous gonadal drainage, 624	exotoxin production, 132 watery diarrhea, 179
collagen in, 50	meningitis, 180	Venous gonadar dramage, 621 Venous return, 286	Vibrio parahaemolyticus, 178
epithelial histology, 626	MRSA, 198	Venous sinus thrombosis, 503	Vibrio vulnificus, 178
genital embryology, 622	toxicity of, 251	Venous thrombosis	Vigabatrin, 544
zygote implantation, 633	Vanillylmandelic acid (VMA)	heparin for, 436	Vilazodone, 576
Uveitis, 536	in neuroblastomas, 350	paroxysmal nocturnal	Vimentin, 48, <b>227</b>
inflammatory bowel disease, 382	Vanishing bile duct syndrome,	hemoglobinuria, 422	Vinblastine, 441
in sarcoidosis, 676	119	Ventilation, 664	microtubules and, 48
seronegative spondyloarthritis, 469	Varenicline, 576	high altitude, 670	Vinca alkaloids, 438
U wave in ECG, 293	Variable expressivity, 56	perfusion and, 669	Vincristine, 441
V	Variance, 262	Ventilation/perfusion (V/Q) defects,	microtubules and, 48
	Variant angina, 304	664	toxicities of, 444
Vaccines	Variceal bleeding, 245	Ventilation/perfusion (V/Q) ratio	Vinyl chloride
B-cell disorders, 116	Varicella zoster virus (VZV), <b>165</b> ,	exercise response, 670	angiosarcomas, 392, <b>478</b>
Bordetella pertussis, 143 capsular polysaccharide and	475, 479 guanosine analogs, 201	mismatch, 669 Ventral lateral (VL) nucleus, 498	as carcinogen, 225 VIPomas
protein conjugates in, 127	immunodeficient patients, 118	Ventral pancreatic bud, 360	MEN 1 syndrome, 351
diphtheria, 139	meningitis, 180	Ventral panereatic bud, 500 Ventral posterolateral (VPL) nucleus,	octreotide for, 400
encapsulated bacteria, 127	rash, 183	498	regulatory substances, 371
Haemophilus influenzae, <b>142</b> , 180	vaccine, 110	Ventral posteromedial (VPM)	Viral envelopes, 163
Poliovirus, 167	Varices	nucleus, 498	Virchow nodes, 379
PPSV23, 105	Budd-Chiari syndrome, 392	Ventral tegmentum, 495	Viridans streptococci, 136
rabies, 171	Varicocelectomy, 651	Ventricles	α-hemolysis, 135
rotavirus, 168	Varicocele (scrotal), 628, 651	contractility of, 285	bacterial endocarditis, 311
Salmonella typhi, 144	Vasa previa, 641	embryology, 281	biofilm production, 128
splenectomy and, 98	Vasa vasorum	morphogenesis of, 281	brain abscesses, 180
thymus-independent antigens,	syphilis, 147	Ventricular action potential, 292	gram-positive algorithm, 134
105	Vascular dementia, 521	Ventricular aneurysm	normal flora, 178
toxoids as, 131 types of, 111	Vascular function curves, 286 Vascular tumors of skin, 478	pseudoaneurysm, 307 true, 305, <b>307</b>	Virilization, 335
types 01, 111	vasculai tulliois oi skill, T/O	1110, 202, <b>307</b>	Virology, 162–177

FAS1\_2019\_21\_Index\_749-806.indd 801 11/21/19 12:27 PM

802 INDEX

Virulence factors
bacterial, 129
Bordetella pertussis, 143
Escherichia coli, 145
Salmonella/Shigella, 144
Staphylococcus aureus, 135
Strobtococcus aureus, 137
Streptococcus pneumoniae, 136
β-hemolytic bacteria, 135
Viruses
diarrhea with, 179
fluorescent antibody stain, 125
genetics, 162
immunocompromised patients, 179
in immunodeficiency, 118
as cause of myocarditis, 313
negative-stranded, 168
pneumonia, 179
receptors for, 166
segmented, 168
skin, 479
structure of, 162
Visceral leishmaniasis, 158
Viscosity (blood), 286
Visual cortex, <b>501</b> , 515
Visual disturbance
drug-related, 251
Visual field defects, 542
saccular aneurysms and, 516
with stroke, 514, 515
Visual hallusinations FFO
Visual hallucinations, 559
Vital capacity (VC), 664
Vitamin A (retinol), <b>66</b>
free radical elimination by, 210
idiopathic intracranial
hypertension, 251, <b>521</b>
measles morbidity and mortality, 170
teratogenicity, 614
Vitamin B <sub>1</sub> (thiamine), <b>66</b>
brain lesions and, 511
deficiency of, 66
functions of, 74
pyruvate dehydrogenase complex,
76
solubility of, 65
Vitamin B <sub>2</sub> (riboflavin), <b>67</b>
pyruvate dehydrogenase complex,
76
solubility, 65
Vitamin B <sub>3</sub> (niacin), <b>67</b>
pyruvate dehydrogenase complex,
76
solubility, 65
vitamin B <sub>6</sub> and, 67
Vitamin B <sub>5</sub> (pantothenic acid), <b>67</b>
pyruvate dehydrogenase complex
pyruvate denydrogenase complex
and, 76
solubility of, 65
Vitamin B <sub>6</sub> (pyridoxine), <b>67</b>
deficiency, 67
isoniazid, 197
sideroblastic anemia, 419
Vitamin B <sub>7</sub> (biotin), <b>68</b>
activated carriers, 75
functions of, 73
pyruvate metabolism, 77, 78
solubility of, 65
Vitamin B <sub>9</sub> (folate), <b>68</b>
deficiency, 406, 420
functions, 68
solubility, 65
Vitamin B <sub>12</sub> (cobalamin), <b>69</b>
absorption of, 374
deficiency, 160, 161

