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FIRST AID FOR THE®

USMLE STEP 1 2016

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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.

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Contents

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

▶ SECTION I GUIDE TO EFFICIENT EXAM PREPARATION 1

Introduction	2	Test-Taking Strategies	19
USMLE Step 1—The Basics	2	Clinical Vignette Strategies	20
Defining Your Goal	12	If You Think You Failed	21
Excelling in the Preclinical Years	12	If You Failed	22
Timeline for Study	14	Testing Agencies	22
Study Materials	18	References	22

▶ SECTION I SUPPLEMENT SPECIAL SITUATIONS 25

▶ SECTION II HIGH-YIELD GENERAL PRINCIPLES 27

How to Use the Database	28	Immunology	189
Behavioral Science	31	Pathology	215
Biochemistry	47	Pharmacology	235
Microbiology	107		

▶ SECTION III HIGH-YIELD ORGAN SYSTEMS 257

Approaching the Organ Systems	258	Neurology	449
Cardiovascular	261	Psychiatry	507
Endocrine	305	Renal	529
Gastrointestinal	337	Reproductive	561
Hematology and Oncology	377	Respiratory	605
Musculoskeletal, Skin, and Connective Tissue	415	Rapid Review	629

▶ SECTION IV TOP-RATED REVIEW RESOURCES 649

How to Use the Database	650	Biochemistry	654
Question Banks	652	Cell Biology and Histology	655
Question Books	652	Microbiology and Immunology	655
Internet Sites	652	Pathology	656
Mobile Apps	652	Pharmacology	657
Comprehensive	653	Physiology	657
Anatomy, Embryology, and Neuroscience	653	Abbreviations and Symbols	659
Behavioral Science	654	Photo Acknowledgments	667
Index	687	About the Editors	761

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Preface

With the 26th 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 facts, including a new section on quality improvement principles and safety science.
- Hundreds of major fact updates culled from more than 100,000 comments and suggestions.
- Extensive text revisions, new mnemonics, clarifications, and corrections curated by a team of more than 30 student authors who excelled on their Step 1 examinations and verified by a team of expert faculty advisors and nationally recognized USMLE instructors.
- Updated with more than 250 new or revised full-color photos to help visualize various disorders, descriptive findings, and basic science concepts. Labeled and captioned photographs have been optimized to aid retention by engaging visual memory in a manner complementary to mnemonics.
- Updated with dozens of new and revised diagrams. We continue to expand our collaboration with USMLE-Rx (MedIQ Learning, LLC) to develop and enhance illustrations with improved information design to help students integrate pathophysiology, therapeutics, and diseases into memorable frameworks for annotation and personalization.
- Thicker, embossed cover and heavy-duty binding for increased durability and longevity.
- A revised exam preparation guide with updated data from the NBME and NRMP. The guide also features new high-yield techniques for efficient and effective test preparation. The updated supplemental guide for IMGs, osteopathic and podiatry students, and students with a disability can be found at our blog, www.firstaidteam.com.
- An updated summary guide to student-recommended USMLE Step 1 review resources, including mobile apps for iOS and Android. The full resource guide with detailed descriptions can be found at our blog, www.firstaidteam.com.
- Real-time Step 1 updates and corrections can also be found exclusively on our blog.

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.)

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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).

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: **firstaidteam@yahoo.com**.

Contributions submitted by **May 15, 2016**, receive priority consideration for the 2017 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.

▶ 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 2016, 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, and software development.

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

How to Use This Book

CONGRATULATIONS: You now possess the book that has guided nearly two million students to USMLE success for over 25 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.

LET FIRST AID BE YOUR GUIDE: 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, green for UWorld Step 1 Qbank, blue for USMLE-Rx Step 1 Qmax).
- 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, such as course syllabi.

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.**

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)	< 200 mg/dL	< 5.2 mmol/L
* Creatinine, serum (Total)	0.6–1.2 mg/dL	53–106 μmol/L
Electrolytes, serum		
Sodium	136–145 mEq/L	136–145 mmol/L
Chloride	95–105 mEq/L	95–105 mmol/L
* Potassium	3.5–5.0 mEq/L	3.5–5.0 mmol/L
Bicarbonate	22–28 mEq/L	22–28 mmol/L
Magnesium	1.5 mEq/L	0.75–1.0 mmol/L
Gases, arterial blood (room air)		
P _{O₂}	75–105 mm Hg	10.0–14.0 kPa
P _{CO₂}	33–44 mm Hg	4.4–5.9 kPa
pH	7.35–7.45	[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)	6.0–7.8 g/dL	60–78 g/L
Albumin	3.5–5.5 g/dL	35–55 g/L
Globulins	2.3–3.5 g/dL	23–35 g/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)

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 ³ Female: 3.5–5.5 million/mm ³	4.3–5.9 × 10 ¹² /L 3.5–5.5 × 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	4500–11,000/mm ³	4.5–11.0 × 10 ⁹ /L
Segmented neutrophils	54–62%	0.54–0.62
Band forms	3–5%	0.03–0.05
Eosinophils	1–3%	0.01–0.03
Basophils	0–0.75%	0–0.0075
Lymphocytes	25–33%	0.25–0.33
Monocytes	3–7%	0.03–0.07
Mean corpuscular hemoglobin	25.4–34.6 pg/cell	0.39–0.54 fmol/cell
Mean corpuscular volume	80–100 μm ³	80–100 fL
Partial thromboplastin time (activated)	25–40 seconds	25–40 seconds
Platelet count	150,000–400,000/mm ³	150–400 × 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		
Proteins, total	< 150 mg/24 h	< 0.15 g/24 h

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.

Years Prior

- Select top-rated review resources as study guides for first-year medical school courses.
- Ask for advice from those who have recently taken the USMLE Step 1.

Months Prior

- Review computer test format and registration information.
- Register six months in advance. Carefully verify name and address printed on scheduling permit. Call Prometric or go online for test date ASAP.
- Define goals for the USMLE Step 1 (eg, comfortably pass, beat the mean, ace the test).
- Set up a realistic timeline for study. Cover less crammable subjects first. Review subject-by-subject emphasis and clinical vignette format.
- Simulate the USMLE Step 1 to pinpoint strengths and weaknesses in knowledge and test-taking skills.
- Evaluate and choose study methods and materials (eg, review books, question banks).

Weeks Prior

- Simulate the USMLE Step 1 again. Assess how close you are to your goal.
- Pinpoint remaining weaknesses. Stay healthy (exercise, sleep).
- Verify information on admission ticket (eg, location, date).

One Week Prior

- Remember comfort measures (loose clothing, earplugs, etc).
- Work out test site logistics such as location, transportation, parking, and lunch.
- Call Prometric and confirm your exam appointment.

One Day Prior

- Relax.
- Lightly review short-term material if necessary. Skim high-yield facts.
- Get a good night's sleep.
- Make sure the name printed on your photo ID appears EXACTLY the same as the name printed on your scheduling permit.

Day of Exam

- Relax. Eat breakfast. Minimize bathroom breaks during the exam by avoiding excessive morning caffeine.
- Analyze and make adjustments in test-taking technique. You are allowed to review notes/study material during breaks on exam day.

After the Exam

- Celebrate, regardless.
- Send feedback to us on our website at www.firstaidteam.com.

Guide to Efficient Exam Preparation

“A mind of moderate capacity which closely pursues one study must infallibly arrive at great proficiency in that study.”

—Mary Shelley, *Frankenstein*

“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

▶ Introduction	2
▶ USMLE Step 1—The Basics	2
▶ Defining Your Goal	12
▶ Excelling in the Preclinical Years	12
▶ Timeline for Study	14
▶ Study Materials	18
▶ Test-Taking Strategies	19
▶ Clinical Vignette Strategies	20
▶ If You Think You Failed	21
▶ If You Failed	22
▶ Testing Agencies	22
▶ References	22

▶ 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 more resources than you can ever use
- 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

▶ *The test at a glance:*

- 8-hour exam
- Total of 308 multiple choice items
- 7 test blocks (60 min/block)
- 44 test items per block
- 45 minutes of break time, plus another 15 if you skip the tutorial

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

▶ 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.

The Step 1 exam includes test items drawn from the following content areas¹:

DISCIPLINE	ORGAN SYSTEM
Behavioral Sciences	Behavioral Health & Nervous
Biochemistry	Systems/Special Senses
Genetics	Biostatistics & Epidemiology/ Population Health
Gross Anatomy & Embryology	Blood & Lymphoreticular System
Histology & Cell Biology	Cardiovascular System
Microbiology & Immunology	Endocrine System
Nutrition	Gastrointestinal System
Pathology	General Principles of Foundational Science
Pharmacology	Immune System
Physiology	Multisystem Processes & Disorders
	Musculoskeletal, Skin, & Subcutaneous Tissue
	Renal/Urinary System
	Reproductive System
	Respiratory System

In 2015, a new, detailed, 31-page content outline was released. However, it is too early to say how useful the information will be in determining high-yield topics.

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 44 questions each for a total of 308 questions, 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—**unless** the questions are part of a sequential item test set (see p. 4).

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. In fact, you can easily add up to 15 minutes to your break time! This is because the 15-minute tutorial offered on exam day may be skipped if you are already

► *If you know the format, you can skip the tutorial and add up to 15 minutes to your break time!*

familiar with the exam procedures and the testing interface. The 15 minutes is then added to your allotted break time of 45 minutes for a total of 1 hour of potential break time. You can download the tutorial from the USMLE website and do it before test day. 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 also gain experience with the CBT format by taking the 132 practice questions available online or by signing up for a practice session at a test center.

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 question*
- *Esc—exit pop-up Lab and Exhibit windows*
- *Alt-T—countdown timers for current session and overall test*

The typical question screen in the CBT consists of a question followed by a number of choices on which an examinee can click, together with several navigational buttons on the top of the screen. 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.

► *Heart sounds are tested via media questions. Make sure you know how different heart diseases sound on auscultation.*

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.

► *Be sure to test your headphones during the tutorial.*

The USMLE also has a sequential item test format. These questions are grouped together in the list of questions on the left side of the screen and must be completed in order. After an examinee answers the first question, he or she will be given the option to proceed to the next item but will be warned that the answer to the first question will be locked. **After proceeding, examinees will not be able to change the answer selected for that question.**

The question stem and the answer chosen will be available to the examinee as he or she answers the next question(s) in the sequence.

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. Finally, 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. Being familiar with these features can save time and may help you better 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 (150 questions) available on the USMLE website, www.usmle.org, are used at these sessions. **No new items will be presented.** The session is divided into a short tutorial and three 1-hour blocks of 44 test items each at a cost of \$75, if your testing region is in the United States or Canada. 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.

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-

▶ *Illustrations on the test include:*

- *Gross specimen photos*
- *Histology slides*
- *Medical imaging (eg, x-ray, CT, MRI)*
- *Electron micrographs*
- *Line drawings*

- ▶ *Familiarize yourself with the commonly tested lab values.*

- ▶ *Ctrl-Alt-Delete are the keys of death during the exam. Don't touch them at the same time!*

- ▶ *You can take a shortened CBT practice test at a Prometric center.*

- ▶ *The Prometric Web site will display a calendar with open test dates.*

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 confirmation emails that Prometric and NBME send are not the same as the 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. **Do not lose your permit!** You will not be allowed to take the exam unless you present this permit along with 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.

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 contact Prometric as soon as you receive your permit. After you’ve scheduled your exam, it’s a good idea to confirm your exam appointment with Prometric at least one week before your test date. Prometric will provide appointment confirmation on a print-out and by email. Be sure to read the *2015 USMLE Bulletin of Information* for further details.

► *Test scheduling is done on a “first-come, first-served” basis. It’s important to call and schedule an exam date as soon as you receive your scheduling permit.*

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 voice-mail 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.

► Register six months in advance for seating and scheduling preference.

Where Can I Take the Exam?

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

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. 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 78 seconds).

The computer will 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

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

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.

Forty-five minutes is the minimum break time for the day, 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 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.

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

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.

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?

One-best-answer multiple choice items (either singly or as part of a sequential item set) are the only question type on the exam. 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.

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

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, and a graphic depiction of the examinee's performance by discipline and organ system or subject area. The actual organ system profiles reported may depend on the statistical characteristics of a given administration of the examination.

The USMLE score report is divided into two sections: performance by discipline and performance by organ system. Each of the 308 questions (minus experimental questions) is tagged according to any or all relevant content areas. Your performance in each discipline and each organ system is represented by a line of X's, where the width of the line is related to the confidence interval for your performance, which is often a direct consequence of the total number of questions for each discipline/system. If any lines have an asterisk (*) at the far right, this means your performance was exemplary in that area—not necessarily representing a perfect score, but often close to it.

The NBME provides a three-digit test score based on the total number of items answered correctly on the examination (see Figure 1). Your three-digit score will be qualified by the mean and standard deviation of US and Canadian medical school first-time examinees. The translation from the lines of X's and number of asterisks you receive on your report to the three-digit score is unclear, but higher three-digit scores are associated with more asterisks.

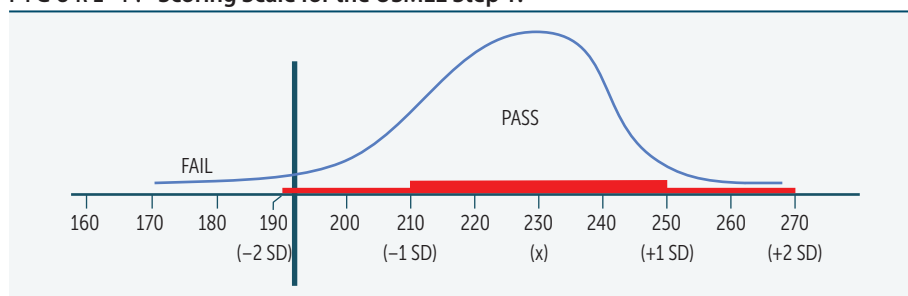
Since some questions may be experimental and are not counted, it is possible to get different scores for the same number of correct answers. The most recent mean score was 230 with a standard deviation of 20.

A score of 192 or higher is required to pass Step 1. 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 2015.

FIGURE 1. Scoring Scale for the USMLE Step 1.



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 1 shows, the majority of students pass the exam, so remember, we told you to relax.

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 2). 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.

► *Practice questions may be easier than the actual exam.*

TABLE 1. Passing Rates for the 2013–2014 USMLE Step 1.²

	2013		2014	
	No. Tested	% Passing	No. Tested	% Passing
Allopathic 1st takers	19,108	97%	19,582	96%
Repeaters	915	72%	812	68%
Allopathic total	20,023	95%	20,394	95%
Osteopathic 1st takers	2,680	94%	2,810	93%
Repeaters	46	74%	36	69%
Osteopathic total	2,726	94%	2,846	93%
Total US/Canadian	22,749	95%	23,240	95%
IMG 1st takers	14,649	79%	15,149	78%
Repeaters	3,772	44%	2,889	38%
IMG total	18,421	72%	18,038	72%
Total Step 1 examinees	41,170	85%	41,278	85%

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 3). 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 65 minutes to complete each section, reflecting time limits similar to the actual exam. By contrast, the self-paced format places a 4:20 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.

Keep in mind that this bank of questions is available only on the web. The NBME requires that users log on, register, and start the test within 30 days of registration. 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. Please note that the CBSSAs do not list the correct answers to the questions at the end of the session. However, forms can be purchased with an extended feedback option; these tests show you which questions you answered incorrectly, but do not show you the correct answer or explain why your choice was wrong. Feedback from the self-assessment takes the form of a performance profile and nothing more. The NBME charges \$50 for assessments without feedback and \$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

TABLE 2. 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

TABLE 3. CBSSA to USMLE Score Prediction.

CBSSA Score	Approximate USMLE Step 1 Score
150	153
200	164
250	175
300	185
350	196
400	207
450	217
500	228
550	239
600	249
650	260
700	271
750	281
800	292

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

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

project IFOM performance onto the USMLE Step 1 score scale. More information is available at <http://www.nbme.org/ifom/>.

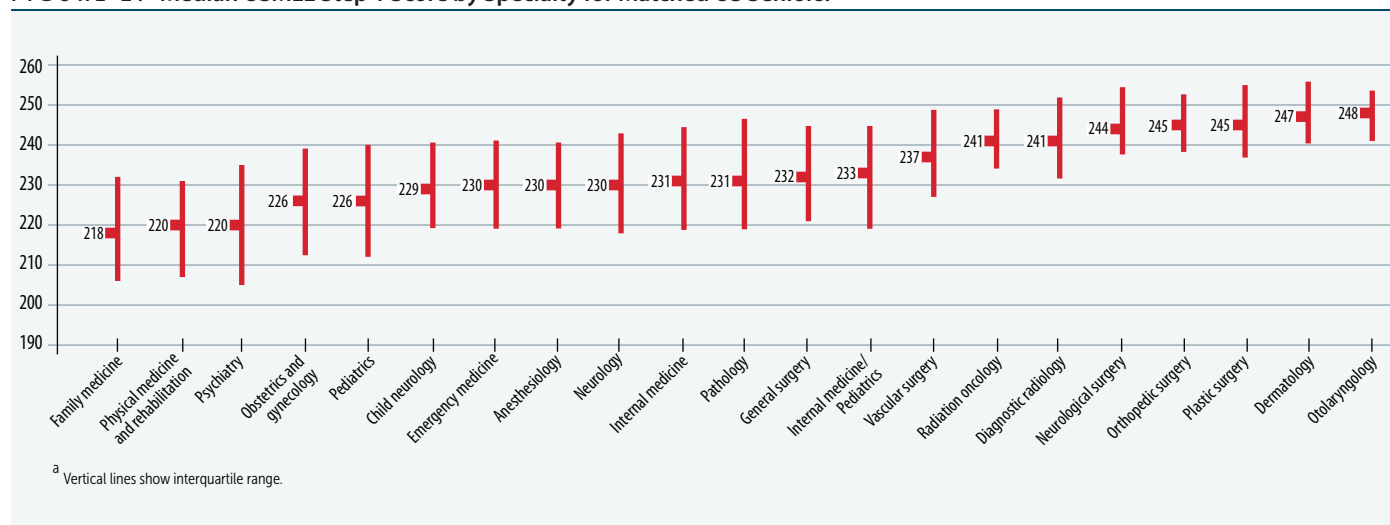
► DEFINING YOUR GOAL

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.

Certain highly competitive residency programs, such as those in plastic surgery and orthopedic surgery, have acknowledged their use of Step 1 scores in the selection process. In such residency programs, greater emphasis may be placed on attaining a high score, so students who seek to enter these programs may wish to consider aiming for a very high score on the Step 1 exam (see Figure 2). 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.

► EXCELLING IN THE PRECLINICAL YEARS

Many students feel overwhelmed during the first few weeks of medical school and struggle to find a workable system. Strategies that worked during your undergraduate years may or may not work as you prepare for the USMLE

FIGURE 2. Median USMLE Step 1 Score by Specialty for Matched US Seniors.^a

Step 1. Below are three study methods to use during the preclinical years and their effectiveness for Step 1 preparation. 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.

Highlight, Read, and Reread

The most passive of the three methods, this generally consists of sitting through lectures and highlighting relevant material (sometimes in an assortment of colors). Notes are jotted in the margins, but the general bulk of information is in the same order presented by the various lecturers. Students then go home and reread the notes, focusing on the highlights. It is difficult to test integration of concepts. These notes (usually in the thousands of pages) are almost useless for Step 1 preparation.

Flash cards

There is no shortage of flash card applications, from make-your-own cards to purchasable premade decks. Self-made flash cards, if done correctly, offer the ability to objectively test necessary facts. Written in an open-ended format and coupled with spaced repetition, they train both recognition and recall. Apps exist for various smartphones and tablets, so the flash cards are always accessible. However, the ease of quickly creating digital cards and sharing 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 many for Step 1 preparation. Unless you have specified high-yield cards (and checked the content with high-yield resources), stick to premade cards by reputable sources that curate the vast amount of knowledge for you.

► *Watch out for flash card overload!*

Tables and Summaries

This is the most active (and time intensive) form of learning. It consists of integrating the pertinent information from paragraphs on each subject into tables that cut across topics within the same category. The key is to synthesize the sequentially presented material. Sensitive and specific findings should be highlighted. While many review sources offer this material in various styles and formats, your own class notes may in fact be concise enough to use as an adjunct for Step 1 preparation, and they have the added benefit of being organized to your liking.

▶ 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.

▶ *Customize your schedule. Tackle your weakest section first.*

Make a Schedule

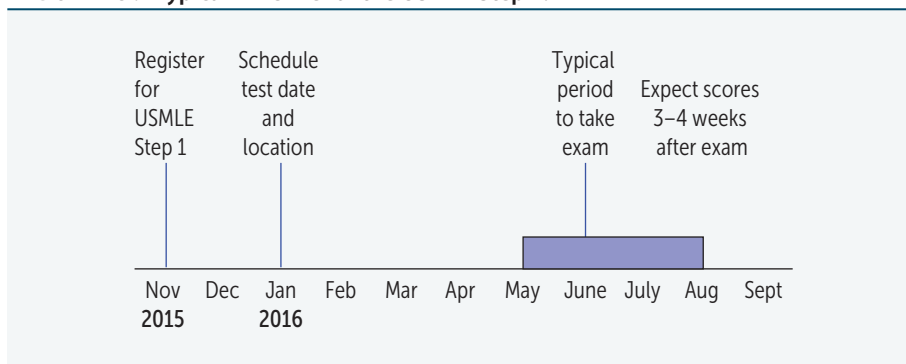
After you have defined your goals, map out a study schedule that is consistent with your objectives, your vacation time, the difficulty of your ongoing coursework, and your family and social commitments (see Figure 3). Determine whether you want to spread out your study time or concentrate it into 14-hour study days in the final weeks. Then factor in your own history in 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.

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.³

▶ *“Crammable” subjects should be covered later and less cramnable subjects earlier.*

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.

FIGURE 3. Typical Timeline for the USMLE Step 1.



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.

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.⁴ Moreover, undergraduate science GPAs as well as MCAT scores are strong predictors of performance on the Step 1 exam.⁵

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.

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

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

▶ *Simulate the USMLE Step 1 under “real” conditions before beginning your studies.*

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)

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

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 school work 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 150 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 46 questions can take upward of two hours. Feedback from CBSSA exams and question banks will help you focus on your weaknesses.

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 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*

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 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.

▶ *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.*

▶ *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.*

▶ 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.

▶ *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.*

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.

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.

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.

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

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

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.

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

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 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

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.

► *Practice! Develop your test-taking skills and strategies well before the test date.*

Pacing

You have seven hours to complete 308 questions. Note that each one-hour block contains 44 questions. This works out to about 82 seconds per question. If you find yourself spending too much time on a question, mark the question, make an educated guess, and move on. If time permits, come back to the question later. 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. 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.

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

► *Be prepared to read fast and think on your feet!*

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.

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.

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.

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

► 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.⁶ 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 192 or above), you are not allowed to retake the exam.*

▶ IF YOU FAILED

Even if you came out of the exam room feeling that you failed, seeing that failing grade can be traumatic, and it is natural to feel upset. Different people react in different ways: For some it is a stimulus to buckle down and study harder; for others it may “take the wind out of their sails” for a few days; and it may even lead to a reassessment of individual goals and abilities. In some instances, however, failure may trigger weeks or months of sadness, feelings of hopelessness, social withdrawal, and inability to concentrate—in other words, true clinical depression. If you think you are depressed, please seek help.

▶ 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)
Fax: (215) 590-9457
Email: webmail@nbme.org
www.nbme.org

- **Educational Commission for Foreign Medical Graduates (ECFMG)**
3624 Market Street
Philadelphia, PA 19104-2685
(215) 386-5900
Fax: (215) 386-9196
Email: info@ecfm.org
www.ecfm.org

▶ REFERENCES

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4. Holtman, Matthew C., Swanson, David B., Ripkey, Douglas R., and Case, Susan M., “Using Basic Science Subject Tests to Identify Students at Risk for Failing Step 1,” *Academic Medicine*, 2001, Vol. 76, No. 10, pp. S48–S51.

5. Basco, William T., Jr., Way, David P., Gilbert, Gregory E., and Hudson, Andy, “Undergraduate Institutional MCAT Scores as Predictors of USMLE Step 1 Performance,” *Academic Medicine*, 2002, Vol. 77, No. 10, pp. S13–S16.
6. United States Medical Licensing Examination. 2014 USMLE Bulletin of Information. <http://www.usmle.org/pdfs/bulletin/2014bulletin.pdf>. Accessed September 26, 2014.

Special Situations

Please visit www.usmle-rx.com/bonus/ to view this section.

- ▶ First Aid for the International Medical Graduate 2
- ▶ First Aid for the Osteopathic Medical Student 12
- ▶ First Aid for the Podiatric Medical Student 17
- ▶ First Aid for the Student with a Disability 19

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.”

—Gandhi

▶ Behavioral Science	31
▶ Biochemistry	47
▶ Microbiology	107
▶ Immunology	189
▶ Pathology	215
▶ Pharmacology	235

▶ HOW TO USE THE DATABASE

The 2016 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 II is devoted to the foundational principles of behavioral science, biochemistry, microbiology, immunology, basic pathology, and basic pharmacology. 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. xvii).

Image Acknowledgments

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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 firstaidteam@yahoo.com.

Behavioral Science

“It is a mathematical fact that fifty percent of all doctors graduate in the bottom half of their class.”

—Author Unknown

“It’s psychosomatic. You need a lobotomy. I’ll get a saw.”

—Calvin, “Calvin & Hobbes”

“There are two kinds of statistics: the kind you look up and the kind you make up.”

—Rex Stout

“On a long enough time line, the survival rate for everyone drops to zero.”

—Chuck Palahniuk

A heterogeneous mix of epidemiology, biostatistics, ethics, psychology, public health, and more falls under the heading of behavioral science. The exam has recently added an emphasis on patient safety and quality improvement topics. Many medical students do not diligently study this discipline because the material is felt to be easy or a matter of common sense. In our opinion, this is a missed opportunity.

Behavioral science questions may seem less concrete than questions from other disciplines, as they require an awareness of the psychosocial aspects of medicine. For example, if a patient does or says something, what should you do or say in response? These so-called quote questions now constitute much of the behavioral science section. Medical ethics and medical law are also appearing with increasing frequency. In addition, the key aspects of the doctor-patient relationship (eg, communication skills, open-ended questions, facilitation, silence) are high yield, as are biostatistics and epidemiology, which are the foundations of evidence-based medicine. Make sure you can apply biostatistical concepts such as sensitivity, specificity, and predictive values in a problem-solving format.

▶ Epidemiology/ Biostatistics	32
▶ Ethics	39
▶ Development and Aging	43
▶ Public Health	44

▶ BEHAVIORAL SCIENCE—EPIDEMIOLOGY/BIOSTATISTICS

Observational studies

STUDY TYPE	DESIGN	MEASURES/EXAMPLE
Cross-sectional study	Collects data from a group of people to assess frequency of disease (and related risk factors) at a particular point in time. Asks, “What is happening?”	Disease prevalence. Can show risk factor association with disease, but does not establish causality.
Case-control study	Compares a group of people with disease to a group without disease. Looks for prior exposure or risk factor. Asks, “What happened?”	Odds ratio (OR). “Patients with COPD had higher odds of a history of smoking 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 affects the likelihood of disease. Can be prospective (asks, “Who will develop disease?”) or historical (asks, “Who developed the disease [exposed vs nonexposed]?”).	Relative risk (RR). “Smokers had a higher risk of developing COPD than nonsmokers.”
Twin concordance study	Compares the frequency with which both monozygotic twins or 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. Compares therapeutic benefits of 2 or more treatments, or of treatment and placebo. Study quality improves when study is randomized, controlled, and double-blinded (ie, neither patient nor doctor knows whether the patient is in the treatment or control group). Triple-blind refers to the additional blinding of the researchers analyzing the data.

DRUG TRIALS	TYPICAL STUDY SAMPLE	PURPOSE
Phase I	Small number of healthy volunteers.	“Is it safe?” Assesses safety, toxicity, pharmacokinetics, and pharmacodynamics.
Phase II	Small 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 best available treatment (or placebo).	“Is it as good or better?” Compares the new treatment to the current standard of care.
Phase IV	Postmarketing surveillance of patients after treatment is approved.	“Can it stay?” Detects rare or long-term adverse effects. Can result in treatment being withdrawn from market.

Evaluation of diagnostic tests

Uses 2 × 2 table comparing test results with the actual presence of disease. TP = true positive; FP = false positive; TN = true negative; FN = false negative.

Sensitivity and specificity are fixed properties of a test. PPV and NPV vary depending on disease prevalence.

	Disease		
	⊕	⊖	
Test	⊕	TP	FP
	⊖	FN	TN
		PPV = TP / (TP + FP)	
		NPV = TN / (TN + FN)	
	Sensitivity = TP / (TP + FN)		Specificity = TN / (TN + FP)

Sensitivity (true-positive rate)

Proportion of all people with disease who test positive, or the probability that when the disease is present, the test is positive. Value approaching 100% is desirable for **ruling out** disease and indicates a **low false-negative rate**. High sensitivity test used for screening in diseases with low prevalence.

$= TP / (TP + FN)$
 $= 1 - \text{false-negative rate}$
SN-N-OUT = highly **Se**Nsitive test, when **N**egative, rules **OUT** disease
 If sensitivity is 100%, $TP / (TP + FN) = 1$, $FN = 0$, and all negatives must be TNs

Specificity (true-negative rate)

Proportion of all people without disease who test negative, or the probability that when the disease is absent, the test is negative. Value approaching 100% is desirable for **ruling in** disease and indicates a **low false-positive rate**. High specificity test used for confirmation after a positive screening test.

$= TN / (TN + FP)$
 $= 1 - \text{false-positive rate}$
SP-P-IN = highly **SP**ecific test, when **P**ositive, rules **IN** disease
 If specificity is 100%, $TN / (TN + FP) = 1$, $FP = 0$, and all positives must be TPs

Positive predictive value

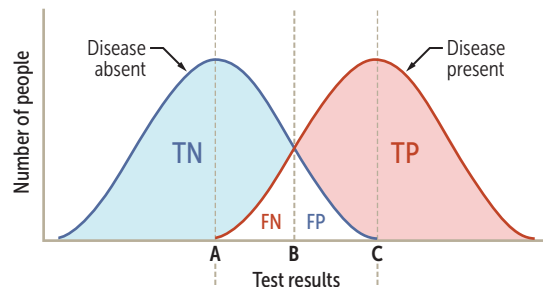
Proportion of positive test results that are true positive. Probability that a person who has a positive test result actually has the disease.

$PPV = TP / (TP + FP)$
 PPV varies directly with pretest probability (baseline risk, such as prevalence of disease): high pretest probability → high PPV

Negative predictive value

Proportion of negative test results that are true negative. Probability that a person with a negative test result actually does not have the disease.

$NPV = TN / (TN + FN)$
 NPV varies inversely with prevalence or pretest probability: high pretest probability → low NPV

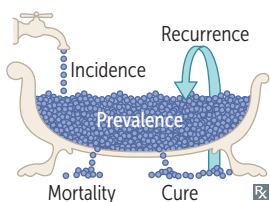


POSSIBLE CUTOFF VALUES

- A = 100% sensitivity cutoff value
- B = practical compromise between specificity and sensitivity
- C = 100% specificity cutoff value

Lowering the cutoff point:	↑ Sensitivity ↑ NPV
B → A (↑ FP ↓ FN)	↓ Specificity ↓ PPV
Raising the cutoff point:	↑ Specificity ↑ PPV
B → C (↑ FN ↓ FP)	↓ Sensitivity ↓ NPV

Incidence vs prevalence



Incidence = $\frac{\text{\# of new cases}}{\text{\# of people at risk}}$ (during a specified time period)

Prevalence = $\frac{\text{\# of existing cases}}{\text{Total \# of people in a population}}$ (at a point in time)

Prevalence ≈ incidence for short duration disease (eg, common cold).

Prevalence > incidence for chronic diseases, due to large # of existing cases (eg, diabetes).

Incidence looks at new cases (**incidents**).

Prevalence looks at **all** current cases.

Prevalence ≈ pretest probability.

Quantifying risk

Definitions and formulas are based on the classic 2×2 or contingency table.

		Disease	
		+	-
Risk factor or intervention	+	a	b
	-	c	d

Odds ratio

Typically used in case-control studies. Odds that the group with the disease (cases) was exposed to a risk factor (a/c) divided by the odds that the group without the disease (controls) was exposed (b/d).

$$OR = \frac{a/c}{b/d} = \frac{ad}{bc}$$

Relative risk

Typically used in cohort studies. Risk of developing disease in the exposed group divided by risk in the unexposed group (eg, if 21% of smokers develop lung cancer vs 1% of nonsmokers, $RR = 21/1 = 21$). If prevalence is low, $OR \approx RR$.

$$RR = \frac{a/(a+b)}{c/(c+d)}$$

Attributable risk

The difference in risk between exposed and unexposed groups, or the proportion of disease occurrences that are attributable to the exposure (eg, if risk of lung cancer in smokers is 21% and risk in nonsmokers is 1%, then 20% of the lung cancer risk in smokers is attributable to smoking).

$$AR = \frac{a}{a+b} - \frac{c}{c+d}$$

Relative risk reduction

The proportion of risk reduction attributable to the intervention as compared to a control (eg, 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 $RRR = 0.75$).

$$RRR = 1 - RR$$

Absolute risk reduction

The difference in risk (not the proportion) attributable to the intervention as compared to a control (eg, if 8% of people who receive a placebo vaccine develop the flu vs 2% of people who receive a flu vaccine, then $ARR = 8\% - 2\% = 6\% = .06$).

$$ARR = \frac{c}{c+d} - \frac{a}{a+b}$$

Number needed to treat

Number of patients who need to be treated for 1 patient to benefit.

$$NNT = 1/ARR$$

Number needed to harm

Number of patients who need to be exposed to a risk factor for 1 patient to be harmed.

$$NNH = 1/AR$$

Precision vs accuracy

Precision

The consistency and reproducibility of a test (reliability).
The absence of random variation in a test.

Random error ↓ precision in a test.
↑ precision → ↓ standard deviation.
↑ precision → ↑ statistical power ($1 - \beta$).

Accuracy

The trueness of test measurements (validity).
The absence of systematic error or bias in a test.

Systematic error ↓ accuracy in a test.



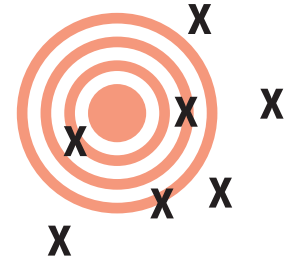
Accurate, not precise



Precise, not accurate



Accurate and precise



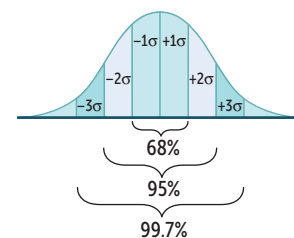
Not accurate, not precise

Bias and study errors

TYPE	DEFINITION	EXAMPLES	STRATEGY TO REDUCE BIAS
Recruiting participants			
Selection bias	Error in assigning subjects to a study group resulting in an unrepresentative sample. Most commonly a sampling bias.	Berkson bias—study population selected from hospital is less healthy than general population Healthy worker effect—study population is healthier than the general population Non-response bias—participating subjects differ from nonrespondents in meaningful ways	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.	Association between HPV and cervical cancer not observed when using non-standardized classifications	Use objective, standardized, and previously tested methods of data collection that are planned ahead of time
Procedure bias	Subjects in different groups are not treated the same.	Patients in treatment group spend more time in highly specialized hospital units	Blinding and use of placebo reduce influence of participants and researchers on procedures and interpretation of outcomes as neither are aware of group allocation
Observer-expectancy bias	Researcher's belief in the efficacy of a treatment changes the outcome of that treatment (aka Pygmalion effect; self-fulfilling prophecy).	If observer expects treatment group to show signs of recovery, then he is more likely to document positive outcomes	
Interpreting results			
Confounding bias	When a factor is related to both the exposure and outcome, but not on the causal pathway → factor distorts or confuses effect of exposure on outcome.	Pulmonary disease is more common in coal workers than the general population; however, people who work in coal mines also smoke more frequently than the general population	Multiple/repeated studies Crossover studies (subjects act as their own controls) Matching (patients with similar characteristics in both treatment and control groups) Restriction Randomization
Lead-time bias	Early detection is confused with ↑ survival.	Early detection makes it seem as though survival has increased, but the natural history of the disease has not changed	Measure “back-end” survival (adjust survival according to the severity of disease at the time of diagnosis)

Statistical distribution

Measures of central tendency	Mean = (sum of values)/(total number of values).	Most affected by outliers (extreme values).
	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 from the mean in a set of values.	σ = SD; n = sample size.
	Standard error of the mean = an estimate of how much variability exists between the sample mean and the true population mean.	Variance = (SD) ² . SEM = σ/\sqrt{n} . SEM ↓ as n ↑.
Normal distribution	Gaussian, also called bell-shaped. Mean = median = mode.	



Nonnormal distributions

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.	
Negative skew	Typically, mean < median < mode. Asymmetry with longer tail on left.	

Statistical hypotheses

Null (H₀)	Hypothesis of no difference or relationship (eg, there is no association between the disease and the risk factor in the population).
Alternative (H₁)	Hypothesis of some difference or relationship (eg, there is some association between the disease and the risk factor in the population).

		Reality	
		H ₁	H ₀
Study results support:	H ₁	Power (1 - β)	α Type I error
	H ₀	β Type II error	Correct

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 not an effect or difference when none exists (null hypothesis not rejected).

Incorrect result

Type I error (α)

Stating that there is an effect or difference when none exists (null hypothesis incorrectly rejected in favor of alternative hypothesis).

α is the probability of making a type I error. p is judged against a preset α level of significance (usually 0.05). If $p < 0.05$, then there is less than a 5% chance that the data will show something that is not really there.

Also known as false-positive error.

α = you “**a**bserved” a difference that did not exist.

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).

β is the probability of making a type II error. β is related to statistical power ($1 - \beta$), which is the probability of rejecting the null hypothesis when it is false.

↑ power and ↓ β by:

- ↑ sample size
- ↑ expected effect size
- ↑ precision of measurement

Also known as false-negative error.

β = you were **blinded** by the truth.

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 = mean \pm Z(SEM).

The 95% CI (corresponding to $p = .05$) is often used.

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.

Common statistical tests

t-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: AN alysis Of VA riance. Example: comparing the mean blood pressure between members of 3 different ethnic groups.
Chi-square (χ^2)	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.
Pearson correlation coefficient (r)	<p>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.</p> <p>Positive r value → positive correlation (as one variable ↑, the other variable ↑).</p> <p>Negative r value → negative correlation (as one variable ↑, the other variable ↓).</p> <p>Coefficient of determination = r^2 (value that is usually reported).</p>	

▶ BEHAVIORAL SCIENCE—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 requires:

- Disclosure: discussion of pertinent information
- Understanding: ability to comprehend
- Capacity: ability to reason and make one's own decisions (distinct from competence, a legal determination)
- Voluntariness: freedom from coercion and manipulation

Patients must have an intelligent understanding 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.

Exceptions to informed consent:

- Patient lacks decision-making capacity or is legally incompetent
- Implied consent in an emergency
- Therapeutic privilege— withholding information when disclosure would severely harm the patient or undermine informed decision-making capacity
- Waiver—patient explicitly waives the right of informed consent

Consent for minors

A minor is generally any person < 18 years old. Parental consent laws in relation to health care vary by state. In general, parental consent should be obtained unless emergent treatment is required (eg, blood transfusion) even if it opposes parental religious/cultural beliefs, or if a minor is legally emancipated (eg, is married, is self supporting, or is in the military).

Situations in which parental consent is usually not required:

- **Sex** (contraception, STIs, pregnancy)
- **Drugs** (substance abuse)
- **Rock and roll** (emergency/trauma)

Physicians should always encourage healthy minor-guardian communication.

Decision-making capacity

Physician must determine whether the patient is psychologically and legally capable of making a particular health care decision.

Components:

- Patient is ≥ 18 years old or otherwise legally emancipated
- Patient makes and communicates a choice
- Patient is informed (knows and understands)
- Decision remains stable over time
- Decision is consistent with patient's values and goals, not clouded by a mood disorder
- Decision is not a result of altered mental status (eg, delirium, psychosis, intoxication)

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.
Living will (written advance directive)	Describes treatments the patient wishes to receive or not receive if he/she loses decision-making capacity. Usually, patient directs physician to withhold or withdraw life-sustaining treatment if he/she develops a terminal disease or enters a persistent vegetative state.
Medical power of attorney	Patient designates an agent to make medical decisions in the event that he/she loses decision-making capacity. Patient may also specify decisions in clinical situations. Can be revoked by patient if decision-making capacity is intact. More flexible than a living will.
Surrogate decision-maker	If a patient loses decision-making capacity and has not prepared an advance directive, individuals (surrogates) who know the patient must determine what the patient would have done. Priority of surrogates: spouse > adult children > parents > adult siblings > other relatives.
Confidentiality	<p>Confidentiality respects patient privacy and autonomy. If patient is not present or is incapacitated, 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).</p> <p>General principles for exceptions to confidentiality:</p> <ul style="list-style-type: none"> ▪ Potential physical harm to others is serious and imminent ▪ Likelihood of harm to self is great ▪ No alternative means exists to warn or to protect those at risk ▪ Physicians can take steps to prevent harm <p>Examples of exceptions to patient confidentiality (many are state-specific) include:</p> <ul style="list-style-type: none"> ▪ Reportable diseases (eg, STIs, TB, hepatitis, food poisoning)—physicians may have a duty to warn public officials, who will then notify people at risk ▪ The Tarasoff decision—California Supreme Court decision requiring physician to directly inform and protect potential victim from harm ▪ Child and/or elder abuse ▪ Impaired automobile drivers (eg, epileptics) ▪ Suicidal/homicidal patients

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 or 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 or 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.
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 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.	In the overwhelming majority of states, refuse involvement in any form of physician-assisted suicide. Physicians may, however, prescribe medically appropriate analgesics that coincidentally 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.
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.
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 that the boy is not responsible. Identify and normalize fears and feelings. Encourage play and healthy coping behaviors (eg, remembering her in his own way).

► BEHAVIORAL SCIENCE—DEVELOPMENT AND AGING

Early developmental milestones 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	<p>Primitive reflexes disappear—Moro (by 3 mo), rooting (by 4 mo), palmar (by 6 mo), Babinski (by 12 mo)</p> <p>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)</p> <p>Picks—passes toys hand to hand (by 6 mo), Pincer grasp (by 10 mo)</p> <p>Points to objects (by 12 mo)</p>	<p>Social smile (by 2 mo)</p> <p>Stranger anxiety (by 6 mo)</p> <p>Separation anxiety (by 9 mo)</p>	<p>Orients—first to voice (by 4 mo), then to name and gestures (by 9 mo)</p> <p>Object permanence (by 9 mo)</p> <p>Oratory—says “mama” and “dada” (by 10 mo)</p>
Toddler	Child	Rearing	Working,
12–36 mo	<p>Cruises, takes first steps (by 12 mo)</p> <p>Climbs stairs (by 18 mo)</p> <p>Cubes stacked—number = age (yr) × 3</p> <p>Cultured—feeds self with fork and spoon (by 20 mo)</p> <p>Kicks ball (by 24 mo)</p>	<p>Recreation—parallel play (by 24–36 mo)</p> <p>Rapprochement—moves away from and returns to mother (by 24 mo)</p> <p>Realization—core gender identity formed (by 36 mo)</p>	<p>Words—200 words by age 2 (2 zeros), 2-word sentences</p>
Preschool	Don’t	Forget, they’re still	Learning!
3–5 yr	<p>Drive—tricycle (3 wheels at 3 yr)</p> <p>Drawings—copies line or circle, stick figure (by 4 yr)</p> <p>Dexterity—hops on one foot (by 4 yr), uses buttons or zippers, grooms self (by 5 yr)</p>	<p>Freedom—comfortably spends part of day away from mother (by 3 yr)</p> <p>Friends—cooperative play, has imaginary friends (by 4 yr)</p>	<p>Language—1000 words by age 3 (3 zeros), uses complete sentences and prepositions (by 4 yr)</p> <p>Legends—can tell detailed stories (by 4 yr)</p>

Changes in the elderly

Sexual changes:

- Men—slower erection/ejaculation, longer refractory period
- Women—vaginal shortening, thinning, and dryness

Sleep patterns: ↓ REM and slow-wave sleep;
↑ sleep onset latency and ↑ early awakenings

↑ suicide rate

↓ vision, hearing, immune response, bladder control

↓ renal, pulmonary, GI function

↓ muscle mass, ↑ fat

Libido is stable in men but decreases in women after menopause.

Intelligence does not decrease.

Presbycusis—sensorineural hearing loss (often of higher frequencies) due to destruction of hair cells at the cochlear base (preserved low-frequency hearing at apex).

► BEHAVIORAL SCIENCE—PUBLIC HEALTH

Disease prevention**Primary**

Prevent disease before it occurs (eg, HPV vaccination)

Secondary

Screen early for and manage existing but asymptomatic disease (eg, Pap smear for cervical cancer)

Tertiary

Treatment to reduce complications from disease that is ongoing or has long-term effects (eg, chemotherapy)

Quaternary—identifying patients at risk of unnecessary treatment, protecting from the harm of new interventions

Medicare and Medicaid

Medicare and Medicaid—federal 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 very low income.

Medicar**E** is for **E**lderly.
Medicai**D** is for **D**estitute.

The 4 parts of Medicare:

- Part **A**: Hospital insurance
- Part **B**: **B**asic medical **b**ills (eg, doctor's fees, diagnostic testing)
- Part **C**: (Parts **A+B**) delivered by approved private **c**ompanies
- Part **D**: Prescription **d**rugs

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	SIDS	Congenital malformations	Homicide	Heart disease	Unintentional injury	Chronic respiratory disease

Hospitalized conditions with frequent readmissions

	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

Readmission for any reason within 30 days of original admission.

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 [EMRs]).

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:

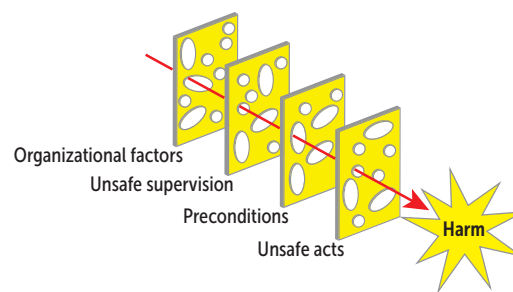
- **P**lan—define problem and solution
- **D**o—test new process
- **S**tudy—measure and analyze data
- **A**ct—integrate new process into regular workflow



Quality measurements Plotted on run and control charts.

	MEASURE	EXAMPLE
Outcome	Impact on patients	Average HbA _{1c} of patients with diabetes
Process	Performance of system as planned	Ratio of patients whose HbA _{1c} was measured in the past 6 months
Balancing	Impact on other systems/outcomes	Incidence of hypoglycemia among those patients

Swiss cheese model In complex organizations, flaws in multiple processes and systems may align to cause patient harm. Focuses on systems and conditions rather than an individual's error.



Types of medical errors May involve patient identification, diagnosis, monitoring, nosocomial infection, medications, procedures, devices, documentation, handoffs. Errors causing harmful outcomes must be disclosed to patients.

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.

Medical error analysis

Root cause analysis	Uses records and participant interviews to identify all the underlying problems that led to an error. Categories of causes include process, people (providers or patients), environment, equipment, materials, management.	R etrospective approach applied after failure event to prevent recurrence. Plotted on fishbone (Ishikawa, cause-and-effect) diagram. Fix causes with corrective action plan.
Failure mode and effects analysis	Uses inductive reasoning to identify all the ways a process might fail and prioritize these by their probability of occurrence and impact on patients.	F orward-looking approach applied before process implementation to prevent failure occurrence.

Biochemistry

“Biochemistry is the study of carbon compounds that crawl.”

—Mike Adams

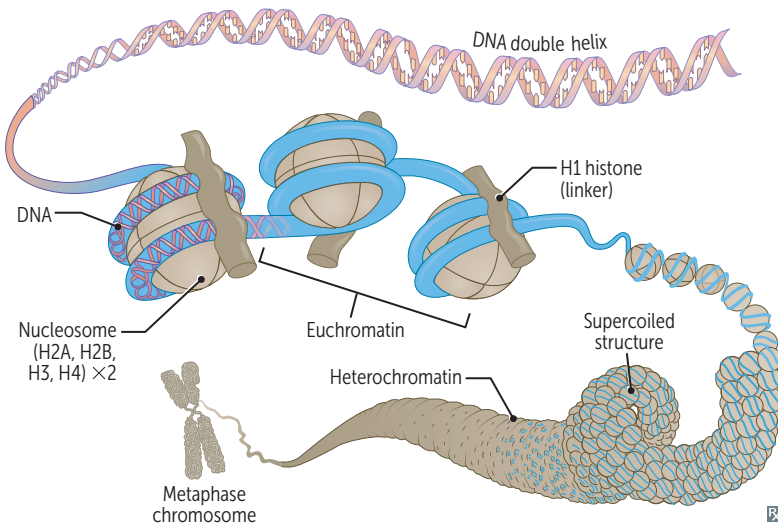
“We think we have found the basic mechanism by which life comes from life.”

—Francis H. C. Crick

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 on hard-core 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	48
▶ Cellular	58
▶ Laboratory Techniques	64
▶ Genetics	68
▶ Nutrition	76
▶ Metabolism	83

► BIOCHEMISTRY—MOLECULAR

Chromatin structure

DNA exists in the condensed, chromatin form in order to fit into the nucleus. Negatively charged DNA loops twice around positively charged histone octamer to form nucleosome “**beads on a string**.” Histones are rich in the amino acids lysine and arginine. H1 binds to the nucleosome and to “linker DNA,” thereby stabilizing the chromatin fiber.