solubility, 65
spinal cord lesions, 530
Vitamin C (ascorbic acid) free radical elimination by, 210
functions, 69
methemoglobin treatment, 248
solubility of, 65 Vitamin D
excess, 70
functions, 70 hyperparathyroidism, 464
hypervitaminosis lab values,
464
osteomalacia/rickets, 463, 464 osteoporosis prophylaxis, 462
signaling pathways for, 337
solubility of, 65 ritamin D (calciferol)
calcitriol production, 589
/itamin E
free radical elimination by, 210 function, 70
solubility of, 65
/itamin K cephalosporins, 189
coagulation cascade, 413
deficiency, <b>413</b> , 426 solubility of, 65
vitamin E interaction, 71
for warfarin toxicity, 436
/itamin/mineral absorption, 374 /itamins
fat-soluble, <b>65</b>
water-soluble, <b>65</b> /itelline duct/fistula, 618
/itiligo, 476
/itreous body
collagen in, 50
collagen in, 50 /LDL (very low-density lipoprotein),
collagen in, 50 /LDL (very low-density lipoprotein), 94
collagen in, 50 /LDL (very low-density lipoprotein), 94 /olume contraction alkalemia from diuretics, 609
collagen in, 50 //LDL (very low-density lipoprotein), 94 /olume contraction alkalemia from diuretics, 609 /olume of distribution, 231
collagen in, 50 /LDL (very low-density lipoprotein), 94 /olume contraction alkalemia from diuretics, 609 /olume of distribution, 231 /olumetric flow rate (Q), 286 /olvulus, 385, <b>386</b>
collagen in, 50 //LDL (very low-density lipoprotein), 94 //olume contraction alkalemia from diuretics, 609 //olume of distribution, 231 //olumetric flow rate (Q), 286 //olvulus, 385, <b>386</b> Meckel diverticulum, 384
collagen in, 50 //LDL (very low-density lipoprotein), 94 //olume contraction alkalemia from diuretics, 609 //olume of distribution, 231 //olumetric flow rate (Q), 286 //olvulus, 385, <b>386</b> Meckel diverticulum, 384 midgut, 386
collagen in, 50 //LDL (very low-density lipoprotein), 94 //olume contraction alkalemia from diuretics, 609 //olume of distribution, 231 //olumetric flow rate (Q), 286 //olvulus, 385, <b>386</b> Meckel diverticulum, 384 midgut, 386 <i>Onchocerca</i> , 158 sigmoid, 386
collagen in, 50 //LDL (very low-density lipoprotein), 94 //olume contraction alkalemia from diuretics, 609 //olume of distribution, 231 //olumetric flow rate (Q), 286 //olvulus, 385, <b>386</b> Meckel diverticulum, 384 midgut, 386 //onchocerca, 158 sigmoid, 386 //omiting
collagen in, 50 //LDL (very low-density lipoprotein), 94 //olume contraction alkalemia from diuretics, 609 //olume of distribution, 231 //olumetric flow rate (Q), 286 //olvulus, 385, <b>386</b> Meckel diverticulum, 384 midgut, 386 Onchocerca, 158 sigmoid, 386 //omiting annular pancreas, 360 biliary colic, 396
collagen in, 50 //LDL (very low-density lipoprotein), 94 //olume contraction alkalemia from diuretics, 609 //olume of distribution, 231 //olumetric flow rate (Q), 286 //olvulus, 385, <b>386</b> Meckel diverticulum, 384 midgut, 386 Onchocerca, 158 sigmoid, 386 //omiting annular pancreas, 360 biliary colic, 396 bilious, 359, 384
collagen in, 50 //LDL (very low-density lipoprotein), 94 //olume contraction alkalemia from diuretics, 609 //olume of distribution, 231 //olumetric flow rate (Q), 286 //olvulus, 385, <b>386</b> Meckel diverticulum, 384 midgut, 386 Onchocerca, 158 sigmoid, 386 //omiting annular pancreas, 360 biliary colic, 396 bilious, 359, 384 diabetic ketoacidosis, 347 Ebola virus, 171
collagen in, 50 //LDL (very low-density lipoprotein), 94 //olume contraction alkalemia from diuretics, 609 //olume of distribution, 231 //olumetric flow rate (Q), 286 //olvulus, 385, <b>386</b> Meckel diverticulum, 384 midgut, 386 Onchocerca, 158 sigmoid, 386 //omiting annular pancreas, 360 biliary colic, 396 bilious, 359, 384 diabetic ketoacidosis, 347 Ebola virus, 171 fructose intolerance, 80
collagen in, 50 //LDL (very low-density lipoprotein), 94 //olume contraction alkalemia from diuretics, 609 //olume of distribution, 231 //olumetric flow rate (Q), 286 //olvulus, 385, <b>386</b> Meckel diverticulum, 384 midgut, 386 Onchocerca, 158 sigmoid, 386 //omiting annular pancreas, 360 biliary colic, 396 bilious, 359, 384 diabetic ketoacidosis, 347 Ebola virus, 171 fructose intolerance, 80 glycylcyclines, 192 Histoplasma capsulatum, 177
collagen in, 50 //LDL (very low-density lipoprotein), 94 //olume contraction alkalemia from diuretics, 609 //olume of distribution, 231 //olumetric flow rate (Q), 286 //olvulus, 385, <b>386</b> Meckel diverticulum, 384 midgut, 386 //onchocerca, 158 sigmoid, 386 //omiting annular pancreas, 360 biliary colic, 396 bilious, 359, 384 diabetic ketoacidosis, 347 Ebola virus, 171 fructose intolerance, 80 glycylcyclines, 192 Histoplasma capsulatum, 177 intestinal atresia, 359
collagen in, 50 //LDL (very low-density lipoprotein), 94 //olume contraction alkalemia from diuretics, 609 //olume of distribution, 231 //olumetric flow rate (Q), 286 //olvulus, 385, <b>386</b> Meckel diverticulum, 384 midgut, 386 Onchocerca, 158 sigmoid, 386 //omiting annular pancreas, 360 biliary colic, 396 bilious, 359, 384 diabetic ketoacidosis, 347 Ebola virus, 171 fructose intolerance, 80 glycylcyclines, 192 Histoplasma capsulatum, 177
collagen in, 50 //LDL (very low-density lipoprotein), 94 //olume contraction alkalemia from diuretics, 609 //olume of distribution, 231 //olumetric flow rate (Q), 286 //olvulus, 385, 386 Meckel diverticulum, 384 midgut, 386 Onchocerca, 158 sigmoid, 386 //omiting annular pancreas, 360 biliary colic, 396 bilious, 359, 384 diabetic ketoacidosis, 347 Ebola virus, 171 fructose intolerance, 80 glycylcyclines, 192 Histoplasma capsulatum, 177 intestinal atresia, 359 Legionella spp, 185 lithium toxicity, 569 Mallory-Weiss syndrome, 377
collagen in, 50 //LDL (very low-density lipoprotein), 94 //olume contraction alkalemia from diuretics, 609 //olume of distribution, 231 //olumetric flow rate (Q), 286 //olvulus, 385, 386 Meckel diverticulum, 384 midgut, 386 Onchocerca, 158 sigmoid, 386 //omiting annular pancreas, 360 biliary colic, 396 bilious, 359, 384 diabetic ketoacidosis, 347 Ebola virus, 171 fructose intolerance, 80 glycylcyclines, 192 Histoplasma capsulatum, 177 intestinal atresia, 359 Legionella spp, 185 lithium toxicity, 569 Mallory-Weiss syndrome, 377 maple syrup urine disease, 84
collagen in, 50 //LDL (very low-density lipoprotein), 94 //olume contraction alkalemia from diuretics, 609 //olume of distribution, 231 //olumetric flow rate (Q), 286 //olumetric flow rate (Q), 286 //olumetric flow rate (Q), 286 //olumetric flow rate (Q), 286 //olumetric flow rate (Q), 286 //olumetric flow rate (Q), 286 //olumetric flow rate (Q), 286 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 3
collagen in, 50 //LDL (very low-density lipoprotein), 94 //olume contraction alkalemia from diuretics, 609 //olume of distribution, 231 //olumetric flow rate (Q), 286 //olumetric flow rate (Q), 286 //olumetric flow rate (Q), 286 //olumetric flow rate (Q), 286 //olumetric flow rate (Q), 286 //olumetric flow rate (Q), 286 //olumetric flow rate (Q), 286 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 360 //omiting annular pancreas, 3
collagen in, 50 //LDL (very low-density lipoprotein), 94 //olume contraction alkalemia from diuretics, 609 //olume of distribution, 231 //olumetric flow rate (Q), 286 //olvulus, 385, 386 Meckel diverticulum, 384 midgut, 386 Onchocerca, 158 sigmoid, 386 //omiting annular pancreas, 360 biliary colic, 396 bilious, 359, 384 diabetic ketoacidosis, 347 Ebola virus, 171 fructose intolerance, 80 glycylcyclines, 192 Histoplasma capsulatum, 177 intestinal atresia, 359 Legionella spp, 185 lithium toxicity, 569 Mallory-Weiss syndrome, 377 maple syrup urine disease, 84 metoclopramide for, 400 MI and, 305 ondansetron for, 400 posttussive, 143 pyloric stenosis, 359
collagen in, 50 //LDL (very low-density lipoprotein), 94 //olume contraction alkalemia from diuretics, 609 //olume of distribution, 231 //olumetric flow rate (Q), 286 //olvulus, 385, 386 Meckel diverticulum, 384 midgut, 386 Onchocerca, 158 sigmoid, 386 //omiting annular pancreas, 360 biliary colic, 396 bilious, 359, 384 diabetic ketoacidosis, 347 Ebola virus, 171 fructose intolerance, 80 glycylcyclines, 192 Histoplasma capsulatum, 177 intestinal atresia, 359 Legionella spp, 185 lithium toxicity, 569 Mallory-Weiss syndrome, 377 maple syrup urine disease, 84 metoclopramide for, 400 MI and, 305 ondansetron for, 400 posttussive, 143 pyloric stenosis, 359 receptors for, 496
collagen in, 50 //LDL (very low-density lipoprotein), 94 //olume contraction alkalemia from diuretics, 609 //olume of distribution, 231 //olumetric flow rate (Q), 286 //olvulus, 385, 386 Meckel diverticulum, 384 midgut, 386 Onchocerca, 158 sigmoid, 386 //omiting annular pancreas, 360 biliary colic, 396 bilious, 359, 384 diabetic ketoacidosis, 347 Ebola virus, 171 fructose intolerance, 80 glycylcyclines, 192 Histoplasma capsulatum, 177 intestinal atresia, 359 Legionella spp, 185 lithium toxicity, 569 Mallory-Weiss syndrome, 377 maple syrup urine disease, 84 metoclopramide for, 400 MI and, 305 ondansetron for, 400 posttussive, 143 pyloric stenosis, 359 receptors for, 496 Salmonella spp, 149 in stroke, 514
collagen in, 50 //LDL (very low-density lipoprotein), 94 //olume contraction alkalemia from diuretics, 609 //olume of distribution, 231 //olumetric flow rate (Q), 286 //olvulus, 385, 386 Meckel diverticulum, 384 midgut, 386 Onchocerca, 158 sigmoid, 386 //omiting annular pancreas, 360 biliary colic, 396 bilious, 359, 384 diabetic ketoacidosis, 347 Ebola virus, 171 fructose intolerance, 80 glycylcyclines, 192 Histoplasma capsulatum, 177 intestinal atresia, 359 Legionella spp, 185 lithium toxicity, 569 Mallory-Weiss syndrome, 377 maple syrup urine disease, 84 metoclopramide for, 400 MI and, 305 ondansetron for, 400 posttussive, 143 pyloric stenosis, 359 receptors for, 496 Salmonella spp, 149