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

Heterochromatin	Condensed, appears darker on EM. Transcriptionally inactive, sterically inaccessible.	Hetero Chromatin = H ighly C ondensed. Barr bodies (inactive X chromosomes) are heterochromatin.
Euchromatin	Less condensed, appears lighter on EM. Transcriptionally active, sterically accessible.	<i>Eu</i> = true, “truly transcribed.”
DNA methylation	Template strand cytosine and adenine are methylated in DNA replication, which allows mismatch repair enzymes to distinguish between old and new strands in prokaryotes. DNA methylation at CpG islands represses transcription.	CpG M ethylation M akes DNA M ute.
Histone methylation	Usually reversibly represses DNA transcription, but can activate it in some cases depending on methylation location.	Histone M ethylation M ostly M akes DNA M ute.
Histone acetylation	Relaxes DNA coiling, allowing for transcription.	Histone A cetylation makes DNA A ctive.

Nucleotides

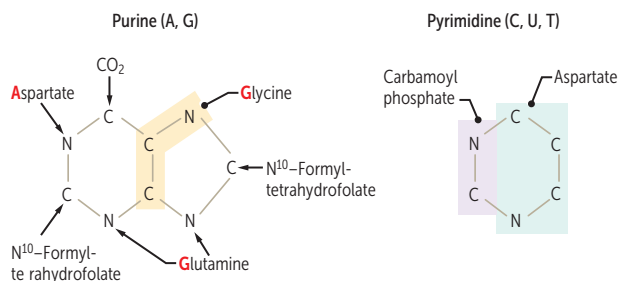
Nucleo**S**ide = base + (deoxy)ribose (**S**ugar).
 Nucleo**T**ide = base + (deoxy)ribose + phospho**T**e;
 linked by 3'-5' phosphodiester bond.

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

Deamination of cytosine makes uracil.
 Uracil found in RNA; thymine in DNA.

PURe **A**s **GO**ld.
CUT the **PY** (pie).
Thymine has a **methy**l.

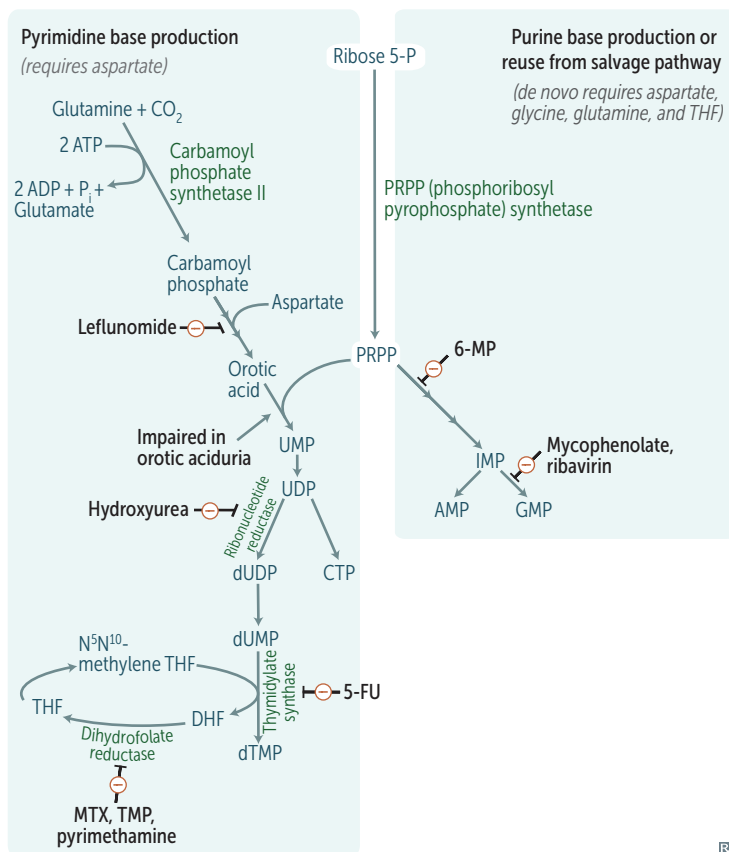
G-C bond (3 H bonds) stronger than A-T bond (2 H bonds). ↑ G-C content → ↑ melting temperature of DNA.



GAG—Amino acids necessary for purine synthesis:
Glycine
Aspartate
Glutamine

De novo pyrimidine and purine synthesis

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



Disrupt pyrimidine synthesis:

- **Leflunomide:** inhibits dihydroorotate dehydrogenase
- **Methotrexate (MTX), trimethoprim (TMP), and pyrimethamine:** inhibit dihydrofolate reductase (↓ deoxythymidine monophosphate [dTMP]) in humans, bacteria, and protozoa, respectively
- **5-fluorouracil (5-FU):** forms 5-F-dUMP, which inhibits thymidylate synthase (↓ dTMP)

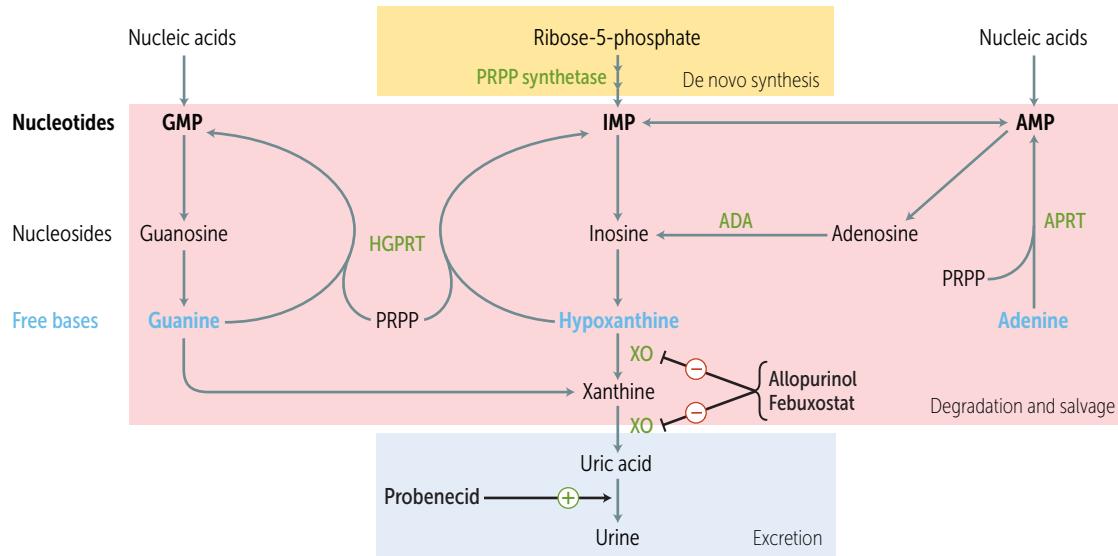
Disrupt purine synthesis:

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

Disrupts purine and pyrimidine synthesis:

- **Hydroxyurea:** inhibits ribonucleotide reductase

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. In ADA deficiency, \uparrow dATP \rightarrow toxicity in lymphocytes.

One of the major causes of autosomal recessive SCID.

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.

Treatment: allopurinol or febuxostat (2nd line).

HGPRT:

Hyperuricemia

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.

Exceptions: methionine and tryptophan encoded by only 1 codon (AUG and UGG, respectively).

Commaless,
nonoverlapping

Read from a fixed starting point as a continuous sequence of bases.

Exceptions: some viruses.

Universal

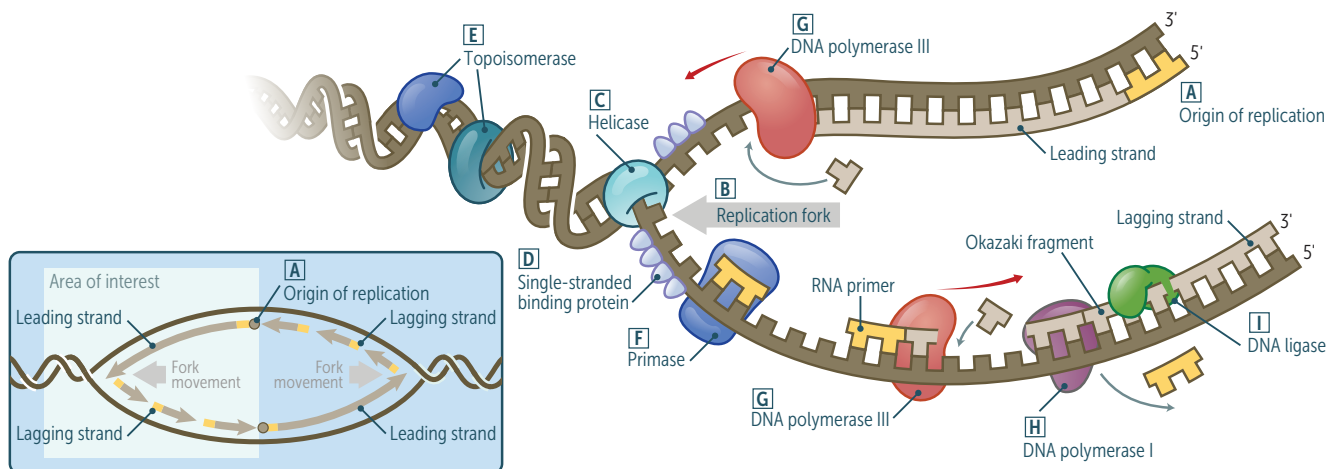
Genetic code is conserved throughout evolution.

Exception in humans: mitochondria.

DNA replication

Eukaryotic DNA replication is more complex than the prokaryotic process but uses many enzymes analogous to those listed below. In both prokaryotes and eukaryotes, DNA replication is semiconservative and involves both continuous and discontinuous (Okazaki fragment) synthesis.

A Origin of replication	Particular consensus sequence of base pairs in genome where DNA replication begins. May be single (prokaryotes) or multiple (eukaryotes).	AT-rich sequences are found in promoters and origins of replication.
B Replication fork	Y-shaped region along DNA template where leading and lagging strands are synthesized.	
C Helicase	Unwinds DNA template at replication fork.	
D Single-stranded binding proteins	Prevent strands from reannealing.	
E DNA topoisomerases	Create a single- or double-stranded break in the helix to add or remove supercoils.	Topoisomerase inhibitors: fluoroquinolones—prokaryotic topoisomerase II [DNA gyrase] and topoisomerase IV; etoposide/teniposide —eukaryotic topoisomerase II .
F Primase	Makes an RNA primer on which DNA polymerase III can initiate replication.	
G DNA polymerase III	Prokaryotic only. Elongates leading strand by adding deoxynucleotides to the 3' end. Elongates lagging strand until it reaches primer of preceding fragment. 3' → 5' exonuclease activity “proofreads” each added nucleotide.	DNA polymerase III has 5' → 3' synthesis and proofreads with 3' → 5' exonuclease.
H DNA polymerase I	Prokaryotic only. Degrades RNA primer; replaces it with DNA.	Has same functions as DNA polymerase III but also excises RNA primer with 5' → 3' exonuclease.
I DNA ligase	Catalyzes the formation of a phosphodiester bond within a strand of double-stranded DNA (ie, joins Okazaki fragments).	
Telomerase	An RNA-dependent DNA polymerase that adds DNA to 3' ends of chromosomes to avoid loss of genetic material with every duplication. Eukaryotes only.	Often dysregulated in cancer cells, allowing unlimited replication.



Mutations in DNA

Severity of damage: silent << missense < nonsense < frameshift.

For point (silent, missense, and nonsense) mutations:

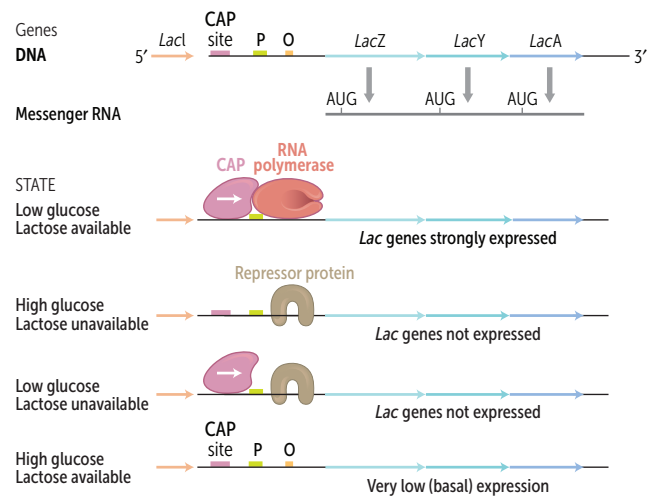
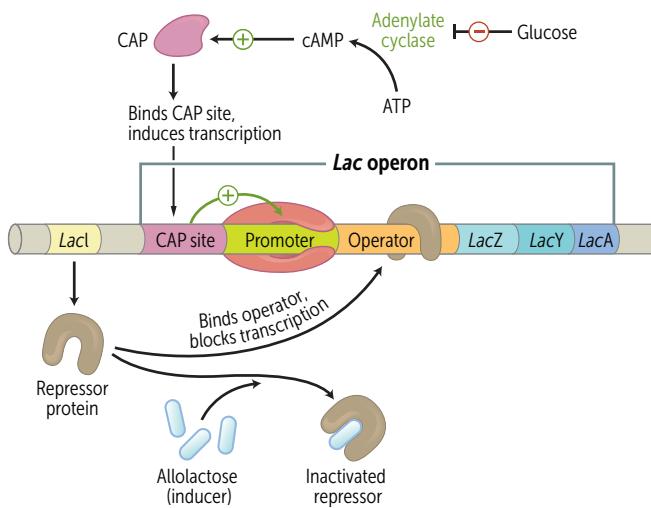
- **Transition**—purine to purine (eg, A to G) or pyrimidine to pyrimidine (eg, C to T).
- **Transversion**—purine to pyrimidine (eg, A to T) or pyrimidine to purine (eg, C to G).

Silent	Nucleotide substitution but codes for same (synonymous) amino acid; often base change in 3rd position of codon (tRNA wobble).	
Missense	Nucleotide substitution resulting in changed amino acid (called conservative if new amino acid is similar in chemical structure).	Sickle cell disease (substitution of glutamic acid with valine).
Nonsense	Nucleotide substitution resulting in early stop codon. Usually results in nonfunctional protein.	Stop the nonsense!
Frameshift	Deletion or insertion of a number of nucleotides not divisible by 3, resulting in misreading of all nucleotides downstream. Protein may be shorter or longer, and its function may be disrupted or altered.	Duchenne muscular dystrophy, Tay-Sachs disease.
Splice site	Mutation at a splice site → retained intron in the mRNA → protein with impaired or altered function.	Rare cause of cancers, dementia, epilepsy, some types of β -thalassemia.

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:

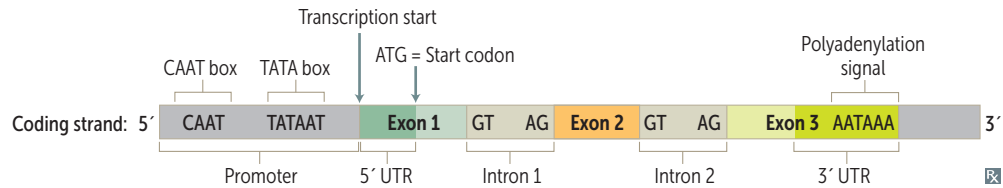
- Low glucose → ↑ adenylate cyclase (adenyl cyclase) activity → ↑ generation of cAMP from ATP → activation of catabolite activator protein (CAP) → ↑ transcription.
- High lactose → unbinds repressor protein from repressor/operator site → ↑ transcription.



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 ₁ phase of cell cycle.	Defective in xeroderma pigmentosum, which prevents repair of pyrimidine dimers because of ultraviolet light exposure.
Base excision repair	Base-specific glycosylase removes altered base and creates AP site (apurinic/aprimidinic). One or more nucleotides are removed by AP-endonuclease, which cleaves the 5' end. Lyase cleaves the 3' end. DNA polymerase-β fills the gap and DNA ligase seals it. Occurs throughout cell cycle.	Important in repair of spontaneous/toxic deamination.
Mismatch repair	Newly synthesized strand is recognized, mismatched nucleotides are removed, and the gap is filled and resealed. Occurs predominantly in G ₂ 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. No requirement for homology. Some DNA may be lost.	Mutated in ataxia telangiectasia; Fanconi anemia.
DNA/RNA/protein synthesis direction	DNA and RNA are both synthesized 5' → 3'. The 5' end of the incoming nucleotide bears the triphosphate (energy source for bond). Protein synthesis is N-terminus to C-terminus.	mRNA is read 5' to 3'. The triphosphate bond is the target of the 3' hydroxyl attack. Drugs blocking DNA replication often have modified 3' OH, preventing addition of the next nucleotide ("chain termination").
Start and stop codons		
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.	
Prokaryotes	Codes for N-formylmethionine (fMet).	fMet stimulates neutrophil chemotaxis.
mRNA stop codons	UGA, UAA, UAG.	UGA = U G o A way. UAA = U A re A way. UAG = U A re G one.

Functional organization of a eukaryotic gene



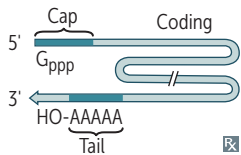
Regulation of gene expression

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	Stretch of DNA that alters gene expression by binding transcription factors.	Enhancers and silencers may be located close to, far from, or even within (in an intron) the gene whose expression it regulates.
Silencer	Site where negative regulators (repressors) bind.	

RNA polymerases

Eukaryotes	<p>RNA polymerase I makes rrRNA (most numerous RNA, rampant).</p> <p>RNA polymerase II makes mmRNA (largest RNA, massive).</p> <p>RNA polymerase III makes 5S rRNA, ttRNA (smallest RNA, tiny).</p> <p>No proofreading function, but can initiate chains. RNA polymerase II opens DNA at promoter site.</p>	<p>I, II, and III are numbered in the same order that their products are used in protein synthesis: large ribosomal RNA, mRNA, then small RNAs.</p> <p>α-amanitin, found in <i>Amanita phalloides</i> (death cap mushrooms), inhibits RNA polymerase II. Causes severe hepatotoxicity if ingested.</p> <p>Rifampin inhibits RNA polymerase in prokaryotes. Actinomycin D inhibits RNA polymerase in both prokaryotes and eukaryotes.</p>
Prokaryotes	I RNA polymerase (multisubunit complex) makes all 3 kinds of RNA.	

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 following transcription:

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

Capped, tailed, and spliced transcript is called mRNA.

mRNA is transported out of the nucleus into the cytosol, where it is translated.

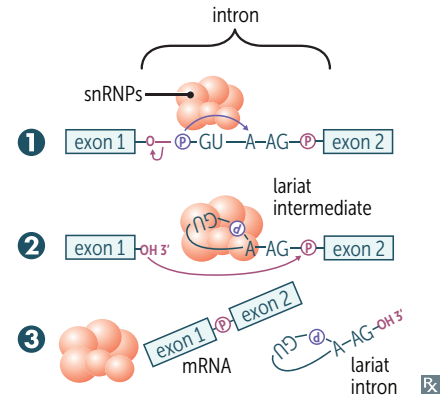
mRNA quality control occurs at cytoplasmic processing bodies (P-bodies), which contain exonucleases, decapping enzymes, and microRNAs; mRNAs may be stored in P-bodies for future translation.

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

Splicing of pre-mRNA

- 1 Primary transcript combines with small nuclear ribonucleoproteins (snRNPs) and other proteins to form spliceosome.
- 2 Lariat-shaped (looped) intermediate is generated.
- 3 Lariat is released to precisely remove intron and join 2 exons.

Antibodies to spliceosomal snRNPs (anti-Smith antibodies) are highly specific for SLE. Anti-U1 RNP antibodies are highly associated with mixed connective tissue disease (MCTD).



Introns vs exons

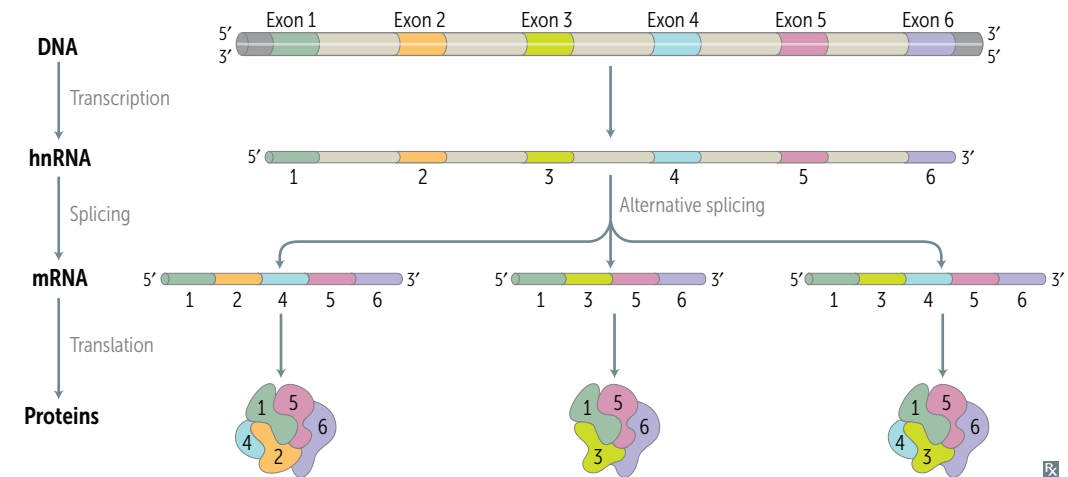
Exons contain the actual genetic information coding for protein.

Introns are intervening noncoding segments of DNA.

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

Introns are **in**tervening sequences and stay **in** the nucleus, whereas **ex**ons **ex**it and are **ex**pressed.

Abnormal splicing variants are implicated in oncogenesis and many genetic disorders (eg, β -thalassemia).



microRNAs

Small, noncoding RNA molecules that posttranscriptionally regulate protein expression. Introns can contain microRNA (miRNA) genes. They can have multiple mRNA targets, typically related to complementary base pairing. miRNA \rightarrow degradation or inactivation of target mRNA \rightarrow \downarrow translation into protein. Abnormal expression of miRNAs contributes to certain malignancies (eg, by silencing an mRNA from a tumor suppressor gene).

tRNA

Structure

75–90 nucleotides, 2° structure, cloverleaf form, anticodon end is opposite 3' aminoacyl end. All 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 tRNA-ribosome binding.

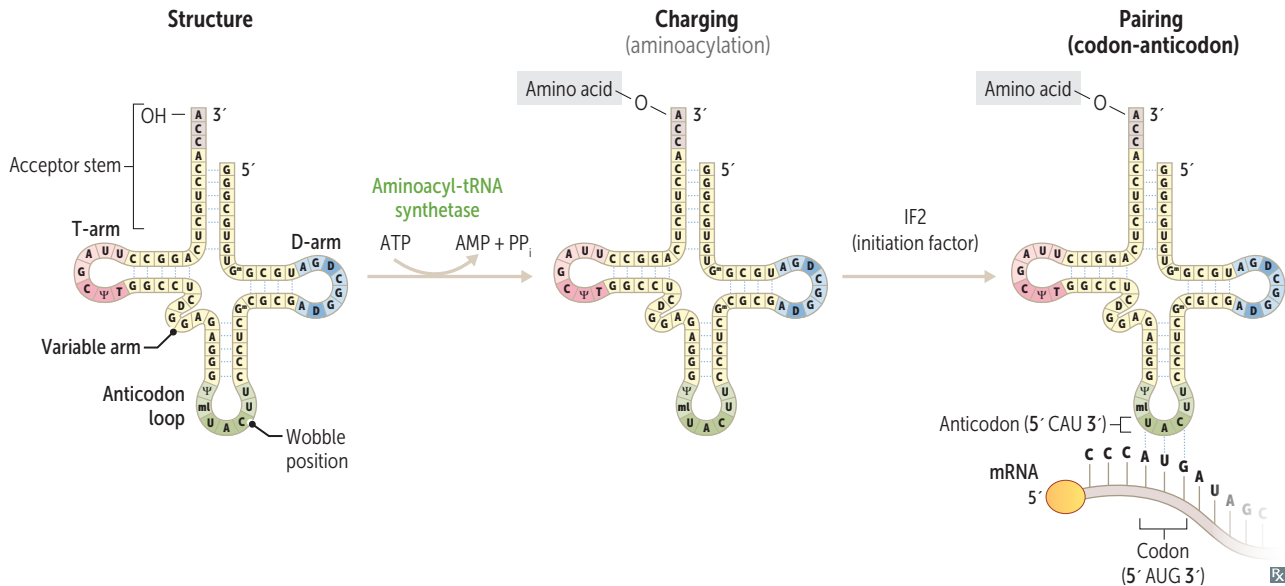
D-arm: contains dihydrouridine residues necessary for tRNA recognition by the correct aminoacyl-tRNA synthetase.

Acceptor stem: the 5'-CCA-3' is the amino acid acceptor site.

Charging

Aminoacyl-tRNA synthetase (1 per amino acid; “matchmaker”; uses ATP) scrutinizes amino acid before and after it binds to tRNA. If incorrect, bond is hydrolyzed. The amino acid-tRNA bond has energy for formation of peptide bond. A mischarged tRNA reads usual codon but inserts wrong amino acid.

Aminoacyl-tRNA synthetase and binding of charged tRNA to the codon are responsible for accuracy of amino acid selection.



Wobble

Accurate base pairing is usually required only in the first 2 nucleotide positions of an mRNA codon, so codons differing in the 3rd “wobble” position may code for the same tRNA/amino acid (as a result of degeneracy of genetic code).

Protein synthesis**Initiation**

Initiated by GTP hydrolysis; initiation factors (eukaryotic IFs) help assemble the 40S ribosomal subunit with the initiator tRNA and are released when the mRNA and the ribosomal 60S subunit assemble with the complex.

Eukaryotes: 40S + 60S → 80S (**E**ven).

PrOkaryotes: 30S + 50S → 70S (**O**dd).

ATP—tRNA **A**ctivation (charging).

GTTP—tRNA **G**ripping and **G**oing places (translocation).

Elongation

1. Aminoacyl-tRNA binds to A site (except for initiator methionine)
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)

Think of “going **APE**”:

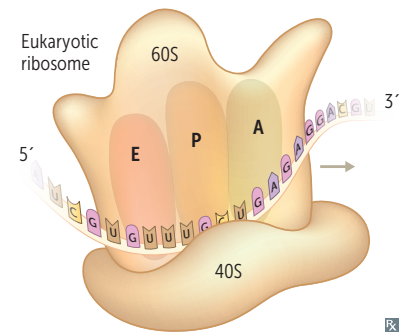
A site = incoming **A**minoacyl-tRNA.

P site = accommodates growing **P**eptide.

E site = holds **E**mpy tRNA as it **E**xits.

Termination

Stop codon is recognized by release factor, and completed polypeptide is released from ribosome.

**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/or maintaining protein folding. For example, in yeast, heat shock proteins (eg, Hsp60) are expressed at high temperatures to prevent protein denaturing/misfolding.

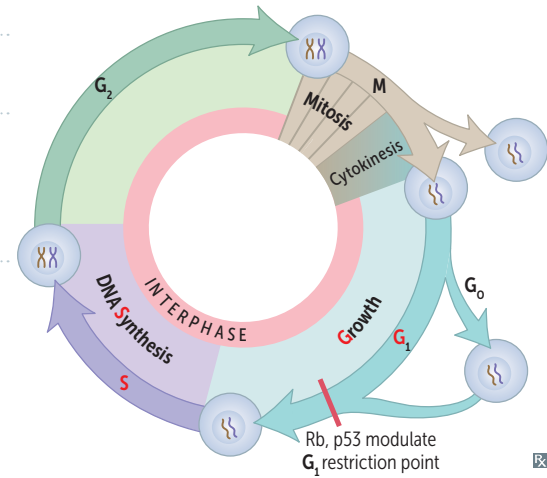
► BIOCHEMISTRY—CELLULAR

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

CDKs	Constitutive and inactive.
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.
Tumor suppressors	p53 induces p21, which inhibits CDKs → hypophosphorylation (activation) of Rb. Hypophosphorylated Rb binds to and inactivates transcription factor E2F → inhibition of G_1 -S progression. Mutations in these genes result in unrestrained cell division (eg, Li-Fraumeni syndrome).



CELL TYPES

Permanent	Remain in G_0 , regenerate from stem cells.	Neurons, skeletal and cardiac muscle, RBCs.
Stable (quiescent)	Enter G_1 from G_0 when stimulated.	Hepatocytes, lymphocytes.
Labile	Never go to G_0 , divide rapidly with a short G_1 . Most affected by chemotherapy.	Bone marrow, gut epithelium, skin, hair follicles, germ cells.

Rough endoplasmic reticulum

Site of synthesis of secretory (exported) proteins and of N-linked oligosaccharide addition to many proteins.
Nissl bodies (RER in neurons)—synthesize peptide neurotransmitters for secretion.
Free ribosomes—unattached to any membrane; site of synthesis of cytosolic and organellar proteins.

Mucus-secreting goblet cells of the small intestine and antibody-secreting plasma cells are rich in RER.

Smooth endoplasmic reticulum

Site of steroid synthesis and detoxification of drugs and poisons. Lacks surface ribosomes.

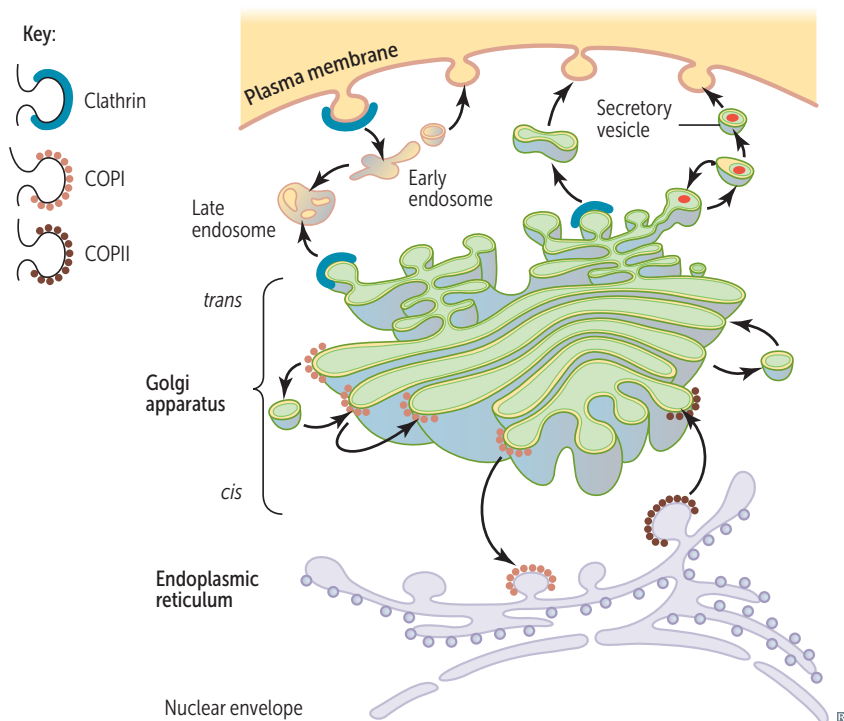
Liver hepatocytes and steroid hormone-producing cells of the adrenal cortex and gonads are rich in SER.

Cell trafficking

Golgi is the distribution center for proteins and lipids from the ER to the vesicles and plasma membrane. Modifies N-oligosaccharides on asparagine. Adds O-oligosaccharides on serine and threonine. Adds mannose-6-phosphate to proteins for trafficking to lysosomes.

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/mucopolipidosis type II)—inherited lysosomal storage disorder; defect in *N*-acetylglucosaminyl-1-phosphotransferase → failure of the Golgi to phosphorylate mannose residues (ie, ↓ mannose-6-phosphate) on glycoproteins → proteins are secreted extracellularly rather than delivered to lysosomes. Results in coarse facial features, clouded corneas, restricted joint movement, and high plasma levels of lysosomal enzymes. Often fatal in childhood.

**Signal recognition particle (SRP)**

Abundant, cytosolic ribonucleoprotein that traffics proteins from the ribosome to the RER. Absent or dysfunctional SRP → proteins accumulate in the cytosol.

Vesicular trafficking proteins

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

COPII: ER → *cis*-Golgi (anterograde).

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

Peroxisome

Membrane-enclosed organelle involved in catabolism of very-long-chain fatty acids (through β -oxidation), branched-chain fatty acids, amino acids, and ethanol.

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.

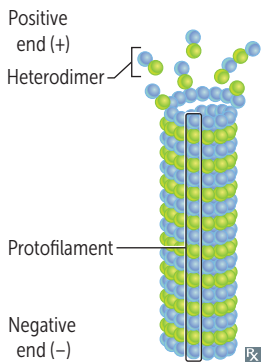
Cytoskeletal elements A network of protein fibers within the cytoplasm that supports cell structure, cell and organelle movement, and cell division.

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

Immunohistochemical stains for intermediate filaments

STAIN	CELL TYPE	IDENTIFIES
Vimentin	Mesenchymal tissue (eg, fibroblasts, endothelial cells, macrophages)	Mesenchymal tumors (eg, sarcoma), but also many other tumors (eg, endometrial carcinoma, renal cell carcinoma, and meningiomas)
DesMin	M uscle	Muscle tumors (eg, rhabdomyosarcoma)
Cytokeratin	Epithelial cells	Epithelial tumors (eg, squamous cell carcinoma)
GFAP	Neuro G lia (eg, astrocytes, Schwann cells, oligodendroglia)	Astrocytoma, glioblastoma
Neurofilaments	Neurons	Neuronal tumors (eg, neuroblastoma)

Microtubule



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

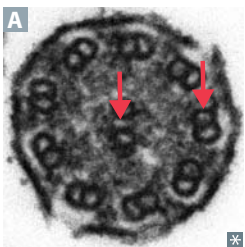
Molecular motor proteins—transport cellular cargo toward opposite ends of microtubule tracks.

- Dynein—retrograde to microtubule (+ \rightarrow -).
- Kinesin—anterograde to microtubule (- \rightarrow +).

Drugs that act on microtubules (**M**icrotubules **G**et **C**onstructed **V**ery **P**oorly):

- **M**ebendazole (antihelminthic)
- **G**riseofulvin (antifungal)
- **C**olchicine (antigout)
- **V**incristine/**V**inblastine (anticancer)
- **P**aclitaxel (anticancer)

Cilia structure



9 + 2 arrangement of microtubule doublets (arrows in **A**). The base of a cilium below the cell membrane, called the basal body, consists of 9 microtubule triplets with no central microtubules.

Axonemal dynein—ATPase that links peripheral 9 doublets and causes bending of cilium by differential sliding of doublets.

Kartagener syndrome (1° ciliary dyskinesia)—

immotile cilia due to a dynein arm defect. Results in male and female infertility due to immotile sperm and dysfunctional fallopian tube cilia, respectively; \uparrow risk of ectopic pregnancy. Can cause bronchiectasis, recurrent sinusitis, and situs inversus (eg, dextrocardia on CXR).

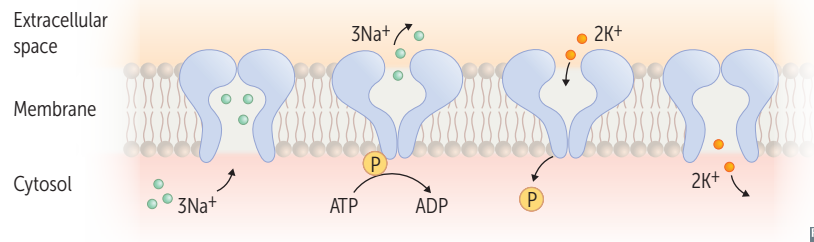
Plasma membrane composition

Asymmetric lipid bilayer.
Contains cholesterol, phospholipids, sphingolipids, glycolipids, and proteins. Fungal membranes contain ergosterol.

Sodium-potassium pump

Na⁺-K⁺ ATPase is located in the plasma membrane with ATP site on cytosolic side.
For each ATP consumed, 3Na⁺ go out of the cell (pump phosphorylated) and 2K⁺ come into the cell (pump dephosphorylated).

Ouabain inhibits by binding to K⁺ site.
Cardiac glycosides (digoxin and digitoxin) directly inhibit the Na⁺-K⁺ ATPase, which leads to indirect inhibition of Na⁺/Ca²⁺ exchange → ↑ [Ca²⁺]; → ↑ cardiac contractility.



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%)—**B**one (made by osteoblasts), **S**kin, **T**endon, dentin, fascia, cornea, late wound repair.

Type **I**: **bone**.
↓ production in osteogenesis imperfecta type I.

Type II

Cartilage (including hyaline), vitreous body, nucleus pulposus.

Type **II**: **cartwo**lage.

Type III

Reticulin—skin, **blood vessels**, uterus, fetal tissue, granulation tissue.

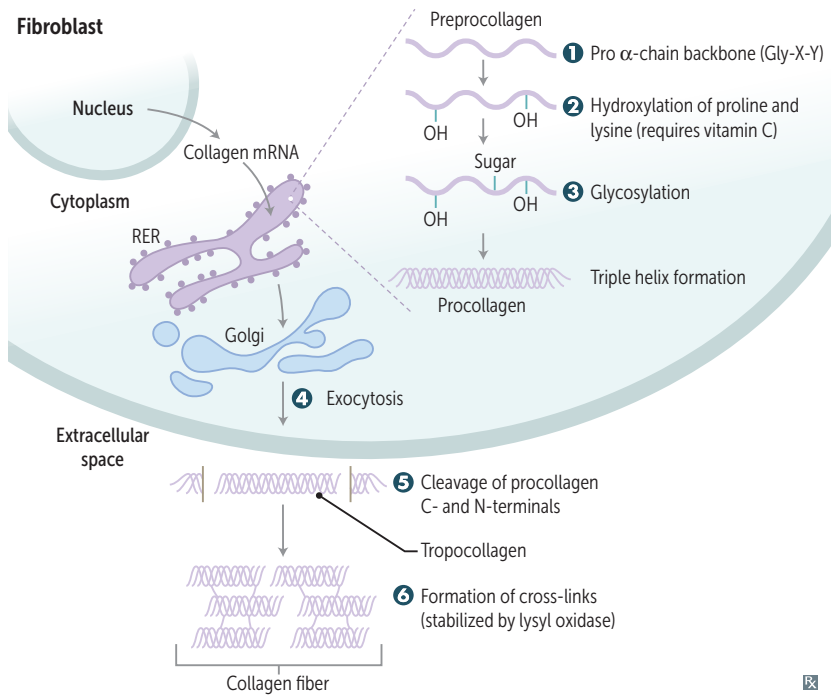
Type **III**: deficient in the uncommon, **vascular** type of **Ehlers-Danlos syndrome (ThreE D)**.

Type IV

Basement membrane, basal lamina, lens.

Type **IV**: under the **floor** (basement membrane).
Defective in Alport syndrome; targeted by autoantibodies in Goodpasture syndrome.

Collagen synthesis and structure



- 1 **Synthesis**—translation of collagen α chains (preprocollagen)—usually Gly-X-Y (X and Y are proline or lysine). Glycine content best reflects collagen synthesis (collagen is $\frac{1}{3}$ glycine).
- 2 **Hydroxylation**—hydroxylation of specific proline and lysine residues. Requires vitamin C; deficiency \rightarrow scurvy.
- 3 **Glycosylation**—glycosylation of pro- α -chain hydroxylysine residues and formation of disulfide bonds (triple helix of 3 collagen α chains). Problems forming triple helix \rightarrow osteogenesis imperfecta.
- 4 **Exocytosis**—exocytosis of procollagen into extracellular space.
- 5 **Proteolytic processing**—cleavage of disulfide-rich terminal regions of procollagen \rightarrow 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 \rightarrow Ehlers-Danlos syndrome, Menkes disease.

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 can include:

- Multiple fractures with minimal trauma **A B**; may occur during the birth process
- Blue sclerae **C** due to the translucent connective tissue over choroidal veins
- Hearing loss (abnormal ossicles)
- Some forms have tooth abnormalities, including opalescent teeth that wear easily due to lack of dentin (dentinogenesis imperfecta)

May be confused with child abuse.



Ehlers-Danlos syndrome

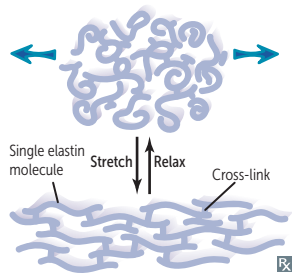


Faulty collagen synthesis causing hyperextensible skin, tendency to bleed (easy bruising), and hypermobile joints **A**. Multiple types. Inheritance and severity vary. Can be autosomal dominant or recessive. May be associated with joint dislocation, berry and aortic aneurysms, organ rupture.

Hypermobility type (joint instability): most common type.
 Classical type (joint and skin symptoms): caused by a mutation in type V collagen.
 Vascular type (vascular and organ rupture): deficient type III collagen.

Menkes disease

X-linked recessive connective tissue disease caused by impaired copper absorption and transport due to defective Menkes protein (*ATP7A*). Leads to ↓ activity of lysyl oxidase (copper is a necessary cofactor). Results in brittle, “kinky” hair, growth retardation, and hypotonia.

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.

Tropoelastin with fibrillin scaffolding.

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

Broken down by elastase, which is normally inhibited by α_1 -antitrypsin.

Marfan syndrome—caused by a defect in fibrillin, a glycoprotein that forms a sheath around elastin.

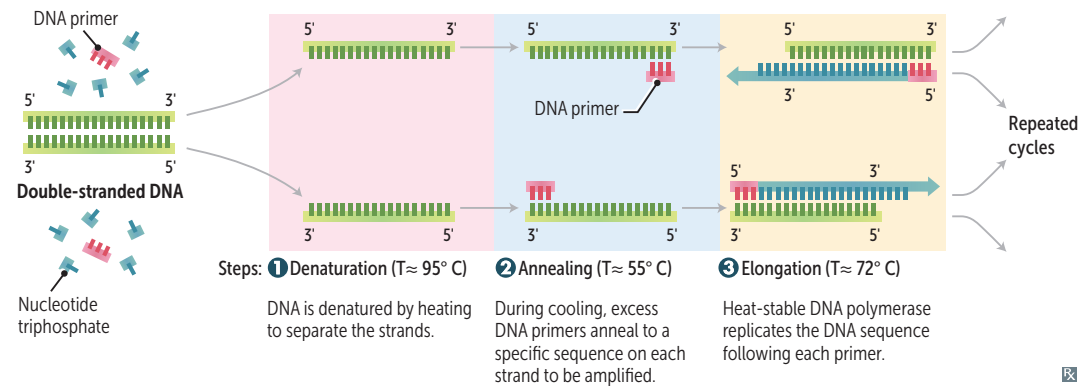
Emphysema—can be caused by α_1 -antitrypsin deficiency, resulting in excess elastase activity.

Wrinkles of aging are due to ↓ collagen and elastin production.

► BIOCHEMISTRY—LABORATORY TECHNIQUES

Polymerase chain reaction

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



Blotting procedures**Southern blot**

1. DNA sample is enzymatically cleaved into smaller pieces, which are separated on a gel by electrophoresis, and then transferred to a filter.
2. Filter is exposed to radiolabeled DNA probe that recognizes and anneals to its complementary strand.
3. Resulting double-stranded, labeled piece of DNA is visualized when filter is exposed to film.

SNoW DRoP:Southern = **D**NANorthern = **R**NAWestern = **P**rotein**Northern blot**

Similar to Southern blot, except that an **RNA** sample is electrophoresed. Useful for studying mRNA levels, which are reflective of gene expression.

Western blot

Sample protein is separated via gel electrophoresis and transferred to a membrane. Labeled antibody is used to bind to relevant **protein**. Confirmatory test for HIV after ⊕ ELISA.

Southwestern blot

Identifies **DNA-binding proteins** (eg, transcription factors) using labeled oligonucleotide probes.

Flow cytometry

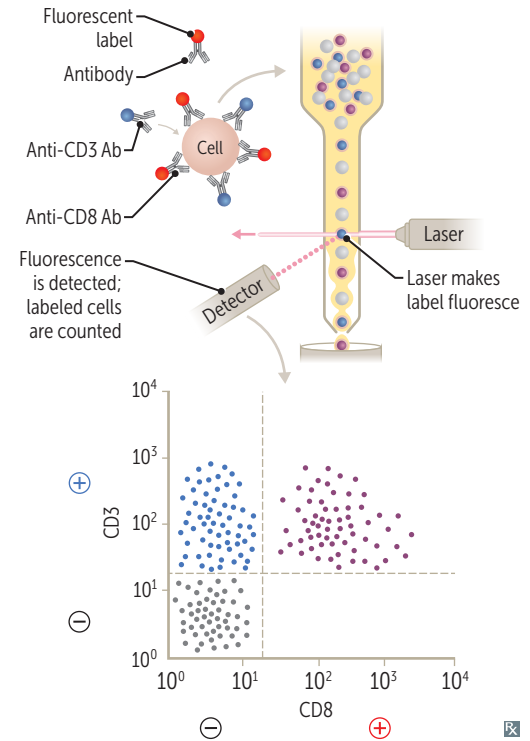
Laboratory technique to assess size, granularity, and protein expression (immunophenotype) of individual cells in a sample.

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 left lower quadrant ⊖ for both CD8 and CD3.
- Cells in right lower quadrant ⊕ for CD8. (Right lower quadrant is empty because all CD8-expressing cells also express CD3.)
- Cells in left upper quadrant ⊕ for CD3.
- Cells in right upper quadrant ⊕ for CD8 and CD3 (red + blue → purple).

Commonly used in workup of hematologic abnormalities (eg, paroxysmal nocturnal hemoglobinuria, fetal RBCs in mother's blood) and immunodeficiencies (eg, CD4 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 (eg, HBsAg) or antibody (eg, anti-HBs) 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 (eg, color change). Major ELISA variations include direct, sandwich, and competitive. Can have high sensitivity and specificity.

Karyotyping

A process in which metaphase chromosomes are stained, ordered, and numbered according to morphology, size, arm-length ratio, and banding pattern. 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. 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 outside the original chromosome
 - Duplication—extra site of fluorescence on one chromosome relative to its homologous chromosome
-

Cloning methods

Cloning is the production of a recombinant DNA molecule that is self-perpetuating.

Steps:

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

Gene expression modifications

Transgenic strategies in mice involve:

- Random insertion of gene into mouse genome
- Targeted insertion or deletion of gene through homologous recombination with mouse gene

Knock-**out** = removing a gene, taking it **out**.
Knock-**in** = **in**serting a gene.

Cre-lox system

Can inducibly manipulate genes at specific developmental points (eg, to study a gene whose deletion causes embryonic death).

RNA interference

dsRNA is synthesized that is complementary to the mRNA sequence of interest. When transfected into human cells, dsRNA separates and promotes degradation of target mRNA, “knocking down” gene expression.

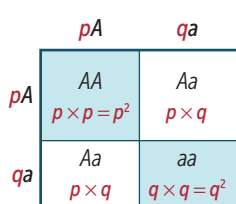
► BIOCHEMISTRY—GENETICS

Genetic terms

TERM	DEFINITION	EXAMPLE
Codominance	Both alleles contribute to the phenotype of the heterozygote.	Blood groups A, B, AB; α_1 -antitrypsin deficiency.
Variable expressivity	Phenotype varies among individuals with same genotype.	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.	<i>BRCA1</i> 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.
Dominant negative mutation	Exerts a dominant effect. A heterozygote produces a nonfunctional altered protein that also prevents the normal gene product from functioning.	Mutation of a transcription factor in its allosteric site. Nonfunctioning mutant can still bind DNA, preventing wild-type transcription factor from binding.
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.	

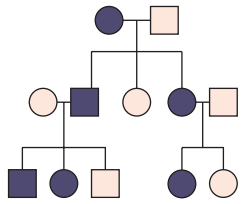
Genetic terms (continued)

TERM	DEFINITION	EXAMPLE
Mosaicism	<p>Presence of genetically distinct cell lines in the same individual.</p> <p>Somatic mosaicism—mutation arises from mitotic errors after fertilization and propagates through multiple tissues or organs.</p> <p>Gonadal mosaicism—mutation only in egg or sperm cells.</p>	McCune-Albright syndrome —due to mutation affecting G-protein signaling. Presents with unilateral café-au-lait spots, polyostotic fibrous dysplasia, precocious puberty, multiple endocrine abnormalities. 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.	
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), not aneuploid. Most occurrences of UPD → normal phenotype. Consider UPD in an individual manifesting a recessive disorder when only one parent is a carrier.
Hardy-Weinberg population genetics	<p>If a population is in Hardy-Weinberg equilibrium and if p and q are the frequencies of separate alleles, then: $p^2 + 2pq + q^2 = 1$ and $p + q = 1$, which implies that:</p> <p>p^2 = frequency of homozygosity for allele p q^2 = frequency of homozygosity for allele q $2pq$ = frequency of heterozygosity (carrier frequency, if an autosomal recessive disease). The frequency of an X-linked recessive disease in males = q and in females = q^2.</p>	<p>Hardy-Weinberg law assumptions include:</p> <ul style="list-style-type: none"> ▪ No mutation occurring at the locus ▪ Natural selection is not occurring ▪ Completely random mating ▪ No net migration
Imprinting	At some loci, only one allele is active; the other is inactive (imprinted/inactivated by methylation). With one allele inactivated, deletion of the active allele → disease.	Both Prader-Willi and Angelman syndromes are due to mutation or deletion of genes on chromosome 15.
Prader-Willi syndrome	Maternal imprinting: gene from mom is normally silent and P aternal gene is deleted/mutated. Results in hyperphagia, obesity, intellectual disability, hypogonadism, and hypotonia.	25% of cases due to maternal uniparental disomy (two maternally imprinted genes are received; no paternal gene received).
Angelman syndrome	Paternal imprinting: gene from dad is normally silent and M aternal gene is deleted/mutated. Results in inappropriate laughter (“happy puppet”), seizures, ataxia, and severe intellectual disability.	5% of cases due to paternal uniparental disomy (two paternally imprinted genes are received; no maternal gene received).



Modes of inheritance

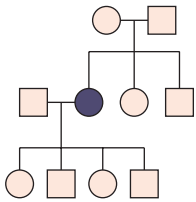
Autosomal dominant



Often due to defects in structural genes. Many generations, both male and female, 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, $\frac{1}{2}$ of children affected.