trichinosis, 159
vitamin C toxicity, 69
Von Gierke disease, 87
von Hippel-Lindau disease, 525
chromosome association, 64 renal cell carcinoma and, 605
tumor suppressor genes and, 224
von Willebrand disease, 411, <b>428</b>
Voriconazole, 199
Vortioxetine, 576 VRE (vancomycin-resistant
enterococci)
daptomycin, 195
enterococci, 137 highly resistant, 198
oxazolidinones, 193
Vulnerable child syndrome, <b>556</b>
Vulvar carcinoma, <b>644</b>
Vulvar lymphatic drainage, 624 Vulvar pathology, 644
neoplastic, 644
non-neoplastic, 644
Vulvovaginitis, 153, <b>181</b>
vWF (von Willebrand factor) receptor for, 407
in thrombocytes, 407
in thrombogenesis, 411
V <sub>max</sub> , 230
W
WAGR complex/syndrome, 606
"Waiter's tip" (Erb palsy), 448
Waiving right to confidentiality, 267 Waldenstrom macroglobulinemia,
431
Walking milestone, 635
Wallenberg syndrome, 514
W/-11: 1
Wallerian degeneration, 495 Wall tension, 284, 285
Wallerian degeneration, 495 Wall tension, 284, 285 Warburg effect, 221
Wall tension, 284, 285 Warburg effect, 221 Warfarin, 436
Wall tension, 284, 285 Warburg effect, 221 Warfarin, 436 adverse effects of, 428
Wall tension, 284, 285 Warburg effect, 221 Warfarin, 436 adverse effects of, 428 coagulation cascade, 413
Wall tension, 284, 285 Warburg effect, 221 Warfarin, 436 adverse effects of, 428 coagulation cascade, 413 griseofulvin and, 200 heparin vs, 436, 437
Wall tension, 284, 285 Warburg effect, 221 Warfarin, 436 adverse effects of, 428 coagulation cascade, 413 griseofulvin and, 200 heparin vs, 436, 437 PT measurement, 426
Wall tension, 284, 285 Warburg effect, 221 Warfarin, 436 adverse effects of, 428 coagulation cascade, 413 griseofulvin and, 200 heparin vs, 436, 437 PT measurement, 426 teratogenicity, 614
Wall tension, 284, 285 Warburg effect, 221 Warfarin, 436 adverse effects of, 428 coagulation cascade, 413 griseofulvin and, 200 heparin vs, 436, 437 PT measurement, 426 teratogenicity, 614 therapeutic index of, 234
Wall tension, 284, 285 Warburg effect, 221 Warfarin, 436 adverse effects of, 428 coagulation cascade, 413 griseofulvin and, 200 heparin vs, 436, 437 PT measurement, 426 teratogenicity, 614 therapeutic index of, 234 toxicity treatment, 248, 429 vitamin K antagonist, 71
Wall tension, 284, 285 Warburg effect, 221 Warfarin, 436 adverse effects of, 428 coagulation cascade, 413 griseofulvin and, 200 heparin vs, 436, 437 PT measurement, 426 teratogenicity, 614 therapeutic index of, 234 toxicity treatment, 248, 429 vitamin K antagonist, 71 Warthin-Finkeldey giant cells, 170
Wall tension, 284, 285 Warburg effect, 221 Warfarin, 436 adverse effects of, 428 coagulation cascade, 413 griseofulvin and, 200 heparin vs, 436, 437 PT measurement, 426 teratogenicity, 614 therapeutic index of, 234 toxicity treatment, 248, 429 vitamin K antagonist, 71 Warthin-Finkeldey giant cells, 170 Warthin tumors, 376
Wall tension, 284, 285 Warburg effect, 221 Warfarin, 436 adverse effects of, 428 coagulation cascade, 413 griseofulvin and, 200 heparin vs, 436, 437 PT measurement, 426 teratogenicity, 614 therapeutic index of, 234 toxicity treatment, 248, 429 vitamin K antagonist, 71
Wall tension, 284, 285 Warburg effect, 221 Warfarin, 436 adverse effects of, 428 coagulation cascade, 413 griseofulvin and, 200 heparin vs, 436, 437 PT measurement, 426 teratogenicity, 614 therapeutic index of, 234 toxicity treatment, 248, 429 vitamin K antagonist, 71 Warthin-Finkeldey giant cells, 170 Warthin tumors, 376 Waterhouse-Friderichsen syndrome, 349 meningococci, 142
Wall tension, 284, 285 Warburg effect, 221 Warfarin, 436 adverse effects of, 428 coagulation cascade, 413 griseofulvin and, 200 heparin vs, 436, 437 PT measurement, 426 teratogenicity, 614 therapeutic index of, 234 toxicity treatment, 248, 429 vitamin K antagonist, 71 Warthin-Finkeldey giant cells, 170 Warthin tumors, 376 Waterhouse-Friderichsen syndrome, 349 meningococci, 142 Watershed zones, 210, 502
Wall tension, 284, 285 Warburg effect, 221 Warfarin, 436 adverse effects of, 428 coagulation cascade, 413 griseofulvin and, 200 heparin vs, 436, 437 PT measurement, 426 teratogenicity, 614 therapeutic index of, 234 toxicity treatment, 248, 429 vitamin K antagonist, 71 Warthin-Finkeldey giant cells, 170 Warthin tumors, 376 Waterhouse-Friderichsen syndrome, 349 meningococci, 142 Watershed zones, 210, 502 Water-soluble vitamins, 65
Wall tension, 284, 285 Warburg effect, 221 Warfarin, 436 adverse effects of, 428 coagulation cascade, 413 griseofulvin and, 200 heparin vs, 436, 437 PT measurement, 426 teratogenicity, 614 therapeutic index of, 234 toxicity treatment, 248, 429 vitamin K antagonist, 71 Warthin-Finkeldey giant cells, 170 Warthin tumors, 376 Waterhouse-Friderichsen syndrome, 349 meningococci, 142 Watershed zones, 210, 502
Wall tension, 284, 285 Warburg effect, 221 Warfarin, 436 adverse effects of, 428 coagulation cascade, 413 griseofulvin and, 200 heparin vs, 436, 437 PT measurement, 426 teratogenicity, 614 therapeutic index of, 234 toxicity treatment, 248, 429 vitamin K antagonist, 71 Warthin-Finkeldey giant cells, 170 Warthin tumors, 376 Waterhouse-Friderichsen syndrome, 349 meningococci, 142 Watershed zones, 210, 502 Water-soluble vitamins, 65 Waxy casts (urine), 594 WBC casts (urine), 594, 600 Weak acid overdose
Wall tension, 284, 285 Warburg effect, 221 Warfarin, 436 adverse effects of, 428 coagulation cascade, 413 griseofulvin and, 200 heparin vs, 436, 437 PT measurement, 426 teratogenicity, 614 therapeutic index of, 234 toxicity treatment, 248, 429 vitamin K antagonist, 71 Warthin-Finkeldey giant cells, 170 Warthin tumors, 376 Waterhouse-Friderichsen syndrome, 349 meningococci, 142 Watershed zones, 210, 502 Water-soluble vitamins, 65 Waxy casts (urine), 594 WBC casts (urine), 594, 600 Weak acid overdose treatment, 233
Wall tension, 284, 285 Warburg effect, 221 Warfarin, 436 adverse effects of, 428 coagulation cascade, 413 griseofulvin and, 200 heparin vs, 436, 437 PT measurement, 426 teratogenicity, 614 therapeutic index of, 234 toxicity treatment, 248, 429 vitamin K antagonist, 71 Warthin-Finkeldey giant cells, 170 Warthin tumors, 376 Waterhouse-Friderichsen syndrome, 349 meningococci, 142 Watershed zones, 210, 502 Water-soluble vitamins, 65 Waxy casts (urine), 594 WBC casts (urine), 594 WBC casts (urine), 594 Weak acid overdose treatment, 233 Weak bases overdose treatment, 233
Wall tension, 284, 285 Warburg effect, 221 Warfarin, 436 adverse effects of, 428 coagulation cascade, 413 griseofulvin and, 200 heparin vs, 436, 437 PT measurement, 426 teratogenicity, 614 therapeutic index of, 234 toxicity treatment, 248, 429 vitamin K antagonist, 71 Warthin-Finkeldey giant cells, 170 Warthin tumors, 376 Waterhouse-Friderichsen syndrome, 349 meningococci, 142 Watershed zones, 210, 502 Water-soluble vitamins, 65 Waxy casts (urine), 594 WBC casts (urine), 594 WBC casts (urine), 594 Weak acid overdose treatment, 233 Weak bases overdose treatment, 233 "Wear and tear" pigment, 211 Wegener granulomatosis, 315
Wall tension, 284, 285 Warburg effect, 221 Warfarin, 436 adverse effects of, 428 coagulation cascade, 413 griseofulvin and, 200 heparin vs, 436, 437 PT measurement, 426 teratogenicity, 614 therapeutic index of, 234 toxicity treatment, 248, 429 vitamin K antagonist, 71 Warthin-Finkeldey giant cells, 170 Warthin tumors, 376 Waterhouse-Friderichsen syndrome, 349 meningococci, 142 Watershed zones, 210, 502 Water-soluble vitamins, 65 Waxy casts (urine), 594 WBC casts (urine), 594 WBC casts (urine), 594 Weak acid overdose treatment, 233 Weak bases overdose treatment, 233 "Wear and tear" pigment, 211 Wegener granulomatosis, 315 autoantibody, 115
Wall tension, 284, 285 Warburg effect, 221 Warfarin, 436 adverse effects of, 428 coagulation cascade, 413 griseofulvin and, 200 heparin vs, 436, 437 PT measurement, 426 teratogenicity, 614 therapeutic index of, 234 toxicity treatment, 248, 429 vitamin K antagonist, 71 Warthin-Finkeldey giant cells, 170 Warthin tumors, 376 Waterhouse-Friderichsen syndrome, 349 meningococci, 142 Watershed zones, 210, 502 Water-soluble vitamins, 65 Waxy casts (urine), 594 WBC casts (urine), 594 WBC casts (urine), 594, 600 Weak acid overdose treatment, 233 Weak bases overdose treatment, 233 "Wear and tear" pigment, 211 Wegener granulomatosis, 315 autoantibody, 115 restrictive lung disease, 675
Wall tension, 284, 285 Warburg effect, 221 Warfarin, 436 adverse effects of, 428 coagulation cascade, 413 griseofulvin and, 200 heparin vs, 436, 437 PT measurement, 426 teratogenicity, 614 therapeutic index of, 234 toxicity treatment, 248, 429 vitamin K antagonist, 71 Warthin-Finkeldey giant cells, 170 Warthin tumors, 376 Waterhouse-Friderichsen syndrome, 349 meningococci, 142 Watershed zones, 210, 502 Water-soluble vitamins, 65 Waxy casts (urine), 594 WBC casts (urine), 594 WBC casts (urine), 594 WBC casts (urine), 594 Weak acid overdose treatment, 233 Weak bases overdose treatment, 233 "Wear and tear" pigment, 211 Wegener granulomatosis, 315 autoantibody, 115 restrictive lung disease, 675 Weight gain
Wall tension, 284, 285 Warburg effect, 221 Warfarin, 436 adverse effects of, 428 coagulation cascade, 413 griseofulvin and, 200 heparin vs, 436, 437 PT measurement, 426 teratogenicity, 614 therapeutic index of, 234 toxicity treatment, 248, 429 vitamin K antagonist, 71 Warthin-Finkeldey giant cells, 170 Warthin tumors, 376 Waterhouse-Friderichsen syndrome, 349 meningococci, 142 Watershed zones, 210, 502 Water-soluble vitamins, 65 Waxy casts (urine), 594 WBC casts (urine), 594 WBC casts (urine), 594 Weak acid overdose treatment, 233 Weak bases overdose treatment, 233 "Wear and tear" pigment, 211 Wegener granulomatosis, 315 autoantibody, 115

chronic mesenteric ischemia, 386
diabetes mellitus, 346
esophageal cancer, 378
gastric ulcers, 380
glucagonoma, 351
Histoplasma capsulatum, 177
malabsorption syndromes, 381
Mycobacterium avium-
intracellulare, 177
orlistat for, 400
pancreatic cancer, 398
polyarteritis nodosa, 314
polymyalgia rheumatica, 470
pseudotumor cerebri treatment,
521
renal cell carcinoma, 605
sleep apnea, 679
stomach cancer, 379
for stress incontinence, 599
tuberculosis, 140
Weil disease, 147
Well-patient care, 270–271
Wenckebach AV block, 295
Werdnig-Hoffmann disease, 530
Wernicke aphasia, 514, <b>516</b>
Wernicke area, 501
stroke effects, 514
Wernicke encephalopathy, 66, <b>571</b>
Wernicke-Korsakoff syndrome, 511,
571
vitamin B <sub>1</sub> deficiency, 66
Western blot, 53
West Nile virus, <b>167</b> , 180
West wife with a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a constant and a cons
Wet beriberi, 66
Wharton duct, 376
Wharton jelly, 618
Wheal
urticaria, 477
Wheals, 475
Wheezing
1
lung cancer, 684
Whipple disease, 381
periodic acid-Schiff stain for, 125
periodic acid-Schiff stain for, 125 Whipple procedure for pancreatic cancer, 398
for pancreatic cancer, 398
Whipple triad
insulinomas and, 351
William and a set of large (00)
Whispered pectoriloquy, 680
White matter
axonal injury, 515
demyelinating disorders, 524
glial cells in, 494
multiple sclerosis, 523
White pulp (spleen), 98
Whooping cough
Bordetella pertussis, 143
pertussis toxin, 132
Wickham striae, 482
Wide splitting, 289
Williams syndrome, 64
cardiac defect association, 300
Wilms tumor, 606
dactinomycin for, 439

FAS1\_2019\_21\_Index\_749-806.indd 802 11/21/19 12:27 PM

### INDEX

"Wire looping" of capillaries, 596 "Wire lupus," 596 Wiskott-Aldrich syndrome, 117 X-linked recessive disorder, 61 Withdrawal (psychoactive drugs), 570 Wobble, 37 Wolff-Chaikoff effect, 341 Wolffian duct, 622 Wolff-Parkinson-White syndrome, 294 Woolsorter's disease, 137 'word salad," 559 Wound healing keratinocytes, 216 phases of, 216 scar/keloid formation, 218 Woven bone, 458 Wright-Giemsa stain, 407 Wright stain Borrelia spp, 146 Wrinkles of aging, 52 injuries of, 459 bones, 449 Wrist drop, 447 lead poisoning, 419 Written advance directives, 266 WT1/WT2 genes in renal disease, 224, 606 oncogenicity of, 224 Wuchereria bancrofti, 158, 159

### X Xanthine oxidase inhibitors, 467 Xanthogranulomatous pyelonephritis, Xanthomas familial dyslipidemias, 94 hyperlipidemia and, 301 Xeroderma pigmentosum DNA repair defects in, 40 Xerosis cutis, 66 Xerostomia, 240, 243, 468 X-inactivation (lyonization) Barr body formation, 61 X-linked agammaglobulinemia, 116 X-linked dominant inheritance, 59 X-linked recessive disorders, 61 agammaglobulinemia, 116 hyper-IgM syndrome, 117 Menkes disease, 51 NADPH oxidase defect, 117 Wiskott-Aldrich syndrome, 117 X-linked recessive inheritance, 59 X-ray/imaging findings Apple core lesion, 388 bamboo spine, 469 Bird's beak sign, 376 Bone-in-bone, 463 Codman triangle, 465