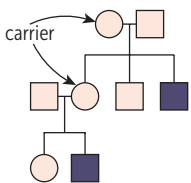
Autosomal recessive



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. With 2 carrier (heterozygous) parents, on average: $\frac{1}{4}$ of children will be affected (homozygous), $\frac{1}{2}$ of children will be carriers, and $\frac{1}{4}$ of children will be neither affected nor carriers.

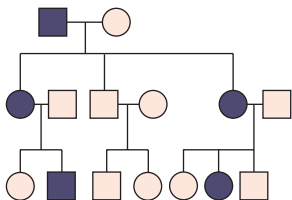
X-linked recessive



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

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

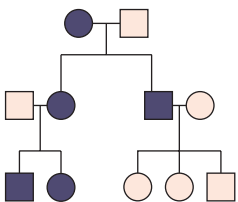
X-linked dominant



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

Hypophosphatemic rickets—formerly known as vitamin D-resistant rickets. Inherited disorder resulting in ↑ phosphate wasting at proximal tubule. Results in rickets-like presentation. Other examples: Rett syndrome, fragile X syndrome, Alport syndrome.

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 encephalopathy, lactic acidosis, and stroke-like episodes). 2° to failure in oxidative phosphorylation. Muscle biopsy often shows “ragged red fibers.”

□ = unaffected male; ■ = affected male; ○ = unaffected female; ● = affected female.

Autosomal dominant diseases

Achondroplasia	Mutation of fibroblast growth factor receptor 3 (<i>FGFR3</i>) inhibits chondrocyte proliferation. Most common cause of dwarfism; limb length affected more than head or torso size. Full penetrance.
Autosomal dominant polycystic kidney disease	Bilateral, massive enlargement of kidneys due to multiple large cysts. 85% of cases are due to mutation in <i>PKD1</i> (chromosome 16; 16 letters in “polycystic kidney”); remainder due to mutation in <i>PKD2</i> (chromosome 4).
Familial adenomatous polyposis	Colon becomes covered with adenomatous polyps after puberty. Progresses to colon cancer unless colon is resected. Mutations on chromosome 5q (<i>APC</i> gene); 5 letters in “polyp.”
Familial hypercholesterolemia	Elevated LDL due to defective or absent LDL receptor. Leads to severe atherosclerotic disease early in life, corneal arcus, tendon xanthomas (classically in the Achilles tendon).
Hereditary hemorrhagic telangiectasia	Inherited disorder of blood vessels. Findings: branching skin lesions (telangiectasias), recurrent epistaxis, skin discolorations, arteriovenous malformations (AVMs), GI bleeding, hematuria. Also known as Osler-Weber-Rendu syndrome.
Hereditary spherocytosis	Spheroid erythrocytes due to spectrin or ankyrin defect; hemolytic anemia; ↑ MCHC, ↑ RDW. Treatment: splenectomy.
Huntington disease	Findings: depression, progressive dementia, choreiform movements, and caudate atrophy. ↑ dopamine, ↓ GABA, ↓ ACh in the brain. Gene on chromosome 4; trinucleotide repeat disorder: (CAG) _n . Demonstrates anticipation: ↑ repeats → ↓ age of onset. “ Hunting 4 CAGs. ”
Li-Fraumeni syndrome	Abnormalities in <i>TP53</i> → multiple malignancies at an early age. Also known as SBLA cancer syndrome (sarcoma, breast, leukemia, adrenal gland).
Marfan syndrome	<i>FBNI</i> gene mutation on chromosome 15 → defective fibrillin (scaffold for elastin) → connective tissue disorder affecting skeleton, heart, and eyes. Findings: tall with long extremities, pectus excavatum, hypermobile joints, and long, tapering fingers and toes (arachnodactyly); cystic medial necrosis of aorta → aortic incompetence and dissecting aortic aneurysms; floppy mitral valve. Subluxation of lenses, typically upward and temporally.
Multiple endocrine neoplasias (MEN)	Several distinct syndromes (1, 2A, 2B) characterized by familial tumors of endocrine glands, including those of the pancreas, parathyroid, pituitary, thyroid, and adrenal medulla. MEN 1 is associated with <i>MEN1</i> gene, MEN 2A and 2B are associated with <i>RET</i> gene.
Neurofibromatosis type 1 (von Recklinghausen disease)	Neurocutaneous disorder characterized by café-au-lait spots, cutaneous neurofibromas, optic gliomas, pheochromocytomas, Lisch nodules (pigmented iris hamartomas). 100% penetrance, variable expression. Caused by mutations in the <i>NF1</i> gene on chromosome 17; 17 letters in “von Recklinghausen.”
Neurofibromatosis type 2	Findings: bilateral acoustic schwannomas, juvenile cataracts, meningiomas, and ependymomas. <i>NF2</i> gene on chromosome 22; type 2 = 22.
Tuberous sclerosis	Neurocutaneous disorder with multi-organ system involvement, characterized by numerous benign hamartomas. Variable expression.
von Hippel-Lindau disease	Disorder characterized by development of numerous tumors, both benign and malignant. Associated with deletion of <i>VHL</i> gene (tumor suppressor) on chromosome 3 (3p). Von Hippel-Lindau = 3 words for chromosome 3.

Autosomal recessive diseases

Albinism, autosomal recessive polycystic kidney disease (ARPKD), cystic fibrosis, 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^- channel that secretes Cl^- in lungs and GI tract, and reabsorbs Cl^- in sweat glands. Most common mutation \rightarrow misfolded protein \rightarrow protein retained in RER and not transported to cell membrane, causing \downarrow Cl^- (and H_2O) secretion; \uparrow intracellular Cl^- results in compensatory \uparrow Na^+ reabsorption via epithelial Na^+ channels \rightarrow \uparrow H_2O reabsorption \rightarrow abnormally thick mucus secreted into lungs and GI tract. \uparrow Na^+ reabsorption also causes more negative transepithelial potential difference.

DIAGNOSIS

\uparrow Cl^- concentration (> 60 mEq/L) in sweat is diagnostic. Can present with contraction alkalosis and hypokalemia (ECF effects analogous to a patient taking a loop diuretic) because of ECF $\text{H}_2\text{O}/\text{Na}^+$ losses and concomitant renal K^+/H^+ wasting. \uparrow immunoreactive trypsinogen (newborn screening).

COMPLICATIONS

Recurrent pulmonary infections (eg, *S aureus* [early infancy], *P aeruginosa* [adolescence]), chronic bronchitis and bronchiectasis \rightarrow reticulonodular pattern on CXR. 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 saline facilitate mucus clearance. Azithromycin used as anti-inflammatory agent. Pancreatic enzymes for insufficiency.

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.

Female carriers can be variably affected depending on the percentage inactivation of the X chromosome carrying the mutant vs normal gene.

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

Muscular dystrophies

Duchenne



X-linked disorder typically due to **frameshift** or nonsense mutations → truncated dystrophin protein → inhibited muscle regeneration. Weakness begins in pelvic girdle muscles and progresses superiorly. Pseudohypertrophy of muscle **A**. Gower maneuver—patients use upper extremities to help them stand up. Waddling gait. Onset before 5 years of age. Dilated cardiomyopathy is common cause of death.

Duchenne = **d**eleted **d**ystrophin.

Dystrophin gene (*DMD*) is the largest protein-coding human gene → ↑ 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 α - and β -dystroglycan, which are connected to the extracellular matrix (ECM). Loss of dystrophin results in myonecrosis. ↑ CK and aldolase are seen; Western blot and muscle biopsy confirm diagnosis.

Becker

X-linked disorder typically due to **non-frameshift** insertions in dystrophin gene (partially functional instead of truncated). Less severe than Duchenne. Onset in adolescence or early adulthood.

Deletions can cause both Duchenne and Becker.

Myotonic type 1

Autosomal dominant. CTG trinucleotide repeat expansion in the *DMPK* gene → abnormal expression of myotonin protein kinase → myotonia, muscle wasting, cataracts, testicular atrophy, frontal balding, arrhythmia.

My Tonia, **My Testicles** (testicular atrophy), **My Toupee** (frontal balding), **My Ticker** (arrhythmia).

Fragile X syndrome

X-linked dominant inheritance. Trinucleotide repeat in *FMRI* gene → methylation → ↓ expression. The 2nd most common cause of genetic intellectual disability (after Down syndrome). Findings: post-pubertal macroorchidism (enlarged testes), long face with a large jaw, large everted ears, autism, mitral valve prolapse.

Trinucleotide repeat disorder $(CGG)_n$. Fragile **X** = **eXtra** large testes, jaw, ears.

Trinucleotide repeat expansion diseases

Huntington disease, **myotonic** dystrophy, **Friedreich** ataxia, fragile **X** syndrome.
 Fragile **X** syndrome = $(CGG)_n$.
Friedreich ataxia = $(GAA)_n$.
Huntington disease = $(CAG)_n$.
Myotonic dystrophy = $(CTG)_n$.

Try (trinucleotide) **hunting** for **my fried** eggs (X).

X-Girlfriend's First Aid Helped Ace My Test.
 May show genetic anticipation (disease severity ↑ and age of onset ↓ in successive generations).

Autosomal trisomies

Down syndrome
(trisomy 21)

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

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. 1% of cases due to mosaicism (no maternal association; post-fertilization 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; ↓ serum PAPP-A, ↑ free β-hCG.

Second-trimester quad screen shows ↓ α-fetoprotein, ↑ β-hCG, ↓ estriol, ↑ inhibin A.

Edwards syndrome
(trisomy 18)

Findings: severe intellectual disability, rocker-bottom feet, micrognathia (small jaw), low-set **E**ars, clenched hands with overlapping fingers, prominent occiput, congenital heart disease. Death usually occurs within 1 year of birth.

Incidence 1:8000.

Election age (18).

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

PAPP-A and free β-hCG are ↓ in first trimester.

Quad screen shows ↓ α-fetoprotein, ↓ β-hCG, ↓ estriol, ↓ or normal inhibin A.

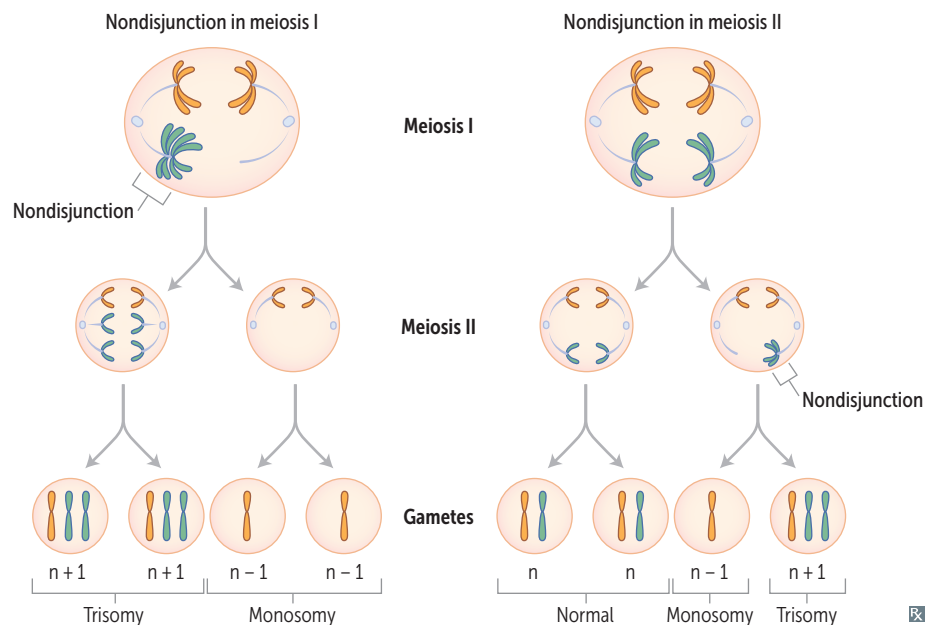
Patau syndrome
(trisomy 13)

Findings: severe intellectual disability, rocker-bottom feet, microphthalmia, microcephaly, cleft **li**P/Palate, holo**P**rosencephaly, **P**olydactyly, congenital heart disease, cutis aplasia. Death usually occurs within 1 year of birth.

Incidence 1:15,000.

Puberty (13).

First-trimester pregnancy screen shows ↓ free β-hCG, ↓ PAPP-A.



Genetic disorders by chromosome

CHROMOSOME	SELECTED EXAMPLES
3	von Hippel-Lindau disease, renal cell carcinoma
4	ADPKD (<i>PKD2</i>), achondroplasia, Huntington disease
5	Cri-du-chat syndrome, familial adenomatous polyposis
6	Hemochromatosis (<i>HFE</i>)
7	Williams syndrome, cystic fibrosis
9	Friedreich ataxia
11	Wilms tumor, β -globin gene defects (eg, sickle cell disease, β -thalassemia)
13	Patau syndrome, Wilson disease, retinoblastoma (<i>RBI</i>), <i>BRCA2</i>
15	Prader-Willi syndrome, Angelman syndrome, Marfan syndrome
16	ADPKD (<i>PKD1</i>), α -globin gene defects (eg, α -thalassemia)
17	Neurofibromatosis type 1, <i>BRCA1</i>
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 13, 14, 15, 21, and 22. 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

Congenital microdeletion of short arm of chromosome 5 (46,XX or XY, 5p⁻). Findings: microcephaly, moderate to severe intellectual disability, high-pitched crying/**mewing**, epicanthal folds, cardiac abnormalities (VSD).

Cri du chat = cry of the **cat**.

Williams syndrome

Congenital microdeletion of long arm of chromosome 7 (deleted region includes elastin gene). Findings: distinctive “elfin” facies, intellectual disability, hypercalcemia (\uparrow sensitivity to vitamin D), well-developed verbal skills, extreme friendliness with strangers, cardiovascular problems.

22q11 deletion syndromes

Microdeletion at chromosome 22q11 → variable presentations including **C**left palate, **A**bnormal facies, **T**hymic aplasia → T-cell deficiency, **C**ardiac defects, and **H**ypocalcemia 2° to parathyroid aplasia.

DiGeorge syndrome—thymic, parathyroid, and cardiac defects.

Velocardiofacial syndrome—palate, facial, and cardiac defects.

CATCH-22.

Due to aberrant development of 3rd and 4th branchial pouches.

▶ BIOCHEMISTRY—NUTRITION

Vitamins: fat soluble

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

Malabsorption syndromes with steatorrhea, such as cystic fibrosis and sprue, or mineral oil intake can cause fat-soluble vitamin deficiencies.

Vitamins: water soluble

B₁ (thiamine: TPP)
 B₂ (riboflavin: FAD, FMN)
 B₃ (niacin: NAD⁺)
 B₅ (pantothenic acid: CoA)
 B₆ (pyridoxine: PLP)
 B₇ (biotin)
 B₉ (folate)
 B₁₂ (cobalamin)
 C (ascorbic acid)

All wash out easily from body except B₁₂ and B₉ (folate). B₁₂ stored in liver for ~ 3–4 years. B₉ stored in liver for ~ 3–4 months.

B-complex deficiencies often result in dermatitis, glossitis, and diarrhea.

Can be coenzymes (eg, ascorbic acid) or precursors to organic cofactors (eg, FAD, NAD⁺).

Vitamin A (retinol)

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 AML subtype M3.	Retinol is vitamin A , so think retin-A (used topically for wrinkles and Acne). Found in liver and leafy vegetables. Use oral isotretinoin to treat severe cystic acne. Use <i>all-trans</i> retinoic acid to treat acute promyelocytic leukemia.
DEFICIENCY	Night blindness (nyctalopia); dry, scaly skin (xerosis cutis); corneal degeneration (keratomalacia); Bitot spots on conjunctiva; immunosuppression.	
EXCESS	Acute toxicity—nausea, vomiting, vertigo, and blurred vision. Chronic toxicity—alopecia, dry skin (eg, scaliness), hepatic toxicity and enlargement, arthralgias, and pseudotumor cerebri. Teratogenic (cleft palate, cardiac abnormalities), therefore a \ominus pregnancy test and two forms of contraception are required before isotretinoin (vitamin A derivative) is prescribed.	Isotretinoin is teratogenic.

Vitamin B₁ (thiamine)

FUNCTION	In thiamine pyrophosphate (TPP), a cofactor for several dehydrogenase enzyme reactions: <ul style="list-style-type: none"> ▪ Pyruvate dehydrogenase (links glycolysis to TCA cycle) ▪ α-ketoglutarate dehydrogenase (TCA cycle) ▪ Transketolase (HMP shunt) ▪ Branched-chain ketoacid dehydrogenase 	Think ATP : α -ketoglutarate dehydrogenase, T ransketolase, and P yruvate dehydrogenase. Spell beriberi as Ber1Ber1 to remember vitamin B₁ . Wernicke-Korsakoff syndrome —confusion, ophthalmoplegia, ataxia (classic triad) + confabulation, personality change, memory loss (permanent). Damage to medial dorsal nucleus of thalamus, mammillary bodies. Dry beriberi —polyneuritis, symmetrical muscle wasting. Wet beriberi —high-output cardiac failure (dilated cardiomyopathy), edema.
DEFICIENCY	Impaired glucose breakdown \rightarrow ATP depletion worsened by glucose infusion; highly aerobic tissues (eg, brain, heart) are affected first. Wernicke-Korsakoff syndrome and beriberi. Seen in malnutrition and alcoholism (2° to malnutrition and malabsorption). Diagnosis made by \uparrow in RBC transketolase activity following vitamin B ₁ administration.	

Vitamin B₂ (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 ribo**F**lavin (B₂ ≈ 2 ATP).

DEFICIENCY

Cheilosis (inflammation of lips, scaling and fissures at the corners of the mouth), **C**orneal vascularization.

The **2 C's** of B₂.

Vitamin B₃ (niacin)

FUNCTION

Constituent of NAD⁺, NADP⁺ (used in redox reactions). Derived from tryptophan. Synthesis requires vitamins B₂ and B₆. Used to treat dyslipidemia; lowers levels of VLDL and raises levels of HDL.

NAD derived from **N**iacin (B₃ ≈ 3 ATP).

DEFICIENCY



Glossitis. Severe deficiency leads to pellagra, which can be caused by Hartnup disease, malignant carcinoid syndrome (↑ tryptophan metabolism), and isoniazid (↓ vitamin B₆). Symptoms of pellagra: **D**iarrhea, **D**ementia (also hallucinations), **D**ermatitis (C3/C4 dermatome circumferential “broad collar” rash [Casal necklace], hyperpigmentation of sun-exposed limbs **A**).

The **3 D's** of B₃.

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 high-protein diet and nicotinic acid.

EXCESS

Facial flushing (induced by prostaglandin, not histamine; can avoid by taking aspirin with niacin), hyperglycemia, hyperuricemia.

Vitamin B₅ (pantothenic acid)

FUNCTION

Essential component of coenzyme A (CoA, a cofactor for acyl transfers) and fatty acid synthase.

B₅ is “**pento**”thenic acid.

DEFICIENCY

Dermatitis, enteritis, alopecia, adrenal insufficiency.

Vitamin B₆ (pyridoxine)

FUNCTION

Converted to pyridoxal phosphate (PLP), a cofactor used in transamination (eg, ALT and AST), decarboxylation reactions, glycogen phosphorylase. Synthesis of 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 anemias due to impaired hemoglobin synthesis and iron excess.

Vitamin B₇ (biotin)

FUNCTION	<p>Cofactor for carboxylation enzymes (which add a 1-carbon group):</p> <ul style="list-style-type: none"> ▪ Pyruvate carboxylase: pyruvate (3C) → oxaloacetate (4C) ▪ Acetyl-CoA carboxylase: acetyl-CoA (2C) → malonyl-CoA (3C) ▪ Propionyl-CoA carboxylase: propionyl-CoA (3C) → methylmalonyl-CoA (4C) 	<p>“Avidin in egg whites avidly binds biotin.”</p>
DEFICIENCY	<p>Relatively rare. Dermatitis, alopecia, enteritis. Caused by antibiotic use or excessive ingestion of raw egg whites.</p>	

Vitamin B₉ (folate)

FUNCTION	<p>Converted to tetrahydrofolic acid (THF), a coenzyme for 1-carbon transfer/methylation reactions. Important for the synthesis of nitrogenous bases in DNA and RNA.</p>	<p>Found in leafy green vegetables. Absorbed in jejunum. Folate from foliage. Small reserve pool stored primarily in the liver.</p>
DEFICIENCY	<p>Macrocytic, megaloblastic anemia; hypersegmented polymorphonuclear cells (PMNs); glossitis; no neurologic symptoms (as opposed to vitamin B₁₂ deficiency). Labs: ↑ homocysteine, normal methylmalonic acid levels. Most common vitamin deficiency in the United States. Seen in alcoholism and pregnancy.</p>	<p>Deficiency can be caused by several drugs (eg, phenytoin, sulfonamides, methotrexate). Supplemental maternal folic acid in early pregnancy ↓ risk of neural tube defects.</p>

Vitamin B₁₂ (cobalamin)

FUNCTION

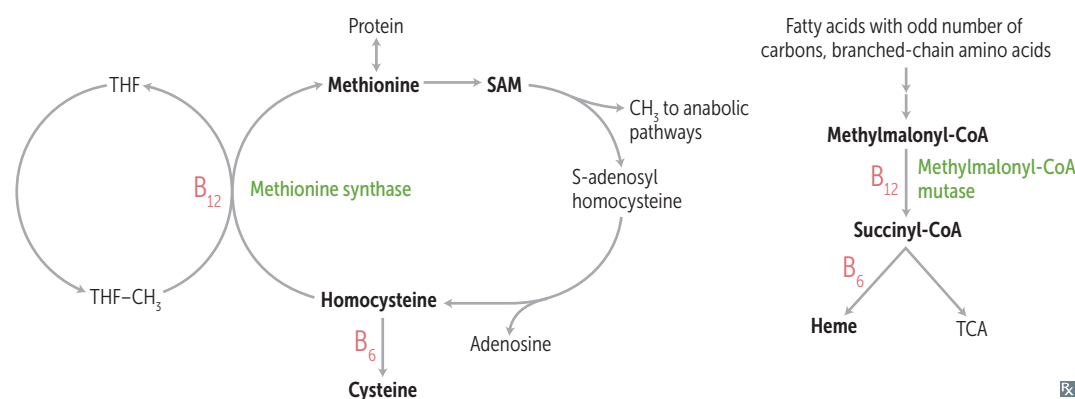
Cofactor for methionine synthase (transfers CH₃ groups as methylcobalamin) and methylmalonyl-CoA mutase.

Found in animal products.

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. Prolonged deficiency → irreversible nerve damage.

Synthesized only by microorganisms. Very large reserve pool (several years) stored primarily in the liver. Deficiency caused by malabsorption (eg, sprue, enteritis, *Diphyllobothrium latum*), lack of intrinsic factor (pernicious anemia, gastric bypass surgery), absence of terminal ileum (surgical resection, eg, for Crohn disease), or insufficient intake (eg, veganism). Anti-intrinsic factor antibodies diagnostic for pernicious anemia.

**Vitamin C (ascorbic acid)**

FUNCTION

Antioxidant; also facilitates iron absorption by reducing it to Fe²⁺ 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 Fe³⁺ to Fe²⁺.

DEFICIENCY

Scurvy—swollen gums, bruising, petechiae, hemarthrosis, anemia, poor wound healing, perifollicular and subperiosteal hemorrhages, “corkscrew” hair.

Vitamin **C** deficiency causes **sCurvy** due to a **C**ollagen synthesis defect.

Weakened immune response.

EXCESS

Nausea, vomiting, diarrhea, fatigue, calcium oxalate nephrolithiasis. Can ↑ risk of iron toxicity in predisposed individuals (eg, those with transfusions, hereditary hemochromatosis).

Vitamin D

D₂ = ergocalciferol—ingested from plants.
 D₃ = cholecalciferol—consumed in milk, formed in sun-exposed skin (stratum basale).
 25-OH D₃ = storage form.
 1,25-(OH)₂ D₃ (calcitriol) = active form.

FUNCTION

↑ intestinal absorption of calcium and phosphate, ↑ bone mineralization at low levels, ↑ bone resorption at higher levels.

DEFICIENCY



Rickets **A** in children (bone pain and deformity), osteomalacia in adults (bone pain and muscle weakness), hypocalcemic tetany. Breastfed infants should receive oral vitamin D. Deficiency is exacerbated by low sun exposure, pigmented skin, prematurity.

EXCESS

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

Vitamin E (tocopherol/tocotrienol)

FUNCTION

Antioxidant (protects RBCs and membranes from free radical damage).

Can enhance anticoagulant effects of warfarin.

DEFICIENCY

Hemolytic anemia, acanthocytosis, muscle weakness, posterior column and spinocerebellar tract demyelination.

Neurologic presentation may appear similar to vitamin B₁₂ deficiency, but without megaloblastic anemia, hypersegmented neutrophils, or ↑ serum methylmalonic acid levels.

Vitamin K (phytomenadione, phylloquinone, phytonadione)

FUNCTION

Cofactor for the γ-carboxylation of glutamic acid residues on various proteins required for blood clotting. Synthesized by intestinal flora.

K is for **K**oagulation. Necessary for the maturation of clotting factors II, VII, IX, X, and proteins C and S. Warfarin—vitamin K antagonist.