Coffee bean sign, 386

Coin lesion, 684

Crew cut (skull x-ray), 422
kidney stones, 598
pencil-in-cup, 469
punched out bone lesions, 431
Steeple sign (x-ray), 170
String sign, 382
Sunburst pattern, 465
Thumbprint sign (imaging), 386
Thumb sign, 142
X-ray teratogenicity, 614
Υ
Yellow fever, 167, <b>168</b>
liver anatomy and, 367
Yersinia enterocolitica, 179
transmission and treatment, 144
Yersinia pestis
animal transmission, 149
facultative intracellular organisms,

## Z

Zafirlukast, 687 Zaleplon, 546

127

Yo antigens, 228

ovarian, 647

testicular, 653

reactive arthritis, 469

Yolk sac tumor

Yersinia spp

Zanamivir, 201 Zellweger syndrome, 47 Zenker diverticulum, 384 Zero-order elimination, 232 Zidovudine, 203 Ziehl-Neelsen stain, 125 Zika virus, 171 Zileuton, 687 Zinc, 71 Wilson disease, 395 Ziprasidone, 573 Zoledronic acid, 486 Zollinger-Ellison syndrome, 352 duodenal ulcer, 380 gastrin in, 371 MEN 1 syndrome, 351 proton pump inhibitors for, 399 Zolpidem, 546 Zona fasciculata, **327**, 336 Zona glomerulosa, 327 Zona reticularis, 327 Zoonotic bacteria, 149 Zymogens, 373

FAS1\_2019\_21\_Index\_749-806.indd 803 11/21/19 12:27 PM

► NOTES	

FAS1\_2019\_21\_Index\_749-806.indd 804 11/21/19 12:27 PM

<b>▶</b> NOTES	

FAS1\_2019\_21\_Index\_749-806.indd 805 11/21/19 12:27 PM

► NOTES	

FAS1\_2019\_21\_Index\_749-806.indd 806 11/21/19 12:27 PM

<b>▶</b> NOTES	

FAS1\_2019\_22\_About the Editors.indd 807 11/8/19 8:35 AM

# **About the Editors**



## Tao Le, MD, MHS

Tao developed a passion for medical education as a medical student. He currently edits more than 15 titles in the *First Aid* series. In addition, he is Founder and Chief Education Officer of USMLE-Rx for exam preparation and ScholarRx for undergraduate medical education. As a medical student, he was editor-in-chief of the University of California, San

Francisco (UCSF) *Synapse*, a university newspaper with a weekly circulation of 9000. Tao earned his medical degree from UCSF in 1996 and completed his residency training in internal medicine at Yale University and fellowship training at Johns Hopkins University. Tao subsequently went on to cofound Medsn, a medical education technology venture, and served as its chief medical officer. He is currently chief of adult allergy and immunology at the University of Louisville.



### Vikas Bhushan, MD

Vikas is a writer, editor, entrepreneur, and teleradiologist on extended sabbatical. In 1990 he conceived and authored the original *First Aid for the USMLE Step 1*. His entrepreneurial endeavors included a student-focused medical publisher (S2S), an e-learning company (medschool.com), and an ER teleradiology practice (24/7 Radiology). Trained on the Left

Coast, Vikas completed a bachelor's degree at the University of California Berkeley; an MD with thesis at UCSF; and a diagnostic radiology residency at UCLA. His eclectic interests include technology, cryptoeconomics, information design, South Asian diasporic culture, and avoiding a day job. Always finding the long shortcut, Vikas is an adventurer, knowledge seeker, and occasional innovator. He enjoys intermediate status as a kiteboarder and father, and strives to raise his three children as global citizens.



## **Matthew Sochat, MD**

Matthew is a third-year hematology/oncology fellow at St. Louis University in St. Louis, Missouri. He completed his internal medicine residency training at Temple University Hospital in Philadelphia. He completed medical school in 2013 at Brown University and is a 2008 graduate of the University of Massachusetts. Amherst, where he studied

biochemistry and the classics. Pastimes include skiing, cooking/baking, traveling, the company of friends/loved ones (especially his wonderful wife), the Spanish language, and computer/video gaming. Be warned: Matt also loves to come up with corny jokes at (in)opportune moments.



# Vaishnavi Vaidyanathan, MD

Vaishnavi is a second-year child neurology resident at Phoenix Children's Hospital in Phoenix, Arizona. She is a graduate of the University of Missouri-Kansas City School of Medicine, where she earned her bachelor's and medical degrees. Her interests include medical education and health advocacy. Outside of medicine, she loves to dance, learn new languages, and watch Bollywood movies.



## Sarah Schimansky, MB BCh BAO

Sarah is a third-year ophthalmology resident in the UK. She grew up in Germany before moving to Dublin, Ireland, to study medicine at the Royal College of Surgeons in Ireland. She has a keen interest in medical education and is currently enrolled in a Masters in Surgical Education program at Imperial College London. An avid traveler, Sarah is always

on the lookout for new destinations to explore and new countries to call home. When she is not on the road, she enjoys yoga, long walks, and red wine in the company of friends and family.



### **Jordan Abrams**

Jordan is a fourth-year medical student at St. George's University School of Medicine who hopes to pursue residency training in anesthesiology. He graduated magna cum laude from the University of Delaware, earning a bachelor's degree in neuroscience with minors in medical humanities and biological sciences. Combining his creative

mindset and passion for drawing, Jordan founded theHYMedicine.com, an educational website that offers free medical study guides, tutoring, and study schedules for students worldwide. Aside from medicine, Jordan enjoys traveling, reading, and playing soccer.



### Kimberly Kallianos, MD

Originally from Atlanta, Kimberly graduated from the University of North Carolina at Chapel Hill in 2006 and from Harvard Medical School in 2011. She completed her radiology residency and fellowship at UCSF and is currently an Assistant Professor of Clinical Radiology at UCSF in the Cardiac and Pulmonary Imaging section.

FAS1\_2019\_22\_About the Editors.indd 808 11/8/19 8:35 AM

# SECTION IV

# **Top-Rated Review Resources**

"Some books are to be tasted, others to be swallowed, and some few to be chewed and digested."

-Sir Francis Bacon

"Always read something that will make you look good if you die in the middle of it."

-P.J. O'Rourke

"So many books, so little time."

—Frank Zappa

"If one cannot enjoy reading a book over and over again, there is no use in reading it at all."

-Oscar Wilde

▶ How to Use the Database	2
▶ Question Banks and Books	4
► Web and Mobile Apps	6
▶ Comprehensive	10
Anatomy, Embryology and Neuroscience	, 12
▶ Behavioral Science	14
<b>▶</b> Biochemistry	15
▶ Cell Biology and Histology	16
► Microbiology and Immunology	17
▶ Pathology	19
▶ Pharmacology	21
▶ Physiology	22

# ► HOW TO USE THE DATABASE

This section is a database of top-rated basic science review books, sample examination books, websites, apps, and commercial review courses that have been marketed to medical students studying for the USMLE Step 1. At the end of the section is a list of publishers and independent bookstores with addresses and phone numbers. For each recommended resource, we list (where applicable) the Title, the First Author (or editor), the Series Name (where applicable), the Current Publisher, the Copyright Year, the Number of Pages, the ISBN, the Approximate List Price, the Format of the resource, and the Number of Test Questions. We also include Summary Comments that describe their style and overall utility for studying. Finally, each recommended resource receives a Rating. Within each section, resources are arranged first by Rating and then alphabetically by the first author within each Rating group.

A letter rating scale with six different grades reflects the detailed student evaluations for **Rated Resources**. Each rated resource receives a rating as follows:

A+	Excellent for boards review.
A A–	Very good for boards review; choose among the group.
B+ B	Good, but use only after exhausting better resources.
В-	Fair, but there are many better resources in the discipline; or low-yield subject material.

The Rating is meant to reflect the overall usefulness of the resource in helping medical students prepare for the USMLE Step 1. This is based on a number of factors, including:

- The cost
- The readability of the text
- The appropriateness and accuracy of the material
- The quality and number of sample questions
- The quality of written answers to sample questions
- The quality and appropriateness of the images and illustrations
- The quality of the user interface and learning experience, for web and mobile apps
- The length of the text (longer is not necessarily better)
- The quality and number of other resources available in the same discipline
- The importance of the discipline for the USMLE Step 1

Please note that ratings do not reflect the quality of the resources for purposes other than reviewing for the USMLE Step 1. Many books with

lower ratings are well written and informative but are not ideal for boards preparation. We have not listed or commented on general textbooks available in the basic sciences.

Evaluations are based on the cumulative results of formal and informal surveys of thousands of medical students at many medical schools across the country. The summary comments and overall ratings represent a consensus opinion, but there may have been a broad range of opinion or limited student feedback on any particular resource.

Please note that the data listed are subject to change in that:

- Publisher and app store prices change frequently.
- Retail and online bookstores may set their own prices.
- New editions and app versions come out frequently, and the quality of updating varies.
- The same book may be reissued through another publisher.

We actively encourage medical students and faculty to submit their opinions and ratings of these basic science review materials so that we may update our database. In addition, we ask that publishers and authors submit for evaluation review copies of basic science review books, including new editions and books not included in our database. We also solicit reviews of new books, mobile apps, websites, flash cards, and commercial review courses.

### **Disclaimer/Conflict of Interest Statement**

None of the ratings reflects the opinion or influence of the publisher. All errors and omissions will gladly be corrected if brought to the attention of the authors through our blog at www.firstaidteam.com. Please note that USMLE-Rx and the entire First Aid for the USMLE series are publications by certain authors of First Aid for the USMLE Step 1; the following ratings are based solely on recommendations from the student authors of First Aid for the USMLE Step 1 as well as data from the student survey and feedback forms.

FAS1 2019 23 BookRev ONLINE.indd 3 11/8/19 6:49 AM

# ▶ QUESTION BANKS AND BOOKS



# **UWorld Qbank** UWorld

**\$249-\$749** Test/2400 q

www.uworld.com

Questions demand multistep reasoning and are often more difficult than those on the actual Step 1 exam. Offers detailed explanations with figures and tables. Features a number of test customization and analysis options. Users can see cumulative results both over time and compared to other test takers. In addition to a desktop version, it can be accessed through iOS or Android mobile apps.



# **NBME Practice Exams**

**\$60** Test/200 q

### NATIONAL BOARD OF MEDICAL EXAMINERS

www.nbme.org/students/sas/Comprehensive.html

The official practice exams published by the NBME are comprised of retired Step 1 questions. NBME research found that they show a "moderate correlation" with actual Step 1 performance. The exams will show you which questions you answered incorrectly, but they will not show any explanations. You will also not be able to review correctly answered questions. Students generally use these as rough gauges of their score progression over their study time. Note that you can sign up to for an in-person practice exam for an additional \$75 to be taken at Prometric, for students who want to practice the logistics of exam day.



## **AMBOSS**

**\$9-\$365** Test/3500 q

### **A**MBOSS

www.amboss.com

Integrated question bank for Step 1 and Step 2 CK exams with an additional interactive online library of medical resources. Contains numerous illustrations within the clinical vignettes. Allows for the selection of questions by difficulty level. Includes personalized study plan. Free trial available, accessible through iOS or Android mobile apps.



# **USMLE-Rx Qmax** USMLE-Rx

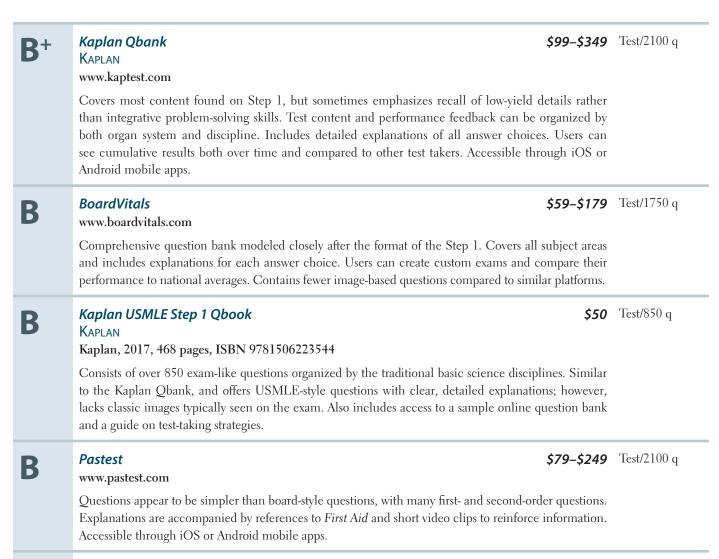
**\$89-\$339** Test/2300 q

www.usmle-rx.com

Offers Step 1–style questions accompanied by thorough explanations. Omits obscure material and distills high yield information. Each explanation includes references from *First Aid*. However, the proportion of questions covering a given subject area does not always reflect the actual exam's relative emphasis. Question stems occasionally rely on "buzzwords." Most useful to help memorize *First Aid* facts. Provides detailed performance analyses. Free trial available, accessible through iOS or Android mobile apps.

B

www.truelearn.com



**TrueLearn Review** \$159–\$399 Test/2200 q

Includes over 2200 USMLE-style practice questions with topics mapped to the NBME blueprint. Uses national benchmarking to show students where they stand in comparison to peers.

FAS1\_2019\_23\_BookRev\_ONLINE.indd 5 11/8/19 6:49 AM

**TOP-RATED REVIEW RESOURCES** 

# ▶ WEB AND MOBILE APPS

Anki

Free Flash cards

### www.ankisrs.net

Flash card-making resource designed for retention of facts through spaced repetition. Free access via desktop and smartphone for Windows, Mac, and Android. The iOS app must be purchased for \$25. Available in different languages.

A

# **Boards and Beyond**

**\$19–\$249** Review

www.boardsbeyond.com

Includes over 400 videos averaging ~26 minutes each, covering the breadth of Step 1 material. Membership includes access to the companion books as PDFs. A collection of videos is offered as free samples on the website. Also includes over 1300 practice questions.

# Physeo

**\$30-\$150** Review

www.physeo.com

Online review containing 32 hours of review videos covering physiology. Accessible via website or mobile app. Includes a supplemental full-color PDF textbook. Videos are concise and focus on highyield material, and board-style practice questions are included after each topic to help solidify understanding. Similar structure to Pathoma, but with physiology focus.

A

# **SketchyMedical**

**\$99–\$369** Review

www.sketchymedical.com

Video library of narrated lectures with thorough explanations that present microbiology, pharmacology, and pathology in a memorable style. Access to the entire gram-positive cocci section is free at signup. Additional content can be purchased on a subscription basis.

 $A^{-}$ 

### **Cram Fighter**

www.cramfighter.com

\$29-\$159

Study plan

Helps organize a study schedule. Highly flexible with customizable settings. Supports more than 650 of the most popular books, video lectures, question banks, and flash cards. Mobile apps available for iOS and Android.

# First Aid Step 1 Express

**\$69-\$299** Review/Test

www.usmle-rx.com

More than 80 hours of high-yield videos explaining material from First Aid for the USMLE Step 1. Videos include more than 600 extra images and multimedia clips. Step-by-step analysis of USMLE-style questions with each video. Subscription includes a color workbook with over 200 pages.

B<sup>+</sup>

## First Aid Step 1 Flash Facts

**\$29-\$149** Flash cards

www.usmle-rx.com

Access to 12,000+ flash cards with intelligent spaced repetition integrated with First Aid for the USMLE Step 1, of which 3500+ are case based. Updated each year to reflect the newest edition of the book; students can access the past 3 editions' worth of flash cards. Searchable by organ system, discipline, and topic.

FAS1 2019 23 BookRev ONLINE.indd 6 11/8/19 6:49 AM



Free online learning and collaboration community for students preparing for their exams. Supplements medical school coursework and Step 1 studying with simplified, to-the-point online search platform that is best used as a reference. Recently added premium content for \$80-\$250 includes an online question bank and adaptive learning system.

#### Free Review Medical School Pathology B<sup>+</sup>

www.medicalschoolpathology.com

supplemental flash cards for integrated learning.

www.lab.anhb.uwa.edu.au/mb140

Offers lectures and slides based on the Robbins Pathology textbook. Lectures can be downloaded.

Free Review **OnlineMedEd** B<sup>+</sup> www.onlinemeded.org

A video lecture series covering primarily clinical science material, with recent addition of biochemistry, cell biology, and immunology topics. Video access is free with registration. A subscription of \$10-\$70/month gains access to ad-free videos, lecture notes, flash cards, question bank, and downloadable audio lectures.

\$179-\$279 Test **Osmosis** B<sup>+</sup> www.osmosis.org

Web platform that includes exam study scheduling tool, 27,000+ variable quality multiple choice questions, flash cards with spaced repetition, and 3000+ curated concept cards with videos, memory anchors, and reference articles. Includes a curriculum analysis and search engine, collaboration features for study groups, and a mobile app with quizzes and videos.

**\$2-\$10** Test/1400 q **USMLE Step 1 Mastery** B<sup>+</sup>

builtbyhlt.com/medical/usmle-step-1-mastery Question bank accessible through website or via free mobile app. Covers all USMLE topics and includes vignettes, images, and mnemonics. Question formatting is generally less representative of actual USMLE questions compared with other widely used question banks. Mobile app contains

WebPath: The Internet Pathology Laboratory Free Review/ B<sup>+</sup> Test/1300 q webpath.med.utah.edu

Features more than 2700 gross and microscopic images, clinical vignette questions, and case studies. Includes nine general pathology exams and 11 system-based pathology exams with approximately 1300 questions. Also features 170 questions associated with images. Questions are useful for reviewing boards content but are typically untimed, easier, and shorter. No multimedia practice questions. Not regularly updated with regard to high-yield Step 1 material.

Free Review/Test **Blue Histology** B

Provides access to 400+ histologic images with thorough explanations. Images searchable by topic, stain, keyword. Website also contains multiple choice practice questions.

FAS1 2019 23 BookRev ONLINE.indd 7 11/8/19 6:49 AM 8 **SECTION IV** 

**TOP-RATED REVIEW RESOURCES** 

### **Digital Anatomist Project: Interactive Atlases** B

Free Review

University of Washington

da.si.washington.edu/da.html

Contains an interactive neuroanatomy course along with a three-dimensional atlas of the brain, thorax, and knee. Atlases have computer-generated images and cadaver sections. Each atlas also has a quiz in which users identify structures in the slide images. However, questions do not focus on high-yield anatomy for Step 1.

Dr. Najeeb Lectures B

\$99 Review

www.drnajeeblectures.com

Hundreds of hours of video lectures covering basic medical sciences and clinical medicine with thousands of hand-drawn illustrations and mnemonics. Website provides mobile video support on smartphones and tablets. Free lectures accessible at www.drnajeeblectures.com/free-medical-videos.html.

**Firecracker** B FIRECRACKER INC. \$39-\$660

Review/ Test/2800 q

firecracker.lww.com

Learning platform divided into modules. The Step 1 module is divided into organ systems and includes review of preclinical lecture material, periodic quizzes on flagged reviewed material, and USMLE-style questions in interface simulating the actual exam. Contains page references to First Aid for the USMLE Step 1 and high-yield diagrams from various textbooks. Users can grade how well they remember the quiz answers (1-5), which allows the program to customize future quizzes. Features detailed performance analysis and a calendar for personalized study plans. Accessible on all smartphones and tablets. Comprehensive; best if started early in preclinical years.

**KISSPrep \$99–\$135** Review B www.kissprep.com

Online lecture videos focused on select subjects from the Step 1 exam. Focuses on harder-to-learn content and teaches it in a simple, easy-to-understand manner. Quizzes and other interactive tools are available to help with knowledge retention. Not all Step 1 content is covered on this platform.

**\$50-\$300** Review/ Lecturio B Test/2150 q www.lecturio.com

Online platform for comprehensive exam preparation, including over 250 hours of lectures, a flash card deck, quizzes, and a question bank. Organized by subject matter and allows users to customize their learning experience. Some content may be beyond the scope of the exam and better suited for medical school coursework. Lectures and quizzes may be accessed for free. iOS and Android apps are available.

**\$19-\$239** Flash cards **Memorang** B MEMORANG INC.

www.memorangapp.com

Platform utilizing spaced repetition, available both in website and app form. Utilizes custom and/or premade flash card "study sets" derived from 15,000 flash cards that focus on specific subject areas and are then tested via various games and quizzing methods. Free 7-day trial, or monthly/annual membership.

FAS1 2019 23 BookRev ONLINE.indd 8 11/8/19 6:49 AM

#### **\$25-\$480** Review B **Picmonic**

## www.picmonic.com

Helpful resource for visual learners. Unique images and stories with daily quizzes and spaced repetition. Contains 1400 images and includes study guides, webinars, and infographics that help cover 15,000+ facts of Step 1 material. Offered via both web and mobile platforms.

#### Free Cases/Test Radiopaedia.org B-

## www.radiopaedia.org

A user-friendly website with thousands of well-organized radiology cases and articles. Encyclopedia entries contain high-yield bullet points of anatomy and pathology. Images contain detailed descriptions but no arrows to demarcate findings. Quiz mode allows students to make a diagnosis based on radiographic findings. Content may be too broad for boards review but is a good complement to classes and clerkships.

#### Free Review The Pathology Guy B-

# FRIEDLANDER

www.pathguy.com

Contains extensive but poorly organized information on a variety of fundamental concepts in pathology. A high-yield summary intended for USMLE review can be found at www.pathguy.com/meltdown.txt, but the information given is limited by a lack of images and frequent digressions.

FAS1\_2019\_23\_BookRev\_ONLINE.indd 9 11/8/19 6:49 AM

# **▶** COMPREHENSIVE

# A

# First Aid for the Basic Sciences: General Principles

**\$55** Review

LE

McGraw-Hill, 2019, 816 pages, ISBN 9781260143676

Comprehensive review of the basic sciences covered in year 1 of medical school. Similar to the first part of *First Aid*, organized by discipline, and includes hundreds of color images and tables. Best if started with first-year coursework and then used as a reference during boards preparation.

# A

# First Aid Cases for the USMLE Step 1

**\$50** Cases

LE

 $McGraw-Hill,\,2018,\,496\;pages,\,ISBN\;9781260143133$ 

A recently updated series of hundreds of high-yield cases organized by organ system. Each case features a clinical vignette with relevant images, followed by questions and short, high-yield explanations. Offers coverage of many frequently tested concepts, and integrates subject matter in the discussion of the vignette. Helpful in reviewing material outlined in *First Aid for the USMLE Step 1*.