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, hypogonadism, ↓ adult hair (axillary, facial, pubic), dysgeusia, anosmia, acrodermatitis enteropathica **A**. May predispose to alcoholic cirrhosis.

**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 **A**.

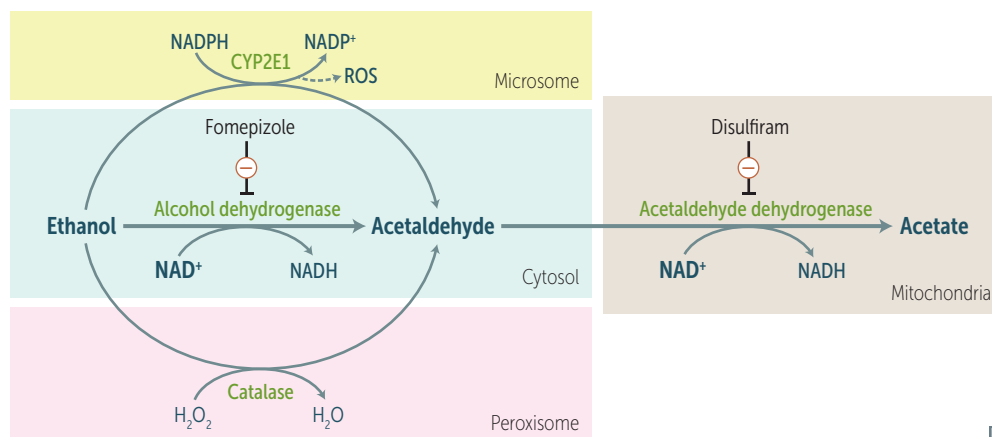
Kwashiorkor results from a protein-deficient **MEAL**:
Malnutrition
Edema
Anemia
Liver (fatty)

Marasmus

Total calorie malnutrition resulting in emaciation (tissue and muscle wasting, loss of subcutaneous fat); +/- edema.

Marasmus results in **M**uscle wasting.

Ethanol metabolism



Fomepizole—inhibits alcohol dehydrogenase and is an antidote for methanol or ethylene glycol poisoning.

Disulfiram—inhibits acetaldehyde dehydrogenase (acetaldehyde accumulates, contributing to hangover symptoms).

NAD⁺ is the limiting reagent.

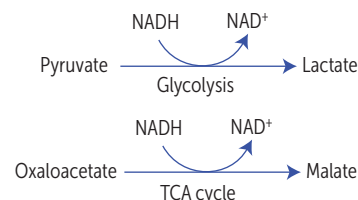
Alcohol dehydrogenase operates via zero-order kinetics.

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

- Pyruvate → lactate (lactic acidosis).
- Oxaloacetate → malate (prevents gluconeogenesis → fasting hypoglycemia)
- Dihydroxyacetone phosphate → glycerol-3-phosphate (combines with fatty acids to make triglycerides → hepatosteatosis)

End result is clinical picture seen in chronic alcoholism.

Additionally, ↑ NADH/NAD⁺ ratio disfavors TCA production of NADH → ↑ utilization of acetyl-CoA for ketogenesis (→ ketoacidosis) and 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 steroids (SER), proteins (ribosomes, RER), fatty acids, cholesterol, and nucleotides.

Both Heme synthesis, Urea cycle, Gluconeogenesis. HUGs take two (ie, both).

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 ₂ 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).

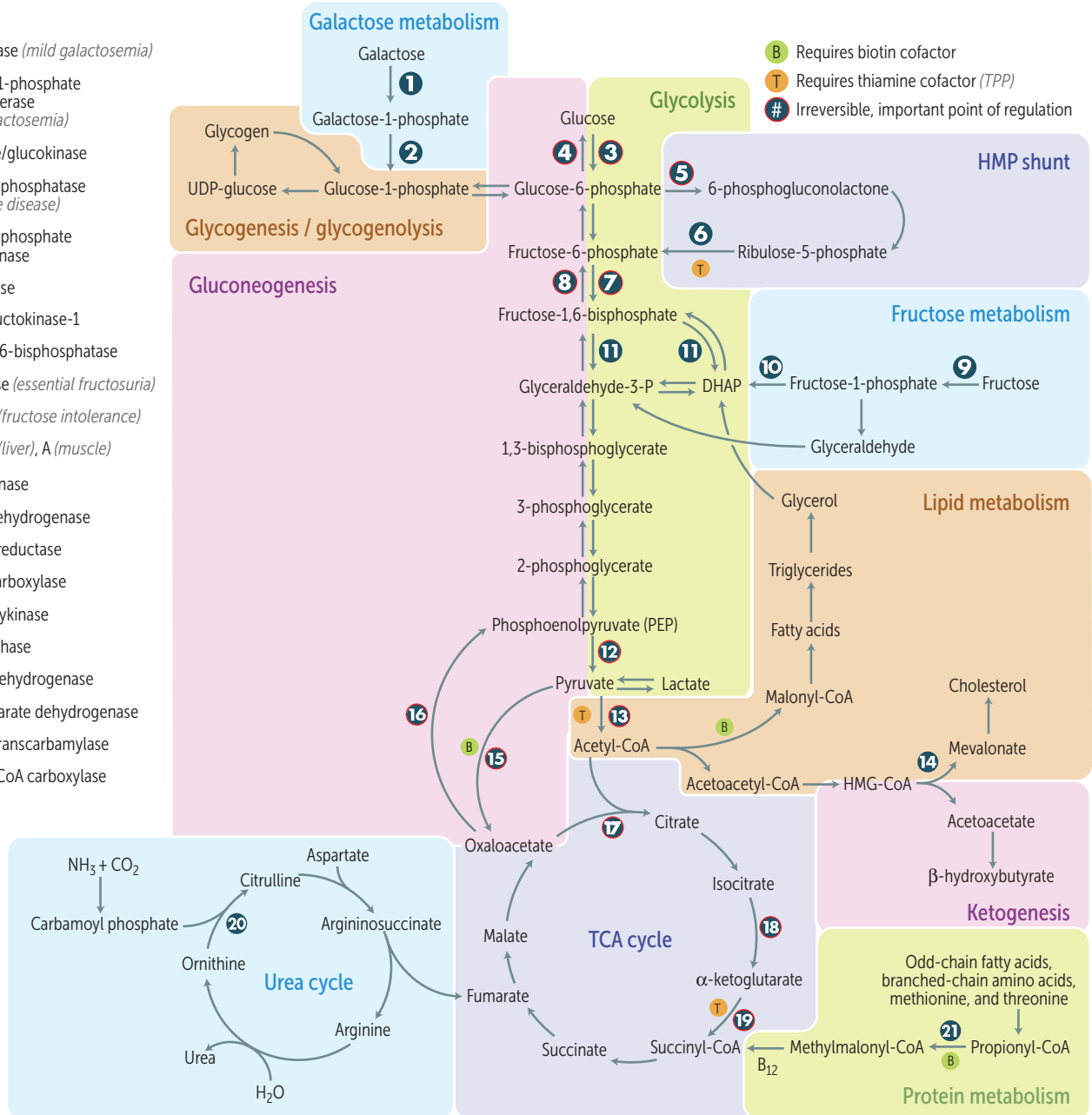
Rate-determining enzymes of metabolic processes

PROCESS	ENZYME	REGULATORS
Glycolysis	Phosphofructokinase-1 (PFK-1)	AMP ⊕, fructose-2,6-bisphosphate ⊕ ATP ⊖, citrate ⊖
Gluconeogenesis	Fructose-1,6-bisphosphatase	AMP ⊖, fructose-2,6-bisphosphate ⊖
TCA cycle	Isocitrate dehydrogenase	ADP ⊕ ATP ⊖, NADH ⊖
Glycogenesis	Glycogen synthase	Glucose-6-phosphate ⊕, insulin ⊕, cortisol ⊕ Epinephrine ⊖, glucagon ⊖
Glycogenolysis	Glycogen phosphorylase	Epinephrine ⊕, glucagon ⊕, AMP ⊕ Glucose-6-phosphate ⊖, insulin ⊖, ATP ⊖
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 ⊖, inosine monophosphate (IMP) ⊖, GMP ⊖
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 ⊕ Glucagon ⊖, cholesterol ⊖

Summary of pathways

- 1 Galactokinase (*mild galactosemia*)
- 2 Galactose-1-phosphate uridylyltransferase (*severe galactosemia*)
- 3 Hexokinase/glucokinase
- 4 Glucose-6-phosphatase (*von Gierke disease*)
- 5 Glucose-6-phosphate dehydrogenase
- 6 Transketolase
- 7 Phosphofruktokinase-1
- 8 Fructose-1,6-bisphosphatase
- 9 Fructokinase (*essential fructosuria*)
- 10 Aldolase B (*fructose intolerance*)
- 11 Aldolase B (*liver*), A (*muscle*)
- 12 Pyruvate kinase
- 13 Pyruvate dehydrogenase
- 14 HMG-CoA reductase
- 15 Pyruvate carboxylase
- 16 PEP carboxykinase
- 17 Citrate synthase
- 18 Isocitrate dehydrogenase
- 19 α -ketoglutarate dehydrogenase
- 20 Ornithine transcarbamylase
- 21 Propionyl-CoA carboxylase

- B Requires biotin cofactor
- T Requires thiamine cofactor (TPP)
- # Irreversible, important point of regulation



ATP production

Aerobic metabolism of glucose 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.

Activated carriers

CARRIER MOLECULE	CARRIED IN ACTIVATED FORM
ATP	Phosphoryl groups
NADH, NADPH, FADH ₂	Electrons
CoA, lipoamide	Acyl groups
Biotin	CO ₂
Tetrahydrofolates	1-carbon units
S-adenosylmethionine (SAM)	CH ₃ groups
TPP	Aldehydes

Universal electron acceptors

Nicotinamides (NAD⁺ from vitamin B₃, NADP⁺) and flavin nucleotides (FAD⁺ from vitamin B₂).

NAD⁺ is generally used in **catabolic** processes to carry reducing equivalents away as NADH.

NADPH is used in **anabolic** processes (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 serves as the 1st committed step of glycolysis (also serves as the 1st step of glycogen synthesis in the liver). Reaction is catalyzed by either hexokinase or glucokinase, depending on the tissue. At low glucose concentrations, hexokinase sequesters glucose in the tissue. At high glucose concentrations, excess glucose is stored in the liver.

	Hexokinase	Glucokinase
Location	Most tissues, except liver and pancreatic β cells	Liver, β cells of pancreas
K _m	Lower (\uparrow affinity)	Higher (\downarrow affinity)
V _{max}	Lower (\downarrow capacity)	Higher (\uparrow capacity)
Induced by insulin	No	Yes
Feedback-inhibited by glucose-6-phosphate	Yes	No
Gene mutation associated with maturity-onset diabetes of the young (MODY)	No	Yes

Glycolysis regulation, key enzymes

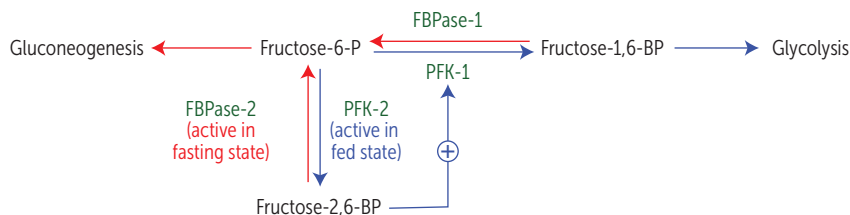
Net glycolysis (cytoplasm):



Equation not balanced chemically, and exact balanced equation depends on ionization state of reactants and products.

REQUIRE ATP	$\text{Glucose} \xrightarrow{\text{Hexokinase/glucokinase}^a} \text{Glucose-6-P}$	Glucose-6-P \ominus hexokinase. Fructose-6-P \ominus glucokinase.
	$\text{Fructose-6-P} \xrightarrow[\text{(rate-limiting step)}]{\text{Phosphofructokinase-1}} \text{Fructose-1,6-BP}$	AMP \oplus , fructose-2,6-bisphosphate \oplus . ATP \ominus , citrate \ominus .
^a Glucokinase in liver and β cells of pancreas; hexokinase in all other tissues.		
PRODUCE ATP	$1,3\text{-BPG} \xrightleftharpoons{\text{Phosphoglycerate kinase}} 3\text{-PG}$	
	$\text{Phosphoenolpyruvate} \xrightarrow{\text{Pyruvate kinase}} \text{Pyruvate}$	Fructose-1,6-bisphosphate \oplus . ATP \ominus , alanine \ominus .

Regulation by fructose-2,6-bisphosphate



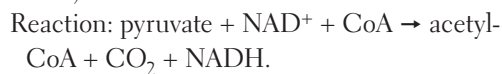
FBPase-2 (fructose bisphosphatase-2) and **PFK-2 (phosphofructokinase-2)** are the same bifunctional enzyme whose function is reversed by phosphorylation by protein kinase A.

Fasting state: \uparrow glucagon \rightarrow \uparrow cAMP \rightarrow \uparrow protein kinase A \rightarrow \uparrow FBPase-2, \downarrow PFK-2, less glycolysis, more gluconeogenesis.

Fed state: \uparrow insulin \rightarrow \downarrow cAMP \rightarrow \downarrow protein kinase A \rightarrow \downarrow FBPase-2, \uparrow PFK-2, more glycolysis, less gluconeogenesis.

Pyruvate dehydrogenase complex

Mitochondrial enzyme complex linking glycolysis and TCA cycle. Differentially regulated in fed/fasting states (active in fed state).



The complex contains 3 enzymes that require 5 cofactors:

1. **T**hiamine pyrophosphate (B_1)
2. **L**ipoic acid
3. **C**oA (B_5 , pantothenic acid)
4. **F**AD (B_2 , riboflavin)
5. **N**AD (B_3 , niacin)

Activated by:

- \uparrow NAD⁺/NADH ratio
- \uparrow ADP
- \uparrow Ca²⁺

The complex is similar to the α -ketoglutarate dehydrogenase complex (same cofactors, similar substrate and action), which converts α -ketoglutarate \rightarrow succinyl-CoA (TCA cycle).

TLC For Nancy.

Arsenic inhibits lipoic acid. Findings: vomiting, rice-water stools, garlic breath.

Pyruvate dehydrogenase complex deficiency

Causes a buildup of pyruvate that gets shunted to lactate (via LDH) and alanine (via ALT). X-linked.

FINDINGS

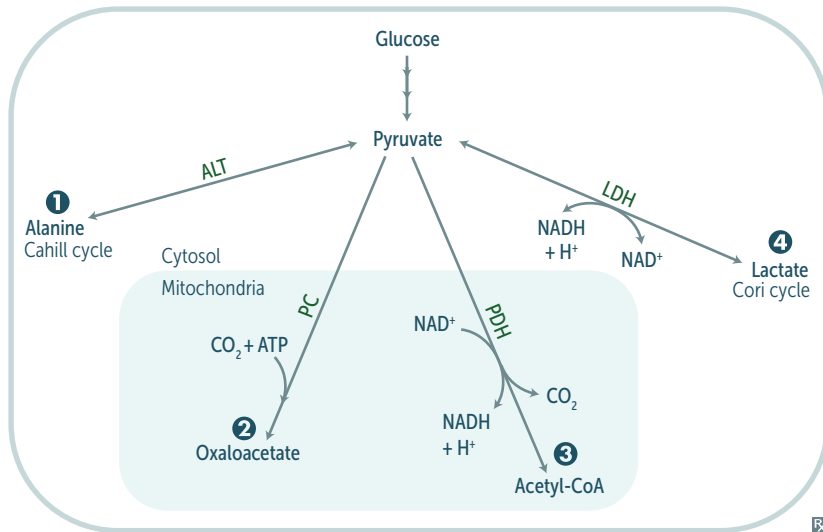
Neurologic defects, lactic acidosis, ↑ serum alanine starting in infancy.

TREATMENT

↑ intake of ketogenic nutrients (eg, high fat content or ↑ lysine and leucine).

Lysine and Leucine—the onLy pureLy ketogenic amino acids.

Pyruvate metabolism

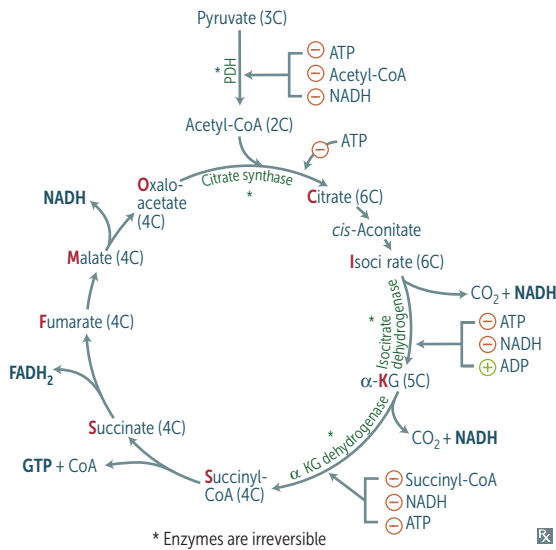


Functions of different pyruvate metabolic pathways (and their associated cofactors):

- 1 Alanine aminotransferase (B₆): 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 (B₁, B₂, B₃, B₅, lipoic acid): transition from glycolysis to the TCA cycle
- 4 Lactic acid dehydrogenase (B₃): end of anaerobic glycolysis (major pathway in RBCs, WBCs, kidney medulla, lens, testes, and cornea)

TCA cycle (Krebs cycle)

Pyruvate → acetyl-CoA produces 1 NADH, 1 CO₂.



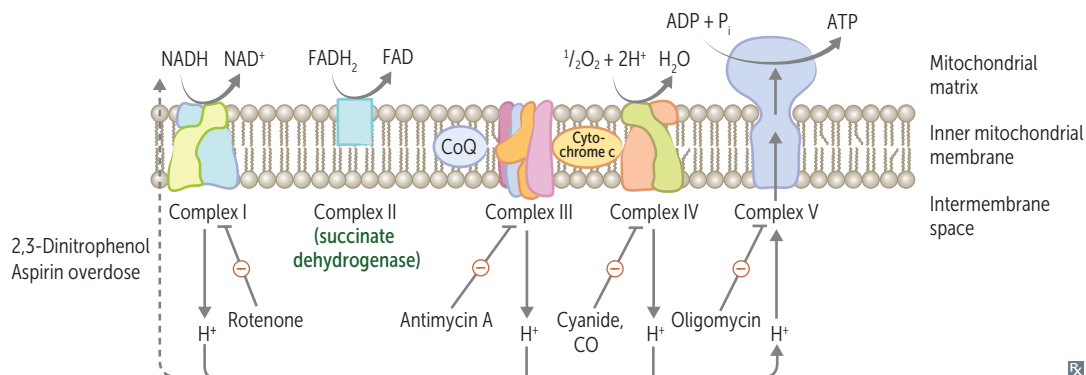
The TCA cycle produces 3 NADH, 1 FADH₂, 2 CO₂, 1 GTP per acetyl-CoA = 10 ATP/ acetyl-CoA (2× everything per glucose). TCA cycle reactions occur in the mitochondria.

α-ketoglutarate dehydrogenase complex requires the same cofactors as the pyruvate dehydrogenase complex (B₁, B₂, B₃, B₅, lipoic acid).

Citrate Is Krebs' Starting Substrate For Making Oxaloacetate.

Electron transport chain and oxidative phosphorylation

NADH electrons from glycolysis enter mitochondria via the malate-aspartate or glycerol-3-phosphate shuttle. FADH₂ 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 FADH₂ → 1.5 ATP.

OXIDATIVE PHOSPHORYLATION POISONS

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.
 CO/CN: complex 4 inhibitors (4 letters).

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 ↑ O₂ consumption. ATP synthesis stops, but electron transport continues. Produces heat.

2,4-Dinitrophenol (used illicitly for weight loss), aspirin (fevers often occur after aspirin overdose), thermogenin in brown fat.

Gluconeogenesis, irreversible enzymes

Pyruvate carboxylase

In mitochondria. Pyruvate → oxaloacetate.

Pathway Produces Fresh Glucose.

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 ⊕, fructose 2,6-bisphosphate ⊖.

Glucose-6-phosphatase

In ER. Glucose-6-phosphate → glucose.

Occurs primarily in liver; serves to maintain euglycemia during fasting. Enzymes also found in kidney, intestinal epithelium. Deficiency of the key gluconeogenic enzymes causes hypoglycemia. (Muscle cannot participate in gluconeogenesis because it lacks glucose-6-phosphatase). Odd-chain fatty acids yield 1 propionyl-CoA during metabolism, which can enter the TCA cycle (as succinyl-CoA), undergo gluconeogenesis, and serve as a glucose source. Even-chain fatty acids cannot produce new glucose, since they yield only acetyl-CoA equivalents.

HMP shunt (pentose phosphate pathway)

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 and glycolytic intermediates. 2 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.

REACTIONS	KEY ENZYMES	PRODUCTS
Oxidative (irreversible)	<p>Glucose-6-P_i $\xrightarrow[\text{NADP}^+ \rightarrow \text{NADPH}]{\text{Glucose-6-P dehydrogenase}}$ \rightarrow \rightarrow</p> <p>Rate-limiting step</p>	<p>CO₂ 2 NADPH Ribulose-5-P_i</p>
Nonoxidative (reversible)	<p>Ribulose-5-P_i $\xrightleftharpoons[\text{Requires B}_1]{\text{Phosphopentose isomerase, transketolases}}$ \rightarrow</p>	<p>Ribose-5-P_i Glyceraldehyde-3-phosphate Fructose-6-P</p>

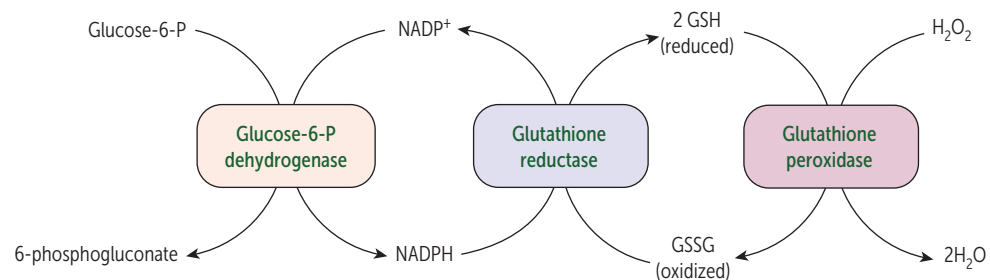
Glucose-6-phosphate dehydrogenase deficiency

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, primaquine, 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 **H**emoglobin precipitates within RBCs due to oxidative stress.

Bite cells—result from the phagocytic removal of **H**einz bodies by splenic macrophages. Think, “**B**ite into some **H**einz ketchup.”



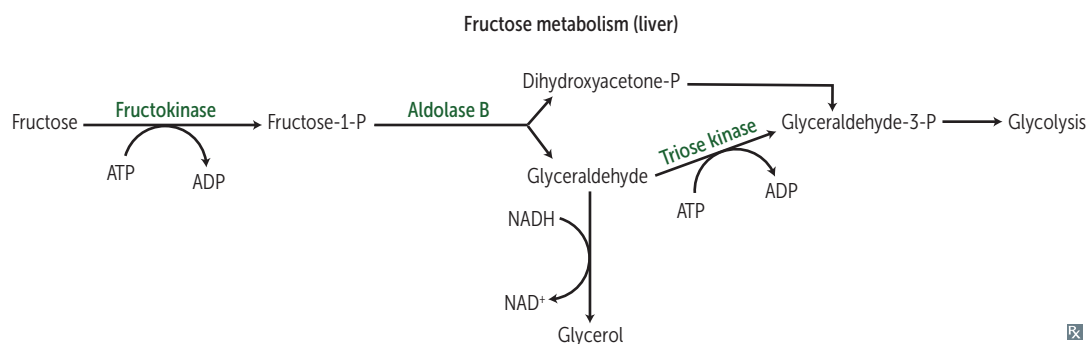
Disorders of fructose metabolism

Essential fructosuria

Involves a defect in **fructokinase**. Autosomal recessive. A benign, asymptomatic condition, since fructose is not trapped in cells.
Symptoms: fructose appears in blood and urine.
Disorders of fructose metabolism cause milder symptoms than analogous disorders of galactose metabolism.

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: ↓ intake of both fructose and sucrose (glucose + fructose).



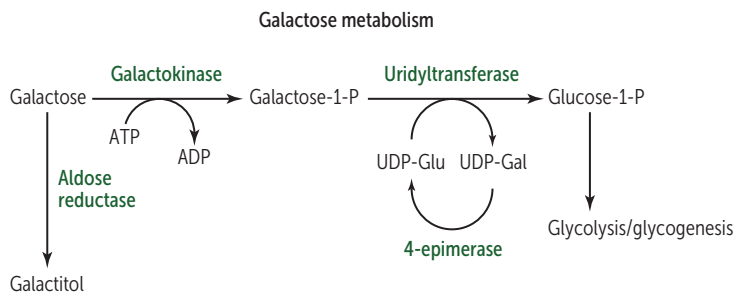
Disorders of galactose metabolism

Galactokinase deficiency

Hereditary deficiency of **galactokinase**. Galactitol accumulates if galactose is present in diet. Relatively mild condition. Autosomal recessive.
Symptoms develop when infant begins feeding (lactose present in breast milk and routine formula).
Symptoms: galactose appears in blood (galactosemia) and urine (galactosuria); infantile cataracts. May present as failure to track objects or to develop a social smile.