# First Aid for the Basic Sciences: Organ Systems

**\$72** Review

LE

McGraw-Hill, 2017, 912 pages, ISBN 9781259587030

A comprehensive review of the basic sciences covered in year 2 of medical school. Similar to the second part of *First Aid*, organized by organ system, and includes hundreds of color images and tables. Each organ system contains discussion of embryology and anatomy, physiology, pathology, and pharmacology. Best if started with second-year coursework and then used as a reference during boards preparation.



# Crush Step 1: The Ultimate USMLE Step 1 Review O'CONNELL

**\$45** Review

Elsevier, 2017, 704 pages, 9780323481632

Detailed, text-heavy review book with practice questions included. Coverage of many high-yield topics but includes some outdated information. Best if used with coursework, but also recommended as a supplemental reference for boards review. Limited student feedback.

A-

# Cracking the USMLE Step 1

\$45 Review

PRINCETON REVIEW

Princeton Review, 2013, 832 pages, ISBN 9780307945068

Comprehensive review book with hundreds of illustrations, charts, and diagrams along with 2 full-length practice tests with detailed answer explanations available online. Limited student feedback.

B<sup>+</sup>

## **USMLE Step 1 Secrets in Color**

\$43 Review

**B**ROWN

Elsevier, 2016, 800 pages, ISBN 9780323396790

Clarifies difficult concepts in a concise, readable manner. Uses a case-based format and integrates information well. High-quality clinical images. Complements other boards study resources, with a focus on understanding preclinical fundamentals rather than on rote memorization. Slightly lengthy for last-minute studying.

#### B+ Step-Up to USMLE Step 1 2015 **J**ENKINS

**\$50** Review

Lippincott Williams & Wilkins, 2014, 528 pages, ISBN 9781469894690

An organ system-based review text with clinical vignettes that is useful for integrating the basic sciences covered on Step 1. Composed primarily of outlines, charts, tables, and diagrams. Limited scope of material covered. Includes access to a sample online question bank.

#### B+ **USMLE Step 1 Lecture Notes 2018** KAPLAN

**\$330** Review

Kaplan Medical, 2018, ~2700 pages, ISBN 9781506221229

Extremely comprehensive review of Step 1 topics through videos and lecture notes. Split into individual sections covering pathology, pharmacology, physiology, biochemistry and medical genetics, immunology and microbiology. Generally best used to fill gaps in understanding and to review unfamiliar topics that one has not come across, and therefore the notes are commonly used by foreign medical graduates. Some sections are quite detailed and go beyond the scope of the Step 1 exam.

#### USMLE Images for the Boards: A Comprehensive Image-Based Review B<sup>+</sup> TULLY

\$42 Review

Elsevier, 2012, 296 pages, ISBN 9781455709038

Contains more than 300 color images of content likely to be tested on the Step 1. Contains a wide variety of images including ECGs and radiographic studies. Some images may be low yield for boards studying, but still excellent as a supplement to preclinical courses.

#### **USMLE Step 1 Made Ridiculously Simple** B CARL

\$30 Review/Test 1000 q

MedMaster, 2017, 416 pages, ISBN 9781935660224

Concise, succinct text. Online access to more than 1000 practice questions. Uses a table and chart format organized by subject, but some charts are poorly labeled. Consider as an adjunct to more comprehensive sources.

### medEssentials for the USMLE Step 1 B

**\$55** Review

Kaplan, 2012, 588 pages, ISBN 9781609780265

A comprehensive review divided into general principles and organ systems, organized using highyield tables and figures. Helpful for visual learners, but can be overly detailed and time consuming. Includes color images in the back along with a monthly subscription to online interactive exercises, although these are of limited value for Step 1 preparation. Comes with a free mobile version.

**SECTION IV** 

**TOP-RATED REVIEW RESOURCES** 

# ► ANATOMY, EMBRYOLOGY, AND NEUROSCIENCE

# **High-Yield Gross Anatomy**

\$43 Review

Lippincott Williams & Wilkins, 2014, 320 pages, ISBN 9781451190236

A good review of gross anatomy with some clinical correlations. Contains color clinical photos and well-labeled, high-yield radiographic images, but often goes into excessive detail that is beyond the scope of the boards.

# A-

# Clinical Anatomy Made Ridiculously Simple

**\$30** Review

GOLDBERG MedMaster, 2016, 175 pages, ISBN 9780940780972

An easy-to-read text offering simple diagrams along with numerous mnemonics, helpful charts, and amusing associations. The humorous style has variable appeal to students, so browse the content before purchasing. Offers good coverage of selected topics. Includes a CD-ROM atlas of normal radiographic anatomy. Best if used during coursework. Includes more detail than typically tested on Step 1.

### High-Yield Embryology B<sup>+</sup>

\$56 Review

DUDEK

Lippincott Williams & Wilkins, 2013, 176 pages, ISBN 9781451176100

A concise review of a relatively less-tested subject. Offers excellent organization with clinical correlations. Includes a high-yield list of embryologic tissue origins and USMLE-style case studies after each chapter. May not be suitable for dedicated Step 1 studying.

# B<sup>+</sup>

# **High-Yield Neuroanatomy** Fix

**\$40** Review/ Test/50 q

Lippincott Williams & Wilkins, 2015, 208 pages, ISBN 9781451193435

An easy-to-read, straightforward format with excellent diagrams and illustrations. Features a useful atlas of brain and spinal cord images, a glossary of important terms, and an appendix of neurologic lesions. Overall, a great resource and quick read, but more detailed than what is required for Step 1.

# B<sup>+</sup>

# Anatomy—An Essential Textbook **GILROY**

\$48 Text/

Test/400 q

Thieme, 2017, 528 pages, ISBN 9781626234390

A thorough, visually appealing approach to learning anatomy. Contains over 650 colorful, helpful illustrations. Presents material in bullet-point format and tables. Includes over 160 clinical correlates and 400 USMLE-style questions, with the opportunity to complete practice questions online.

# B<sup>+</sup>

# **Netter's Anatomy Flash Cards**

\$40 Flash cards

HANSEN

Saunders, 2018, 688 flash cards, ISBN 9780323530507

Netter's illustrations in a question/answer column format that allows for self-testing. Each card includes commentary on the structures with a clinical correlation. More effective as a supplement to coursework, and much too detailed for boards preparation. Lack of embryology correlates limits Step 1 usefulness. Includes online access with additional bonus cards and more than 400 multiple choice questions. Note: an iOS app has a similar cost and additional functionality.

13

#### \$45 Review B+ Crash Course: Anatomy

**S**TENHOUSE

Elsevier, 2015, 288 pages, ISBN 9780723438540

Part of the Crash Course review series for basic sciences, integrating clinical topics. Offers two-color illustrations, handy study tools, and Step 1 review questions. Contains an up-to-date self-assessment section. Provides a solid review of anatomy for Step 1. Best if started early.

#### **\$56** Review/ **BRS Embryology** B Test/220 q

Lippincott Williams & Wilkins, 2014, 336 pages, ISBN 9781451190380

An outline-based review of embryology that is typical of the BRS series. Offers a good review and includes much more detail than is required for Step 1. A discussion of congenital malformations is included at the end of each chapter, along with over 220 USMLE-style questions with answers and explanations. The comprehensive exam at the end of the book is high yield. Includes access to a searchable online text on the free companion website, which also features interactive quizzing.

#### **\$60** Flash cards Anatomy Flash Cards: Anatomy on the Go B **GILROY**

Thieme, 2013, 752 flash cards, ISBN 9781604069105

Flash card deck containing high-quality illustrations and a question/answer format that allows for self-testing. Occasional radiographic image. Best if used with coursework; too long for efficient boards preparation.

#### \$26 Review/Test/ Clinical Neuroanatomy Made Ridiculously Simple B Few q

MedMaster, 2014, 90 pages + CD-ROM, ISBN 9781935660194

An easy-to-read, memorable, and simplified format with clever diagrams. Offers a quick, high-yield review of clinical neuroanatomy, but not a comprehensive resource for boards review. Places appropriate emphasis on clinically relevant pathways, cranial nerves, and neurologic diseases. Includes a CD-ROM with CT and MR images, a tutorial on neurologic localization, and interactive quizzes covering classic neurology cases.

#### **\$20** Review **Netter's Anatomy Coloring Book** B

Elsevier, 2018, 392 pages, ISBN 9780323545037

An easy-to-understand, detailed, interactive book that is an excellent companion to traditional textbooks during preclinical anatomy coursework. Provides multiple views and magnifications of anatomic structures as well as dissection layers. The coloring aspect of the book can be highly beneficial for visual learners. Contains few clinical correlations, which limits its usefulness during dedicated studying for Step 1.

#### **Case Files: Anatomy \$35** Cases B Toy

McGraw-Hill, 2014, 416 pages, ISBN 9780071794862

Review text that includes 58 well-chosen cases with discussion, comprehension questions, and takehome pearls. Tables are helpful, but schematics are black and white and not representative of Step 1. A reasonable book to work through for those who benefit from problem-based learning.

FAS1 2019 23 BookRev ONLINE.indd 13 11/8/19 6:49 AM

### TOP-RATED REVIEW RESOURCES

B-

### Case Files: Neuroscience

**\$35** Cases

Toy

McGraw-Hill, 2014, 432 pages, ISBN 9780071790253

Similar to other *Case Files* books, it includes 49 clinical cases with lengthy discussion and 3–5 multiple choice questions at the end of each case. Cases are helpful, but the discussion is too lengthy. Questions are not the most representative of those seen on boards. Limited student feedback.

### ▶ BEHAVIORAL SCIENCE



### **BRS Behavioral Science**

**\$52** Review/ Test/700 q

Fadem

Lippincott Williams & Wilkins, 2016, 384 pages, ISBN 9781496310477

An easy-to-read outline-format review of behavioral science. Offers detailed coverage of mostly high-yield topics, but at a level of depth that often exceeds what is tested on Step 1. Better used prior to dedicated study period. Incorporates tables and charts as well as a short but complete statistics chapter. Features over 700 review questions, including a 100-question comprehensive exam. References DSM-V criteria.

B<sup>+</sup>

# High-Yield Biostatistics, Epidemiology, and Public Health GLASER

\$43 Review

Lippincott Williams & Wilkins, 2013, 168 pages, ISBN 9781451130171

A well-written, easy-to-read text that offers extensive coverage of epidemiology and biostatistics. Includes helpful review questions and tables, but somewhat lengthy given the low-yield nature of this subject on Step 1.

#### **▶** BIOCHEMISTRY

# Α-

#### **Pixorize**

**\$100-\$130** Review

#### www.pixorize.com

Visual mnemonic system focusing primarily on biochemistry. Step-by-step videos and interactive images aid studying and review. Compare to Sketchy and Picmonic.