Classic galactosemia

Absence of **galactose-1-phosphate uridylyltransferase**. Autosomal recessive. Damage is caused by accumulation of toxic substances (including galactitol, which accumulates in the lens of the eye).
Symptoms: failure to thrive, jaundice, hepatomegaly, infantile cataracts, intellectual disability. Can lead 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_4^{3-} depletion.

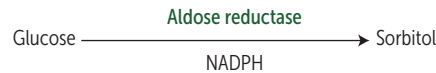
Sorbitol

An alternative method of trapping glucose in the cell is to convert it to its alcohol counterpart, called 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 for 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.



Schwann cells, retina, and kidneys have only aldose reductase. Lens has primarily aldose reductase.

**Lactase deficiency**

Insufficient lactase enzyme → dietary lactose intolerance. Lactase functions on the brush border to digest lactose (in human and cow milk) 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 brush border due to gastroenteritis (eg, rotavirus), autoimmune disease, etc.

Congenital lactase deficiency: rare, due to defective gene.

Stool demonstrates ↓ pH and breath shows ↑ 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

Glucogenic: methionine (Met), valine (Val), histidine (His).

Glucogenic/ketogenic: isoleucine (Ile), phenylalanine (Phe), threonine (Thr), tryptophan (Trp).

Ketogenic: leucine (Leu), lysine (Lys).

All essential amino acids need to be supplied in the diet.

Acidic

Aspartic acid (Asp) and glutamic acid (Glu).
Negatively charged at body pH.

Basic

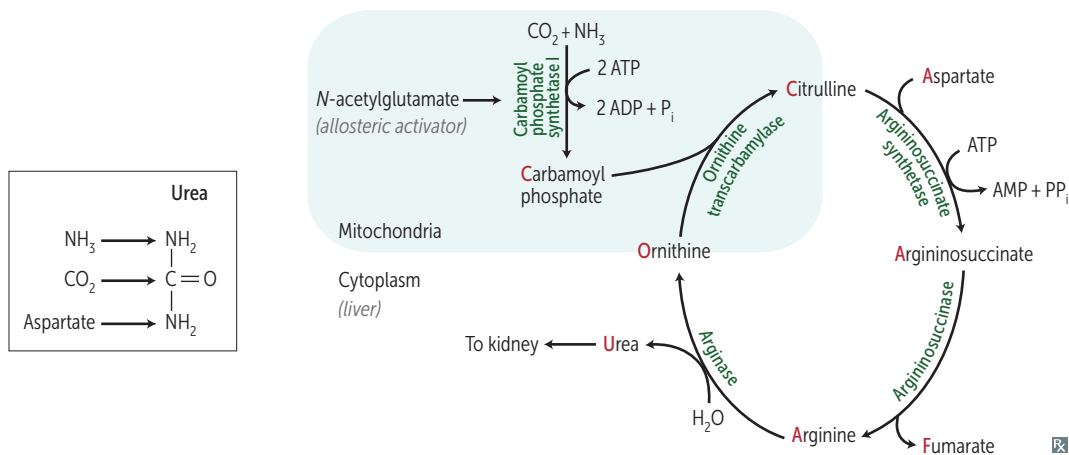
Arginine (Arg), lysine (Lys), histidine (His).
Arg is most basic.
His has no charge at body pH.

Arg and His are required during periods of growth. Arg and Lys are ↑ in histones, which bind negatively charged DNA.

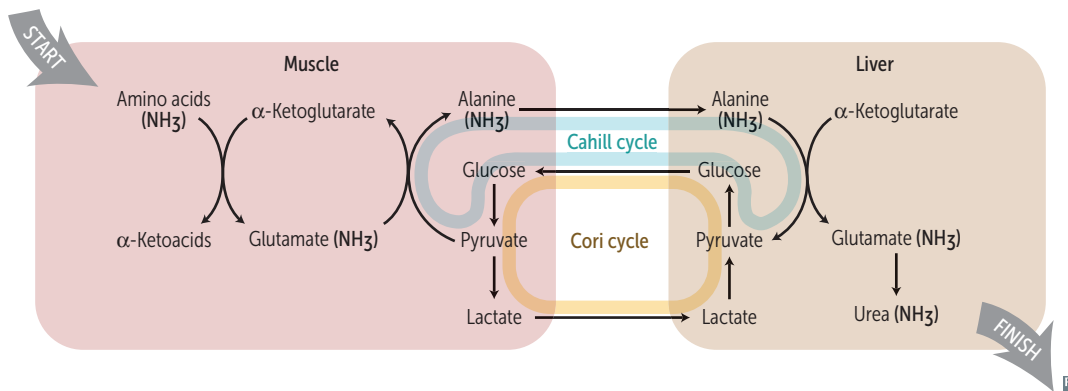
Urea cycle

Amino acid catabolism results in the formation of common metabolites (eg, pyruvate, acetyl-CoA), which serve as metabolic fuels. Excess nitrogen (NH_3) generated by this process is converted to urea and excreted by the kidneys.

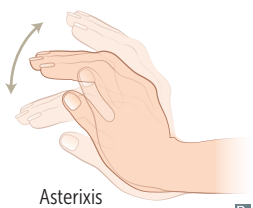
Ordinarily, **Careless Crappers Are Also Frivolous About Urination.**



Transport of ammonia by alanine and glutamate



Hyperammonemia



Can be acquired (eg, liver disease) or hereditary (eg, urea cycle enzyme deficiencies). Results in excess NH_3 , which depletes α -ketoglutarate, leading to inhibition of TCA cycle.

Treatment: limit protein in diet. May be given to ↓ ammonia levels:

- Lactulose to acidify the GI tract and trap NH_4^+ for excretion.
- Rifaximin to ↓ colonic ammoniogenic bacteria.
- Benzoate, phenylacetate, or phenylbutyrate to bind to NH_4^+ and lead to excretion.

Ammonia accumulation—tremor (asterixis), slurring of speech, somnolence, vomiting, cerebral edema, blurring of vision.

***N*-acetylglutamate synthase deficiency**

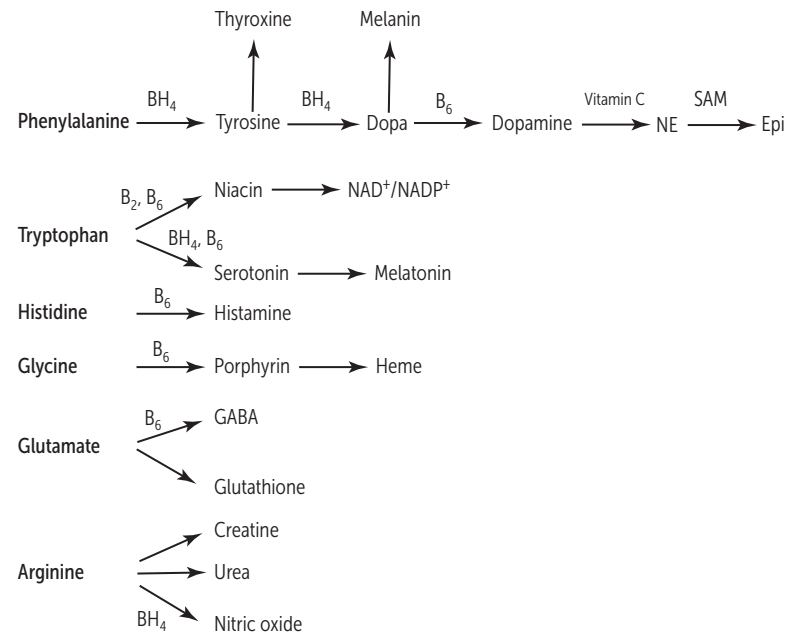
Required cofactor for carbamoyl phosphate synthetase I. Absence of *N*-acetylglutamate → hyperammonemia.

Presents in neonates as poorly regulated respiration and body temperature, poor feeding, developmental delay, intellectual disability (identical to presentation of carbamoyl phosphate synthetase I deficiency).

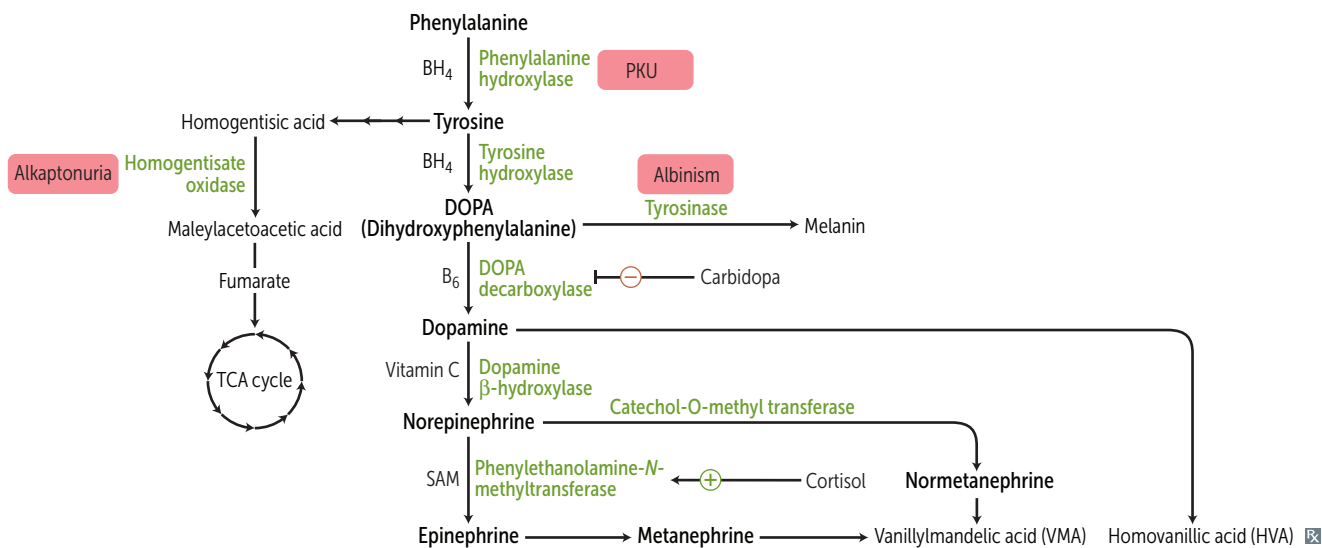
Ornithine transcarbamylase deficiency

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



Phenylketonuria

Due to ↓ phenylalanine hydroxylase or ↓ tetrahydrobiopterin cofactor (malignant PKU). Tyrosine becomes essential. ↑ phenylalanine → excess phenylketones in urine.
 Findings: intellectual disability, growth retardation, seizures, fair skin, 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). Phenylketones—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 (B₁). Causes ↑ α-ketoacids in the blood, especially those of leucine. Causes severe CNS defects, intellectual disability, and death. Treatment: restriction of isoleucine, leucine, valine in diet, and thiamine supplementation.

Autosomal recessive. Presentation: vomiting, poor feeding, urine smells like maple syrup/burnt sugar. **I** Love **V**ermont **m**aple **s**yrup from maple trees (with **B**₁**r**anches).

Alkaptonuria

Congenital deficiency of homogentisate oxidase in the degradative pathway of tyrosine to fumarate → pigment-forming homogentisic acid accumulates in tissue **A**. Autosomal recessive. Usually benign.

Findings: bluish-black connective tissue and sclerae (ochronosis); urine turns black on prolonged exposure to air. May have debilitating arthralgias (homogentisic acid toxic to cartilage).

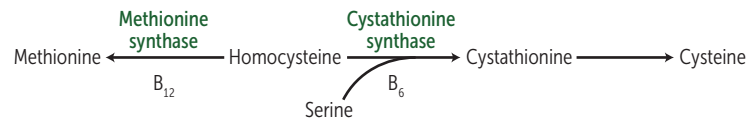
Homocystinuria

Types (all autosomal recessive):

- Cystathionine synthase deficiency (treatment: ↓ methionine, ↑ cysteine, ↑ B₁₂ and folate in diet)
- ↓ affinity of cystathionine synthase for pyridoxal phosphate (treatment: ↑↑ B₆ and ↑ cysteine in diet)
- Methionine synthase (homocysteine methyltransferase) deficiency (treatment: ↑ methionine in diet)

All forms result in excess homocysteine.

Findings: ↑↑ homocysteine in urine, intellectual disability, osteoporosis, marfanoid habitus, kyphosis, lens subluxation (downward and inward), thrombosis, and atherosclerosis (stroke and MI).

**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**.

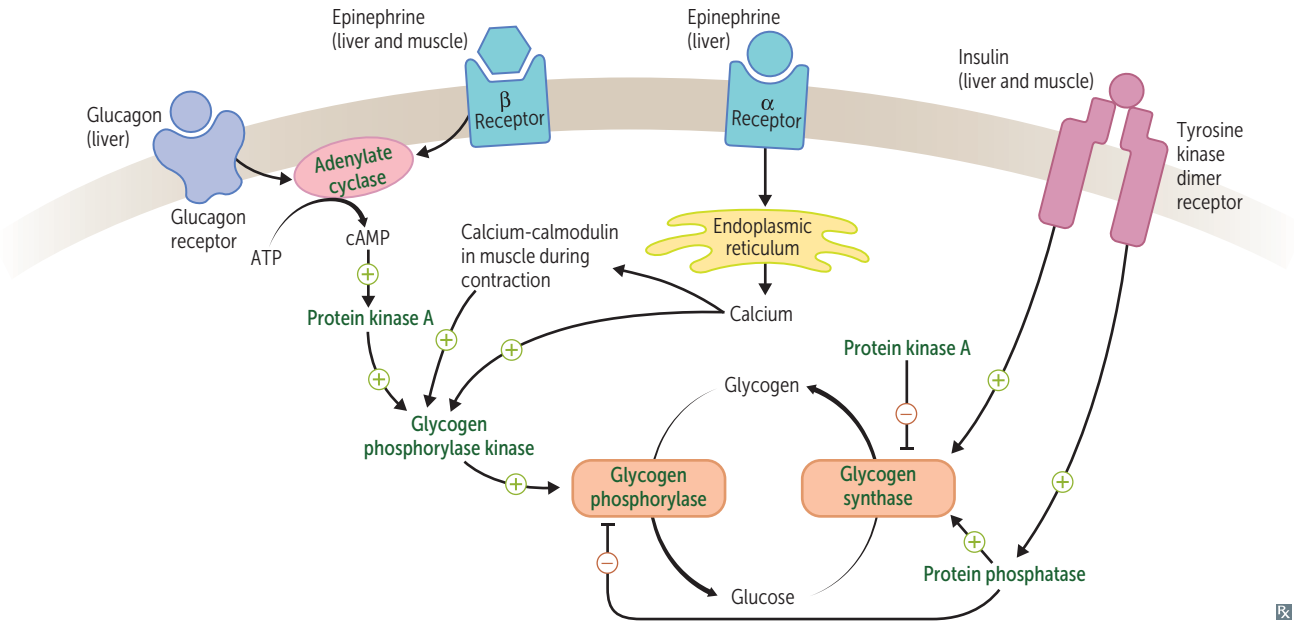
Treatment: urinary alkalinization (eg, potassium citrate, acetazolamide) and chelating agents (eg, penicillamine) ↑ solubility of cystine stones; good hydration.

Autosomal recessive. Common (1:7000).

Urinary cyanide-nitroprusside test is diagnostic.

Cystine is made of 2 cysteines connected by a disulfide bond.

Glycogen regulation by insulin and glucagon/epinephrine



Ⓡ

Glycogen

Branches have α -(1,6) bonds; linkages have α -(1,4) bonds.

Skeletal muscle

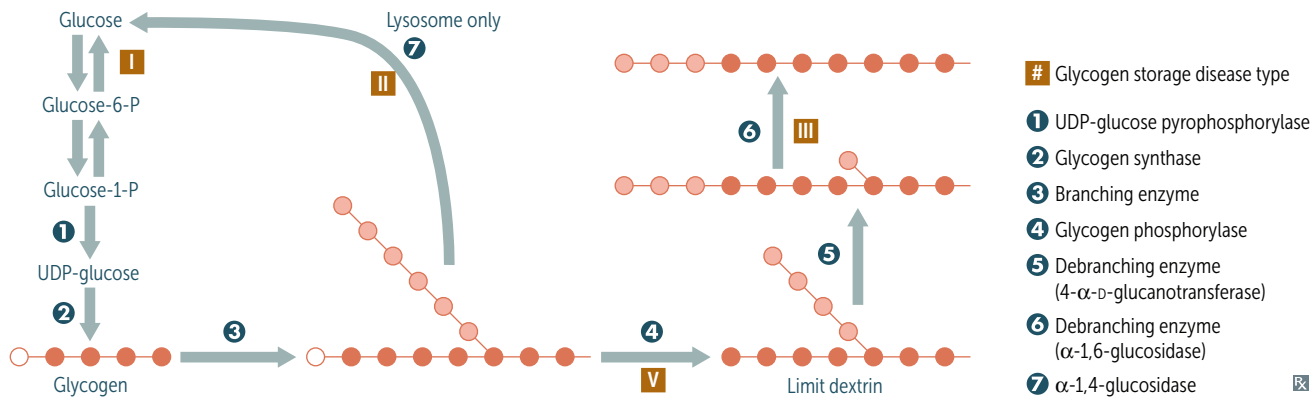
Glycogen undergoes glycogenolysis \rightarrow glucose-1-phosphate \rightarrow glucose-6-phosphate, which is rapidly metabolized during exercise.

Hepatocytes

Glycogen is stored and undergoes glycogenolysis to maintain blood sugar at appropriate levels.

Glycogen phosphorylase liberates glucose-1-phosphate residues off branched glycogen until 4 glucose units remain on a branch. Then 4- α -D-glucanotransferase (debranching enzyme **5**) moves 3 molecules of glucose-1-phosphate from the branch to the linkage. Then α -1,6-glucosidase (debranching enzyme **6**) cleaves off the last residue, liberating glucose.

“Limit dextrin” refers to the one to four residues remaining on a branch after glycogen phosphorylase has already shortened it.



Note: A small amount of glycogen is degraded in lysosomes by α -1,4-glucosidase (acid maltase).

Glycogen storage diseases


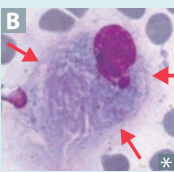


12 types, all resulting in abnormal glycogen metabolism and an accumulation of glycogen within cells. Periodic acid–Schiff stain identifies glycogen and is useful in identifying these diseases.

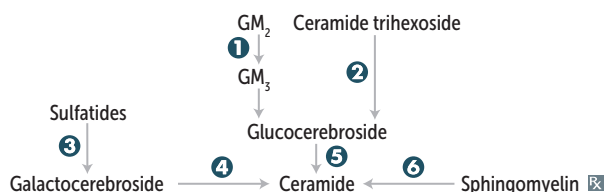
Very Poor Carbohydrate Metabolism. Types I, II, III, and V are autosomal recessive.

DISEASE	FINDINGS	DEFICIENT ENZYME	COMMENTS
Von Gierke disease (type I)	Severe fasting hypoglycemia, ↑↑ Glycogen in liver, ↑ blood lactate, ↑ triglycerides, ↑ uric acid (Gout), and hepatomegaly.	Glucose-6-phosphatase	Treatment: frequent oral glucose/cornstarch; avoidance of fructose and galactose Impaired gluconeogenesis and glycogenolysis
Pompe disease (type II)	Cardiomegaly, hypertrophic cardiomyopathy, exercise intolerance, and systemic finds leading to early death.	Lysosomal α-1,4-glucosidase with α-1,6-glucosidase activity (acid maltase)	Pompe trashes the Pump (heart, liver, and muscle)
Cori disease (type III)	Milder form of von Gierke (type I) with normal blood lactate levels. Accumulation of limit dextrin–like structures in cytosol.	Debranching enzyme (α-1,6-glucosidase)	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)	Blood glucose levels typically unaffected McArdle = Muscle

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				
Fabry disease 	Early: Triad of episodic peripheral neuropathy, angiokeratomas A , hypohidrosis. Late: progressive renal failure, cardiovascular disease.	2 α -galactosidase A	Ceramide trihexoside	XR
Gaucher disease 	Most common. Hepatosplenomegaly, pancytopenia, osteoporosis, aseptically necrotic femur, bone crises, Gaucher cells B (lipid-laden macrophages resembling crumpled tissue paper).	5 Glucocerebrosidase (β -glucosidase); treat with recombinant glucocerebrosidase	Glucocerebroside	AR
Niemann-Pick disease 	Progressive neurodegeneration, hepatosplenomegaly, foam cells (lipid-laden macrophages) C , “cherry-red” spot on macula D .	6 Sphingomyelinase	Sphingomyelin	AR
Tay-Sachs disease 	Progressive neurodegeneration, developmental delay, “cherry-red” spot on macula D , lysosomes with onion skin, no hepatosplenomegaly (vs Niemann-Pick).	1 Hexosaminidase A	GM ₂ ganglioside	AR
Krabbe disease	Peripheral neuropathy, developmental delay, optic atrophy, globoid cells.	4 Galactocerebrosidase	Galactocerebroside, AR psychosine	AR
Metachromatic leukodystrophy	Central and peripheral demyelination with ataxia, dementia.	3 Arylsulfatase A	Cerebroside sulfate	AR
Mucopolysaccharidoses				
Hurler syndrome	Developmental delay, gargoyism, airway obstruction, corneal clouding, hepatosplenomegaly.	α -L-iduronidase	Heparan sulfate, dermatan sulfate	AR
Hunter syndrome	Mild Hurler + aggressive behavior, no corneal clouding.	Iduronate sulfatase	Heparan sulfate, dermatan sulfate	XR



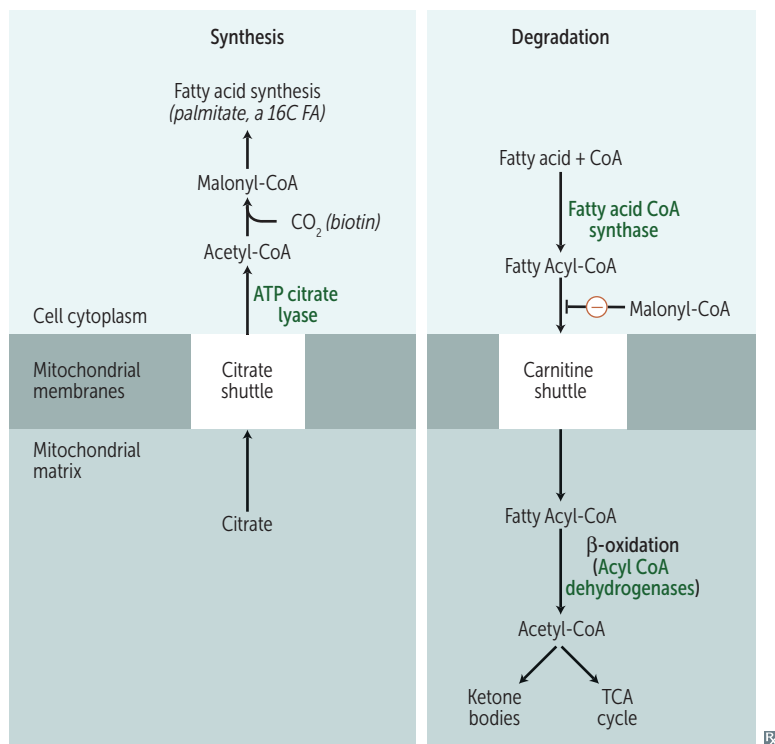
No man picks (Niemann-Pick) his nose with his **sphinger (sphingomyelinase)**.

Tay-Sa**X** lacks he**X**osaminidase.

Hunters see clearly (no corneal clouding) and aggressively aim for the **X (X-linked recessive)**.

↑ incidence of Tay-Sachs, Niemann-Pick, and some forms of Gaucher disease in Ashkenazi Jews.

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.

“**SY**trate” = **SY**nthesis.

CARnitine = **CAR**nage of fatty acids.

Systemic 1° carnitine deficiency—inherited defect in transport of LCFAs into the mitochondria → toxic accumulation. Causes weakness, hypotonia, and hypoketotic hypoglycemia.

Medium-chain acyl-CoA dehydrogenase deficiency

Autosomal recessive disorder of fatty acid oxidation. ↓ ability to break down fatty acids into acetyl-CoA → accumulation of 8- to 10-carbon fatty acyl carnitines in the blood and hypoketotic hypoglycemia. May present in infancy or early childhood with vomiting, lethargy, seizures, coma, and liver dysfunction.

Minor illness can lead to sudden death. Treat by avoiding fasting.