## B<sup>+</sup>

# Medical Biochemistry—An Illustrated Review Panini

**\$40** Review/ Test/400 q

Thieme, 2013, 441 pages, ISBN 9781604063165

A comprehensive medical biochemistry study guide with an emphasis on images. Very detailed and may be better as a supplement to preclinical courses than as a review resource for the Step 1. Images and diagrams are helpful for solidifying knowledge. Online access available for additional content, including 400 USMLE-style practice questions.

# Baron Lange Flash Cards Biochemistry and Genetics Baron

\$40 Flash cards

McGraw-Hill, 2017, 196 flash cards, ISBN 9781259837210

Flash card deck featuring clinical vignettes on one side and concise discussions on the other. Each section contains 2–3 cards on biochemistry principles. High level of detail may make this less ideal for dedicated boards studying. Note that no carrying case for the cards is included.

# **B** *Lippincott Illustrated Reviews: Biochemistry*FERRIER

**\$78** Review/ Test/200 q

Lippincott Williams & Wilkins, 2017, 560 pages, ISBN 9781496344496

An integrative and comprehensive review of biochemistry that includes good clinical correlations and effective color diagrams. Extremely detailed and requires significant time commitment, so it should be started with first-year coursework. High-yield summaries at the end of each chapter. Comes with access to the companion website, which includes over 200 USMLE-style questions.

# BRS Biochemistry, Molecular Biology, and Genetics

**\$54** Review/Test

Lippincott Williams & Wilkins, 2013, 432 pages, ISBN 9781451175363

A highly detailed review featuring many figures and clinical correlations highlighted in colored boxes. The biochemistry portion includes much more detail than required for Step 1, but may be useful for students without a strong biochemistry background or as a reference text. The molecular biology section is more focused and high yield. Also offers a chapter on laboratory techniques and a comprehensive, 120-question exam. Questions are clinically oriented.

# Case Files: Biochemistry

**\$35** Cases

Toy

McGraw-Hill, 2014, 480 pages, ISBN 9780071794886

Includes 51 clinical cases with comprehensive discussion and summary box, albeit too much depth and not enough breadth for boards preparation. Some cases will almost certainly *not* be tested. Questions at the end of each case are not representative of those on Step 1.

FAS1\_2019\_23\_BookRev\_ONLINE.indd 15

B<sup>+</sup>

16 **SECTION IV** 

**TOP-RATED REVIEW RESOURCES** 

#### **PreTest Biochemistry and Genetics** B

**\$38** Test/500 q

WILSON

McGraw-Hill, 2017, 592 pages, ISBN 9780071791441

500 questions with detailed, well-referenced explanations. Features a high-yield introduction and appendix, but may be overly detailed in some cases. A solid supplement to preclinical courses and board studying

### ► CELL BIOLOGY AND HISTOLOGY

# BRS Cell Biology and Histology

**\$54** Review/ Test/320 q

Lippincott Williams & Wilkins, 2018, 448 pages, ISBN 9781496396358

Covers concepts in cell biology and histology in an outline format. Can be used alone for cell biology study, but may have fewer histology images than some other resources. Includes more detail than is required for Step 1, and information is less high yield than that of other books in the BRS series. Interactive quizzes on the free companion website provide additional practice.

#### **Crash Course: Cell Biology and Genetics** B<sup>+</sup> **S**TUBBS

\$47 Review/Print + online

Elsevier, 2015, 216 pages, ISBN 9780723438762

Part of the Crash Course review series for basic sciences, integrating clinical topics. Offers two-color illustrations, handy study tools, and Step 1 review questions. Includes online access. High level of detail makes this resource best suited for coursework.

#### Wheater's Functional Histology B

**\$83** Text

Elsevier, 2013, 464 pages, ISBN 9780702047473

A color atlas with more than 900 high-quality illustrations of normal histology with image captions and accompanying text. Far too detailed to use for boards studying given the low-yield nature of the material, but useful as a coursework text or boards reference. Provides online access to the entire atlas and USMLE-style self-assessment questions.

#### ▶ MICROBIOLOGY AND IMMUNOLOGY

## **Basic Immunology**

**\$70** Review

#### **A**BBAS

Elsevier, 2019, 336 pages, ISBN 9780323549431

A useful text that offers clear explanations of complex topics in immunology. Best if used in conjunction with coursework and later skimmed for quick Step 1 review. Includes colorful diagrams, images, tables, and a glossary for further study. Features online access.

# $A^{-}$

### Clinical Microbiology Made Ridiculously Simple **GLADWIN**

\$38 Review

MedMaster, 2019, 418 pages, ISBN 9781935660330

An excellent, easy-to-read, detailed review of microbiology that includes clever and memorable mnemonics. The sections on bacterial disease are most high yield, less emphasis placed on pharmacology. Recommended to read during coursework and review the concise charts at the end of each chapter during boards review. All images are cartoons; no microscopy images that appear on boards. Requires a supplemental source for immunology.

# $A^{-}$

### Medical Microbiology and Immunology Flash Cards ROSENTHAL

**\$40** Flash cards

Elsevier, 2016, 192 flash cards, ISBN 9780323462242

Flash cards covering the microorganisms most commonly tested on Step 1. Each card features color microscopic images and clinical presentations on one side and relevant bug information in conjunction with a short case on the other side. Also includes Student Consult online access for extra features. Overemphasizes "trigger words" related to each bug. Not a comprehensive resource.

## B<sup>+</sup>

### Lippincott Illustrated Reviews: Immunology DOAN

\$75 Reference/Test/ Few q

Lippincott Williams & Wilkins, 2012, 384 pages, ISBN 9781451109375

A clearly written, highly detailed review of basic concepts in immunology. Features many useful tables and review questions at the end of each chapter. More than 300 color annotated illustrations. Offers abbreviated coverage of immunodeficiencies and autoimmune disorders. Best if started with initial coursework and used as a reference during Step 1 study.

## B<sup>+</sup>

## Microcards: Microbiology Flash Cards **H**ARPAVAT

\$53 Flash cards

Lippincott Williams & Wilkins, 2015, 312 flash cards, ISBN 9781451192353

A well-organized and complete resource for students who like to use flash cards for review. Cards feature the clinical presentation, pathobiology, diagnosis, treatment, and high-yield facts for a particular organism. Some cards also include excellent flow charts organizing important classes of bacteria or viruses. Overall, a good review resource, but at times it is overly detailed, requiring a significant time commitment. Also useful as an aid with coursework. Includes access to online USMLE-style questions with answers.

FAS1 2019 23 BookRev ONLINE.indd 17

#### **TOP-RATED REVIEW RESOURCES**

## B<sup>+</sup> Review of Medical Microbiology and Immunology

**\$63** Review/ Test/654 q

McGraw-Hill, 2018, 832 pages, ISBN 9781259644498

A clear, comprehensive text with outstanding diagrams and tables. Includes an excellent immunology section. Contains a chapter summarizing details on medically important organisms. Can be used as reference for reviewing immunology concepts. Can be detailed and dense at points, so best if started early with coursework. Includes practice questions of mixed quality and does not provide detailed explanation of answers. Compare with Lippincott Illustrated Reviews: Microbiology.

## How the Immune System Works

**\$50** Review

**S**OMPAYRAC

Wiley-Blackwell, 2019, 168 pages, ISBN 9781119542124

A short overview of high-yield immunology designed for those with no prior immunology knowledge. Analogies and images create a "storybook" feel to spruce up a relatively dry subject. The 15 chapters offer a general overview with good supporting details.

#### Case Studies in Immunology: Clinical Companion B **G**EHA

**\$62** Cases

W. W. Norton & Company, 2016, 384 pages, ISBN 9780815345121

A text that was originally designed as a clinical companion to Janeway's Immunobiology. Provides a great synopsis of the major disorders of immunity in a clinical vignette format. Integrates basic and clinical sciences. Features excellent images and illustrations from Janeway, as well as questions and discussions.

#### **Pretest: Microbiology** B

**\$38** Test/500 q

**K**ETTERING

McGraw-Hill, 2013, 480 pages, ISBN 9780071791045

Includes a short section on high-yield facts followed by 500 questions in a clinical vignette format. Questions are more difficult than encountered on the boards and some topics discussed are not likely to be tested. A good book to work through with coursework but too low yield for review purposes.

#### Case Files: Microbiology B

**\$36** Cases

Toy

McGraw-Hill, 2014, 416 pages, ISBN 9780071820233

Provides 54 clinical microbiology cases followed by a clinical correlation, a discussion with boldfaced buzzwords, and questions. Cases are well chosen, but the text lacks the high-yield charts and tables found in other books in the Case Files series. Images are sparse, black and white, and of poor quality.

#### Lange Microbiology and Infectious Diseases Flash Cards, 3e B

**\$46** Flash cards

Somers, 2017

Clinical vignettes presented on one side of the card as a mini-case study of the disease and the flip side presents the etiology and epidemiology, pathogenesis, clinical manifestations, laboratory diagnosis, and treatment and prevention of the disorder. Good for reviewing clinical aspects of many infectious diseases including those caused by bacteria, viruses, and fungi.



# Lippincott Illustrated Reviews: Microbiology Cornelissen

**\$73** Review/Test/ Few q

Lippincott Williams & Wilkins, 2019, 448 pages, ISBN 9781496395856

A comprehensive, highly illustrated review of microbiology that is similar in style to other titles in the Illustrated Reviews series. Has more than 400 color illustrations and color-coded summaries to help visual learners. Contains several hundred USMLE-style review questions to help with exam preparation. Compare with Levinson's *Review of Medical Microbiology and Immunology*.

#### **▶** PATHOLOGY



## Pathoma: Fundamentals of Pathology

**\$85-\$120** Review/Lecture

SATTAR

Pathoma, 2019, 218 pages, ISBN 9780983224631

Integrated approach to pathology review, combining a focused textbook with 35+ hours of online lectures. Book contains more than 350 color images. Videos combine "chalk talk" and slide formats to explain pathogenesis in an easy-to-understand manner. Online subscription needed for full access.



# Rapid Review: Pathology GOLJAN

**\$65** Review/ Test/500 q

Elsevier, 2018, 864 pages, ISBN 9780323476683

A comprehensive source for key concepts in pathology, presented in a bulleted outline format with many high-yield tables and color figures. Features detailed explanations of disease mechanisms. Integrates concepts across disciplines with a strong clinical orientation. Lengthy, so best if started early with coursework. Includes access to online question bank with more than 500 questions. Covers material for both Step 1 and Step 2 exams.



# Robbins and Cotran Review of Pathology KLATT

**\$55** Test/1100 q

Elsevier, 2014, 504 pages, ISBN 9781455751556

A question book that follows the main Robbins textbooks. Questions are more detailed, difficult, and arcane than those on the actual Step 1 exam, but the text offers a great review of pathology integrated with more than 1100 images. Thorough answer explanations reinforce key points. Requires significant time commitment, so best if started with coursework. 2014 edition table of contents closely follows the organization of *Robbins and Cotran Pathologic Basis of Disease*, 8th edition.



## Crash Course: Pathology

**\$40** Review

XIU

Elsevier, 2019, 438 pages, ISBN 9780702073540

Part of the Crash Course review series for basic sciences, integrating clinical topics. Offers two-color illustrations, handy study tools, and Step 1 review questions. Includes online access. Best if started during coursework.

FAS1 2019 23 BookRev ONLINE.indd 19 11/8/19 6:49 AM

**TOP-RATED REVIEW RESOURCES** 

#### **High-Yield Histopathology** B

**\$36** Review

**D**UDEK

Lippincott Williams & Wilkins, 2017, 320 pages, ISBN 9781496353344

Reviews the relationship of basic histology to the pathology, physiology, and pharmacology of clinical conditions that are tested on Step 1. Includes case studies, numerous light and electron micrographs, and pathology photographs. Given its considerable length, should be started with coursework or used as a reference to better identify images.

#### Pathophysiology of Disease: Introduction to Clinical B Medicine

**\$90** Text

HAMMER

McGraw-Hill, 2018, 832 pages, ISBN 9781260026504

An interdisciplinary text useful for understanding the pathophysiology of clinical symptoms. Effectively integrates the basic sciences with mechanisms of disease. Features great graphs, diagrams, and tables. In view of its length, most useful if started during coursework. Includes 120 case studies, checkpoint questions that appear in every chapter, and a few non-boards-style questions. The text's clinical emphasis nicely complements BRS Pathology.

#### Haematology at a Glance B

\$49 Review

Мента

Blackwell Science, 2014, 136 pages, ISBN 9781119969228

A resource that covers common hematologic issues. Includes color illustrations. Presented in a logical sequence that is easy to read. Good for use with coursework.

#### **Pocket Companion to Robbins and Cotran Pathologic** B **Basis of Disease**

\$40 Review

**MITCHELL** 

Elsevier, 2016, 896 pages, ISBN 9781455754168

A condensed version of Robbins and Cotran Pathologic Basis of Disease that is good for reviewing keywords associated with most important diseases. Presented in a highly condensed format, but the text is complete and easy to understand. Contains no photographs or illustrations but does include tables. Useful as a quick reference.

#### **BRS Pathology** B

**\$54** Review/ Test/450 q

SCHNEIDER

Lippincott Williams & Wilkins, 2013, 480 pages, ISBN 9781451115871

An excellent, concise review with appropriate content emphasis. Chapters are organized by organ system and feature an outline format with boldfacing of key facts. Includes good questions with explanations at the end of each chapter plus a comprehensive exam at the end of the book. Offers well-organized tables and diagrams as well as photographs representative of classic pathology. Contains a chapter on lab testing and "key associations" with each disease. Contains excellent color images and access to an online test and interactive question bank. Most effective if started early in conjunction with coursework, as it does not discuss detailed mechanisms of disease pathology.

FAS1 2019 23 BookRev ONLINE.indd 20 11/8/19 6:49 AM

#### **▶** PHARMACOLOGY

#### **Crash Course: Pharmacology** B<sup>+</sup>

\$40 Review

Elsevier, 2019, 336 pages, ISBN 9780702073441

Part of the Crash Course review series for basic sciences, integrating clinical topics. Offers two-color illustrations, handy study tools, and Step 1-style review questions with a self-assessment section. Includes online access. Gives a solid, easy-to-follow overview of pharmacology.

#### B<sup>+</sup> Master the Boards USMLE Step 1 **Pharmacology Flashcards**

**\$55** Flash cards

**FISCHER** 

Kaplan, 2015, 200 flash cards, ISBN 9781618657947

Easy-to-read flash cards with drug and questions on one side and discussion on the other. Useful for a quick pharmacology review. Some drugs/material may be beyond the scope of the Step 1, or more appropriate at the Step 2 level.

#### **BRS Pharmacology** B+ Rosenfeld

**\$55** Review/

Test/200 q

Lippincott Williams & Wilkins, 2019, 384 pages, ISBN 9781975105495

Features two-color tables and figures that summarize essential information for quick recall. A list of drugs organized by drug family is included in each chapter. Too detailed for boards review; best used as a reference. Also offers end-of-chapter review tests with Step 1-style questions and a comprehensive exam with explanations of answers. An additional question bank is available online.

#### Lange Pharmacology Flash Cards B BARON

\$39 Flash cards

McGraw-Hill, 2017, 266 flash cards, ISBN 9781259837241

A total of 230 pocket-sized flash cards of relevant drugs formatted with clinical vignettes on one side and relevant information on the other side (eg, mode of action, adverse effects, clinical uses). Particularly high-yield information is highlighted in bold. Mainly useful as a supplement for pharmacology knowledge, rather than as a primary resource. Printed on less durable material.

#### Pharmacology Flash Cards B

**\$45** Flash cards

**B**RENNER

Elsevier, 2017, 230 flash cards, ISBN 9780323355643

Flash cards for more than 200 of the most commonly tested drugs. Cards include the name of the drug (both generic and brand) on the front and basic drug information on the back, with occasional cards covering high-yield pharmacology pathways. Divided and color coded by class, and comes with a compact carrying case. Lacks figures and clinical vignettes.

FAS1 2019 23 BookRev ONLINE.indd 21 11/8/19 6:49 AM

TOP-RATED REVIEW RESOURCES

# **B** Katzung & Trevor's Pharmacology: Examination and Board Review

**\$54** Review/ Test/800 q

**T**REVOR

McGraw-Hill, 2018, 592 pages, ISBN 9781259641022

A well-organized text with concise explanations. Features good charts and tables; the crammable list in Appendix I is especially high yield for Step 1 review. Also good for reviewing drug interactions and toxicities. Offers two 100-question practice exams. Text includes many low-yield/obscure drugs. Compare with *Lippincott Illustrated Reviews: Pharmacology*, both of which are better suited to complementing coursework than last-minute studying for boards.

# B Lippincott Illustrated Reviews: Pharmacology WHALEN

**\$75** Review/ Test/380 q

Lippincott Williams & Wilkins, 2018, 576 pages, ISBN 9781496384133

A resource presented in outline format with practice questions, many excellent illustrations, and comparison tables. Effectively integrates pharmacology and pathophysiology. Best started alongside coursework, as it is highly detailed and requires significant time commitment. Focuses on basic principles.

## ▶ PHYSIOLOGY



## **BRS Physiology**

**\$54** Review/

Costanzo

Lippincott Williams & Wilkins, 2018, 304 pages, ISBN 9781496367617

Test/350 q

A clear, concise review of physiology that is both comprehensive and efficient, making for fast, easy reading. Includes excellent high-yield charts and tables, but lacks some figures from Costanzo's *Physiology*. Features high-quality practice questions with explanations in each chapter along with a clinically oriented final exam. An excellent reference during times of focused Step 1 studying, but best if started early in combination with coursework. Respiratory and acid-base sections are comparatively weak.



## Pathophysiology of Heart Disease

**\$57** Review

LILLY

Lippincott Williams & Williams, 2015, 480 pages, ISBN 9781451192759

Great resource that outlines an in-depth explanation of both cardiac physiology and pathology. Best used as a supplement when learning the material for the first time, as it helps build a strong foundation. Because the book itself is rather dense, it is not recommend as a primary resource during focused boards studying period.



## PreTest Physiology

**\$38** Test/500 q

**M**ETTING

McGraw-Hill, 2013, 528 pages, ISBN 9780071791427

Contains questions with detailed, well-written explanations. One of the best of the PreTest series. Best for use by the motivated student after extensive review of other sources. Includes a high-yield facts section with useful diagrams and tables.

FAS1\_2019\_23\_BookRev\_ONLINE.indd 22 11/8/19 6:49 AM

#### **Color Atlas of Physiology** $A^{-}$

**\$50** Review

SILBERNAGL

Thieme, 2015, 472 pages, ISBN 9783135450070

Contains more than 180 high-quality illustrations of disturbed physiologic processes that lead to dysfunction. An alternative to standard texts, but not high yield for boards review.

#### **BRS Physiology Cases and Problems** B<sup>+</sup>

**\$58** Cases

Costanzo

Lippincott Williams & Wilkins, 2012, 368 pages, ISBN 9781451120615

Presents 62 classic cases in vignette format with several questions per case. Includes exceptionally detailed explanation of answers along with supplemental diagrams. For students interested in an in-depth discussion of physiology concepts.

#### **Physiology** B<sup>+</sup>

**\$60** Text

**C**OSTANZO

Saunders, 2017, 528 pages, ISBN 9780323478816

A comprehensive, clearly written text that covers concepts outlined in BRS Physiology in greater detail. Offers excellent color diagrams and charts. Each systems-based chapter features a detailed summary of objectives and a Step 1-relevant clinical case. Includes access to online interactive extras. Requires time commitment, but helps develop a strong foundation in physiology concepts. Best if started alongside coursework. Practice questions at end of each chapter.

#### B<sup>+</sup> Vander's Renal Physiology **EATON**

**\$49** Text

McGraw-Hill, 2018, 224 pages, ISBN 9781260019377

Well-written text on renal physiology, with helpful but sparse diagrams and practice questions at the end of each chapter. Too detailed for Step 1 review, however. Best if used with organ-based coursework to understand the principles of renal physiology.

#### Acid-Base, Fluids, and Electrolytes Made B<sup>+</sup> **Ridiculously Simple**

\$24 Review

**PRESTON** 

MedMaster, 2017, 166 pages, ISBN 9781935660293

A resource that covers major acid-base and renal physiology concepts. Provides information beyond the scope of Step 1, but remains a useful companion for studying kidney function, electrolyte disturbances, and fluid management. Includes scattered diagrams and questions at the end of each chapter. Consider using after exhausting more high-yield physiology review resources.

### **Pulmonary Pathophysiology: The Essentials** B<sup>+</sup>

**\$57** Review/ Test/75 q

Lippincott Williams & Wilkins, 2017, 264 pages, ISBN 9781496339447

A volume offering comprehensive coverage of respiratory physiology. Clearly organized with useful charts and diagrams. Review questions at the end of each chapter provide answers but no explanations. Best used as a course supplement during the second year, less ideal for use immediately prior to Step 1.

FAS1 2019 23 BookRev ONLINE.indd 23 11/8/19 6:49 AM

**TOP-RATED REVIEW RESOURCES** 

#### Rapid Review: Physiology B

**\$39** Test/350 q

**B**ROWN

Elsevier, 2011, 384 pages, ISBN 9780323072601

Offers a good review of physiology in a format typical of the Rapid Review series, albeit with more images. Includes online access to 350 questions with concise explanations, along with other extras. Compare with Robbins Physiology.

#### **Endocrine Physiology** B

**\$59** Review

MOLINA

McGraw-Hill, 2018, 320 pages, ISBN 9781260019353

Questions at the end of each chapter are helpful solidify knowledge, but some are not representative of Step 1 questions. Provides more detailed explanations of endocrine physiology than Costanzo review offers, but much too lengthy for Step 1 review. May be useful as a coursework adjunct.

#### **Netter's Physiology Flash Cards** B-

\$40 Flash cards

MULRONEY

Saunders, 2015, 450 flash cards, ISBN 9780323359542

Flash cards contain a high-quality illustration on one side with question and commentary on the other. Good for self-testing, but too fragmented for learning purposes and not comprehensive enough for boards.

# Get more e-books from www.ketabton.com Ketabton.com: The Digital Library