Ketone bodies

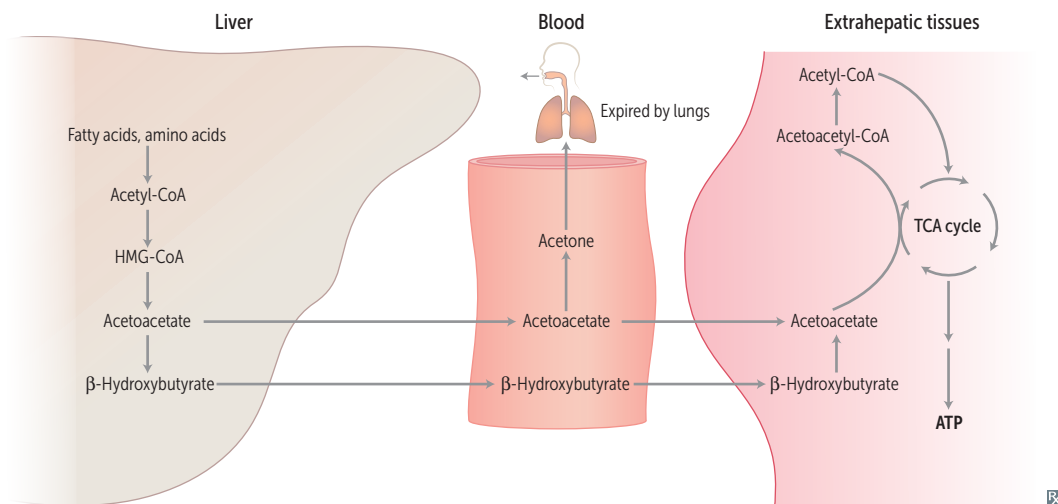
In the liver, fatty acids and amino acids are metabolized to acetoacetate and β -hydroxybutyrate (to be used in muscle and brain).

In prolonged starvation and diabetic ketoacidosis, oxaloacetate is depleted for gluconeogenesis. In alcoholism, excess NADH shunts oxaloacetate to malate. Both processes cause a buildup of acetyl-CoA, which shunts glucose and FFA toward the production of ketone bodies.

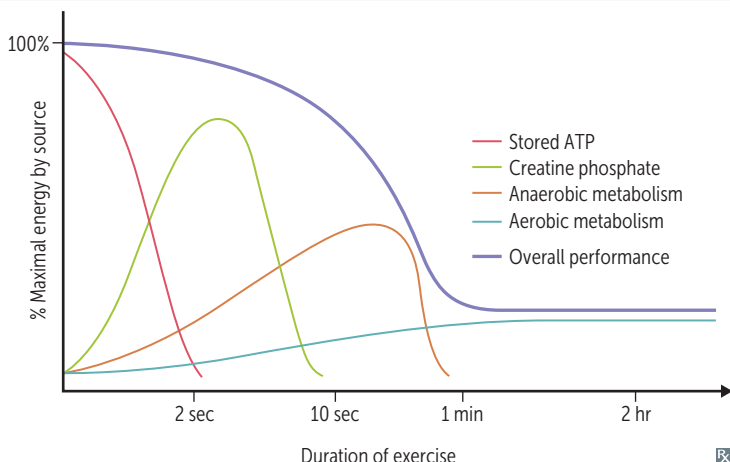
Ketone bodies: acetone, acetoacetate, β -hydroxybutyrate.

Breath smells like acetone (fruity odor).

Urine test for ketones can detect acetoacetate, but not β -hydroxybutyrate.



Metabolic fuel use



1 g protein or carbohydrate = 4 kcal.
 1 g fat = 9 kcal.
 1 g alcohol = 7 kcal.

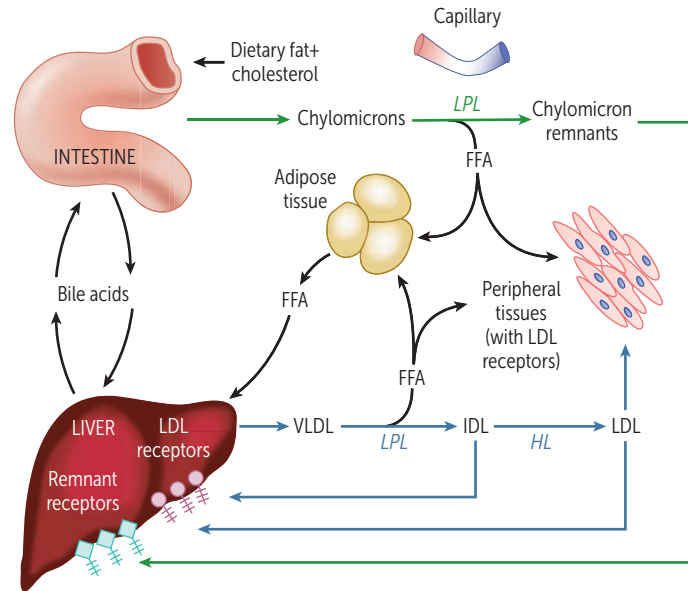
Fasting and starvation	Priorities are to supply sufficient glucose to the brain and RBCs and to preserve protein.	
Fed state (after a meal)	Glycolysis and aerobic respiration.	Insulin stimulates storage of lipids, proteins, and glycogen.
Fasting (between meals)	Hepatic glycogenolysis (major); hepatic gluconeogenesis, adipose release of FFA (minor).	Glucagon and epinephrine stimulate use of fuel reserves.
Starvation days 1–3	Blood glucose levels maintained by: <ul style="list-style-type: none"> ▪ Hepatic glycogenolysis ▪ Adipose release of FFA ▪ Muscle and liver, which shift fuel use from glucose to FFA ▪ 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) 	Glycogen reserves depleted after day 1. RBCs lack mitochondria and therefore cannot use ketones.
Starvation after day 3	Adipose stores (ketone bodies become the main source of energy for the brain). After these are depleted, vital protein degradation accelerates, leading to organ failure and death. Amount of excess stores determines survival time.	

Cholesterol synthesis

Cholesterol needed to maintain cell membrane integrity and to synthesize bile acid, steroids, and vitamin D.
 Rate-limiting step catalyzed by HMG-CoA reductase (induced by insulin), which converts HMG-CoA to mevalonate. $\frac{2}{3}$ of plasma cholesterol esterified by lecithin-cholesterol acyltransferase (LCAT).

Statins (eg, atorvastatin) competitively and reversibly inhibit HMG-CoA reductase.

Lipid transport, key enzymes

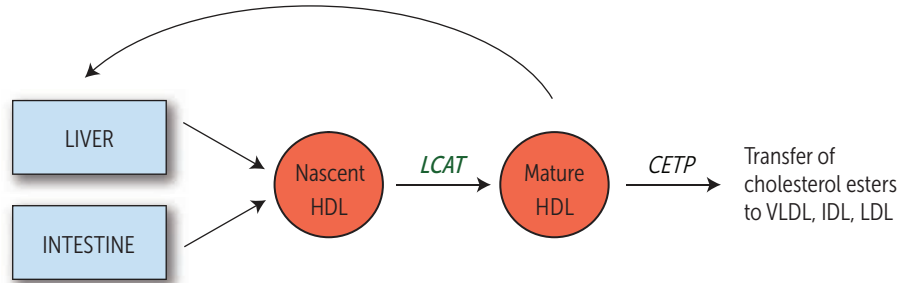


Pancreatic lipase—degradation of dietary triglycerides (TGs) in small intestine.

Lipoprotein lipase (LPL)—degradation of TGs circulating in chylomicrons and VLDLs. Found on vascular endothelial surface.

Hepatic TG lipase (HL)—degradation of TGs remaining in IDL.

Hormone-sensitive lipase—degradation of TGs stored in adipocytes.



LCAT—catalyzes esterification of cholesterol.

Cholesterol ester transfer protein (CETP)—mediates transfer of cholesterol esters to other lipoprotein particles.

Major apolipoproteins

Apolipoprotein	Function	Chylomicron					HDL
		Chylomicron	remnant	VLDL	IDL	LDL	
E	Mediates remnant uptake	✓	✓	✓	✓	✓	✓
A-I	Activates LCAT	✓					✓
C-II	Lipoprotein lipase cofactor	✓		✓			✓
B-48	Mediates chylomicron secretion	✓	✓				
B-100	Binds LDL receptor			✓	✓	✓	

Lipoprotein functions

Lipoproteins are composed of varying proportions of cholesterol, TGs, and phospholipids. LDL and HDL carry the most cholesterol.

LDL transports cholesterol from liver to tissues. **LDL is Lousy.**
 HDL transports cholesterol from periphery to liver. **HDL is Healthy.**

Chylomicron	Delivers dietary TGs to peripheral tissue. 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	Formed in the degradation of VLDL. Delivers TGs and cholesterol to liver.
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.
HDL	Mediates reverse cholesterol transport from periphery 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.

Familial dyslipidemias

TYPE	INHERITANCE	PATHOGENESIS	↑ BLOOD LEVEL	CLINICAL
I—Hyperchylomicronemia	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.
IIa—Familial hypercholesterolemia	AD	Absent or defective LDL receptors	LDL, cholesterol	Heterozygotes (1:500) have cholesterol ≈ 300mg/dL; homozygotes (very rare) have cholesterol ≈ 700+ mg/dL. Accelerated atherosclerosis (may have MI before age 20), tendon (Achilles) xanthomas, and corneal arcus.
IV—Hypertriglyceridemia	AD	Hepatic overproduction of VLDL	VLDL, TG	Hypertriglyceridemia (> 1000 mg/dL) can cause acute pancreatitis.

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

This high-yield material covers the basic concepts of microbiology. The emphasis in previous examinations has been approximately 40% bacteriology (20% basic, 20% quasi-clinical), 25% immunology, 25% virology (10% basic, 15% quasi-clinical), 5% parasitology, and 5% mycology.

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 feature of that organism. 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?”

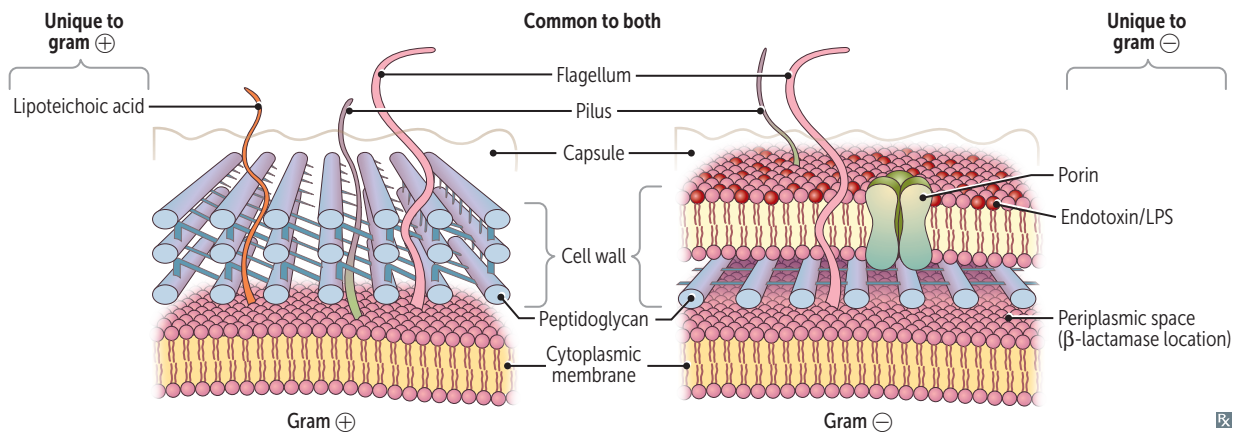
This section therefore presents organisms in two major ways: in individual microbial “profiles” and in the context of the systems they infect and the clinical presentations they produce. You should become familiar with both formats. When reviewing the systems approach, remind yourself of the features 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	108
▶ Clinical Bacteriology	118
▶ Mycology	135
▶ Parasitology	139
▶ Virology	146
▶ Systems	161
▶ Antimicrobials	170

▶ 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		
Spore	Keratin-like coat; dipicolinic acid; peptidoglycan, DNA.	Gram ⊕ only. Survival: resist dehydration, heat, chemicals.
Cell envelope		
Capsule	Organized, discrete polysaccharide layer (except poly-D glutamate on <i>B anthracis</i>).	Protects against phagocytosis.
Glycocalyx	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; O polysaccharide component antigenic. Most OMPs are antigenic. Porins: transport across outer membrane.
Periplasm	Space between cytoplasmic membrane and outer membrane in gram ⊖ bacteria. (Peptidoglycan in middle.)	Gram ⊖ only. Accumulates components exiting gram ⊖ 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 ⊕ only) extend from membrane to exterior.	Site of oxidative and transport enzymes; PBPs involved in cell wall synthesis. Lipoteichoic acids induce TNF and IL-1.

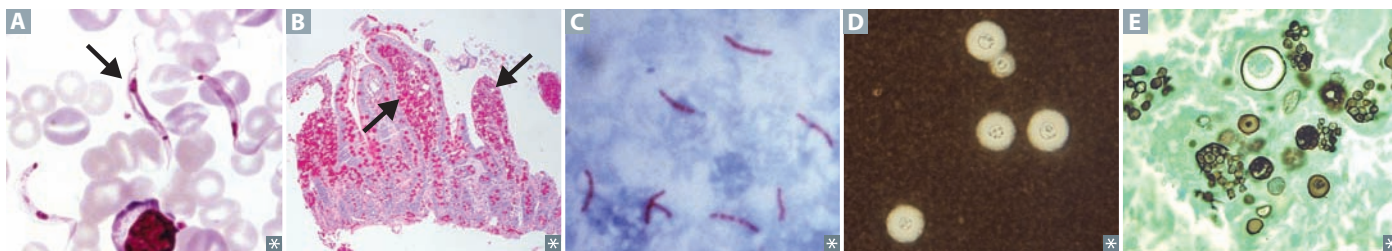
Cell walls

Bacterial taxonomy

MORPHOLOGY	Gram ⊕ examples	Gram ⊖ examples
Spherical (coccus)	<i>Staphylococcus</i> (clusters) <i>Streptococcus</i> (chains or pairs)	<i>Moraxella catarrhalis</i> <i>Neisseria</i>
Rod (bacillus)	<i>Bacillus</i> <i>Clostridium</i> <i>Corynebacterium</i> <i>Gardnerella</i> (gram variable) <i>Lactobacillus</i> <i>Listeria</i> <i>Mycobacterium</i> (acid fast) <i>Propionibacterium</i>	Enterics: <ul style="list-style-type: none"> ▪ <i>Bacteroides</i> ▪ <i>Campylobacter</i> ▪ <i>E coli</i> ▪ <i>Enterobacter</i> ▪ <i>Helicobacter</i> ▪ <i>Klebsiella</i> ▪ <i>Proteus</i> ▪ <i>Pseudomonas</i> ▪ <i>Salmonella</i> ▪ <i>Serratia</i> ▪ <i>Shigella</i> ▪ <i>Vibrio</i> ▪ <i>Yersinia</i> Respiratory: <ul style="list-style-type: none"> ▪ <i>Bordetella</i> ▪ <i>Burkholderia cepacia</i> ▪ <i>Haemophilus</i> (pleomorphic) ▪ <i>Legionella</i> (silver stain) Zoonotic: <ul style="list-style-type: none"> ▪ <i>Bartonella</i> ▪ <i>Brucella</i> ▪ <i>Francisella</i> ▪ <i>Pasteurella</i>
Branching filamentous	<i>Actinomyces</i> <i>Nocardia</i> (weakly acid fast)	
Pleomorphic		Chlamydiae (Giemsa) Rickettsiae (Giemsa)
Spiral		Spirochetes: <ul style="list-style-type: none"> ▪ <i>Borrelia</i> (Giemsa) ▪ <i>Leptospira</i> ▪ <i>Treponema</i>
No cell wall	<i>Mycoplasma</i> , <i>Ureaplasma</i> (contain sterols, which do not Gram stain)	

Stains

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. The bugs below do not Gram stain well. Treponema , <i>Leptospira</i> Mycobacteria <i>Mycoplasma</i> , <i>Ureaplasma</i> <i>Legionella</i> , <i>Rickettsia</i> , <i>Chlamydia</i> , <i>Bartonella</i> , <i>Ehrlichia</i> , <i>Anaplasma</i>	These Microbes May Lack Real Color Too thin to be visualized. Cell wall has high lipid content. No cell wall. Primarily intracellular; also, <i>Chlamydia</i> lack classic peptidoglycan because of ↓ muramic acid.
Giemsa stain	<i>Chlamydia</i> , <i>Borrelia</i> , <i>Rickettsia</i> , Trypanosomes A , <i>Plasmodium</i>	Certain Bugs Really Try my Patience.
Periodic acid–Schiff stain	Stains glycogen , mucopolysaccharides; used to diagnose Whipple disease (<i>Tropheryma whipplei</i> B)	PaSs the sugar.
Ziehl-Neelsen stain (carbol fuchsin)	Acid-fast bacteria, eg, <i>Mycobacteria</i> C (stains mycolic acid in cell wall), <i>Nocardia</i> ; protozoa, eg, <i>Cryptosporidium</i> oocysts	Alternative is auramine-rhodamine stain for screening (inexpensive, more sensitive but less specific).
India ink stain	<i>Cryptococcus neoformans</i> D ; mucicarmine can also be used to stain thick polysaccharide capsule red	
Silver stain	Fungi (eg, <i>Coccidioides</i> E , <i>Pneumocystis jirovecii</i>), <i>Legionella</i> , <i>Helicobacter pylori</i>	
Fluorescent antibody stain	Used to identify many bacteria and viruses.	Example is FTA-ABS for confirming syphilis.



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, eg, 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, eg, MacConkey agar contains a pH indicator; a lactose fermenter like <i>E coli</i> will convert lactose to acidic metabolites → color change.

Special culture requirements

BUG	MEDIA USED FOR ISOLATION	MEDIA CONTENTS/OTHER
<i>H influenzae</i>	Chocolate agar	Factors V (NAD ⁺) and X (hematin)
<i>N gonorrhoeae</i> , <i>N meningitidis</i>	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 <i>Neisseria</i>
<i>B pertussis</i>	Bordet-Gengou agar (Bordet for <i>Bordetella</i>) Regan-Lowe medium	Potato Charcoal, blood, and antibiotic
<i>C diphtheriae</i>	Tellurite agar, Löffler medium	
<i>M tuberculosis</i>	Löwenstein-Jensen agar	
<i>M pneumoniae</i>	Eaton agar	Requires cholesterol
Lactose-fermenting enterics	MacConkey agar	Fermentation produces acid, causing colonies to turn pink
<i>E coli</i>	Eosin–methylene blue (EMB) agar	Colonies with green metallic sheen
<i>Legionella</i>	Charcoal yeast extract agar buffered with cysteine and iron	
Fungi	Sabouraud agar	“ Sab’s a fun guy! ”

Aerobes

Use an O₂-dependent system to generate ATP. Examples include *Nocardia*, *Pseudomonas aeruginosa*, and *Mycobacterium tuberculosis*. Reactivation of *M tuberculosis* (eg, after immunocompromise or TNF-α inhibitor use) has a predilection for the apices of the lung.

Nagging Pests **M**ust **B**reathe.

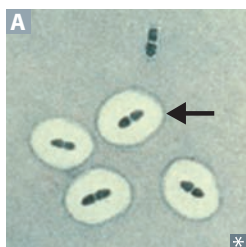
Anaerobes

Examples include *Clostridium*, *Bacteroides*, *Fusobacterium*, and *Actinomyces*. 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 (CO₂ and H₂).

Anaerobes **C**an’t **B**reathe **F**resh **A**ir.
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.

Intracellular bugs

Obligate intracellular	<i>Rickettsia</i> , <i>Chlamydia</i> , <i>Coxiella</i> . Rely on host ATP.	Stay inside (cells) when it is Really CHilly and COLD.
Facultative intracellular	<i>Salmonella</i> , <i>Neisseria</i> , <i>Brucella</i> , <i>Mycobacterium</i> , <i>Listeria</i> , <i>Francisella</i> , <i>Legionella</i> , <i>Yersinia pestis</i> .	Some Nasty Bugs May Live Facultatively.

Encapsulated bacteria

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. Asplenic have ↓ opsonizing ability and thus ↑ risk for severe infections. Give *S pneumoniae*, *H influenzae*, *N meningitidis* vaccines.

Encapsulated bacteria vaccines

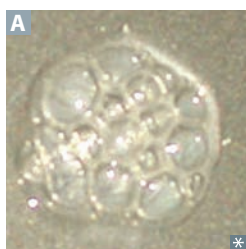
Some vaccines containing polysaccharide capsule antigens are conjugated to a carrier protein, enhancing immunogenicity by promoting T-cell activation and subsequent class switching. A polysaccharide antigen alone cannot be presented to T cells.

Pneumococcal vaccine: PCV (pneumococcal conjugate vaccine, ie, Prevnar); PPSV (pneumococcal polysaccharide vaccine with no conjugated protein, ie, Pneumovax)
H influenzae type B (conjugate vaccine)
Meningococcal vaccine (conjugate vaccine)

Urease-positive organisms

Proteus, *Cryptococcus*, *H pylori*, *Ureaplasma*, *Nocardia*, *Klebsiella*, *S epidermidis*, *S saprophyticus*. Potentiate struvite (ammonium magnesium phosphate) stones. Urease hydrolyzes urea to release ammonia and CO₂ → ↑ pH.

Pee CHUNKSS.

Catalase-positive organisms

Catalase degrades H₂O₂ into H₂O and bubbles of O₂ **A** 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 ⊕ organisms.

Examples: *Nocardia*, *Pseudomonas*, *Listeria*, *Aspergillus*, *Candida*, *E coli*, Staphylococci, *Serratia*, *B cepacia*, *H pylori*.

Cats Need PLACESS to Belch their Hairballs.

Pigment-producing bacteria	<i>Actinomyces israelii</i> —yellow “sulfur” granules, which are composed of filaments of bacteria.	Israel has yellow sand.
	<i>S aureus</i> —yellow pigment.	<i>Aureus</i> (Latin) = gold.
	<i>P aeruginosa</i> —blue-green pigment.	<i>Aerugula</i> is green.
	<i>Serratia marcescens</i> —red pigment.	<i>Serratia marcescens</i> —think red maraschino cherries.
In vivo biofilm-producing bacteria	<i>S epidermidis</i>	Catheter and prosthetic device infections
	Viridans streptococci (<i>S mutans</i> , <i>S sanguinis</i>)	Dental plaques, infective endocarditis
	<i>P aeruginosa</i>	Respiratory tree colonization in cystic fibrosis patients, contact lens–associated keratitis
	Nontypeable (unencapsulated) <i>H influenza</i>	Otitis media
Bacterial virulence factors	These promote evasion of host immune response.	
Protein A	Binds Fc region of IgG. Prevents opsonization and phagocytosis. Expressed by <i>S aureus</i> .	
IgA protease	Enzyme that cleaves IgA. Secreted by <i>S pneumoniae</i> , <i>H influenzae</i> type B, and <i>Neisseria</i> (SHiN) in order to colonize respiratory mucosa.	
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.	
Type III secretion system	Also known as “injectisome.” Needle-like protein appendage facilitating direct delivery of toxins from certain gram \ominus bacteria (eg, <i>Pseudomonas</i> , <i>Salmonella</i> , <i>Shigella</i> , <i>E coli</i>) to eukaryotic host cell.	

Bacterial genetics**Transformation**

Ability to take up naked DNA (ie, from cell lysis) from environment (also known as “competence”). A feature of many bacteria, especially *S pneumoniae*, *H influenzae* type B, and *Neisseria* (SHiN). Any DNA can be used. Adding deoxyribonuclease to environment will degrade naked DNA in medium → no transformation seen.

ConjugationF⁺ × F⁻

F⁺ plasmid contains genes required for sex pilus and conjugation. Bacteria without this plasmid are termed F⁻. Sex pilus on F⁺ bacterium contacts F⁻ bacterium. A single strand of plasmid DNA is transferred across the conjugal bridge (“mating bridge”). No transfer of chromosomal DNA.

Hfr × F⁻

F⁺ plasmid can become incorporated into bacterial chromosomal DNA, termed high-frequency recombination (Hfr) cell. Replication of incorporated plasmid DNA may include some flanking chromosomal DNA. Transfer of plasmid and chromosomal genes.

Transposition

Segment of DNA (eg, transposon) that can “jump” (excision and reintegration) from one location to another, can transfer genes from plasmid to chromosome and vice versa. When excision occurs, may include some flanking chromosomal DNA, which can be incorporated into a plasmid and transferred to another bacterium (eg, *vanA* gene from vancomycin-resistant *Enterococcus* to *S aureus*).

Transduction

Generalized

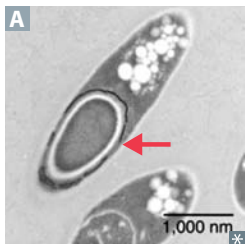
A “packaging” event. Lytic phage infects bacterium, leading to cleavage of bacterial DNA. Parts of bacterial chromosomal DNA may become packaged in phage capsid. Phage infects another bacterium, transferring these genes.

Specialized

An “excision” event. Lysogenic phage infects bacterium; viral DNA incorporates into 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
- Cholera toxin
- Diphtheria toxin
- Shiga toxin

Spore-forming bacteria

Some bacteria can form spores **A** at the end of the stationary phase when nutrients are limited.

Spores are highly resistant to heat and chemicals. Have dipicolinic acid in their core. Have no metabolic activity. Must autoclave to potentially kill spores (as is done to surgical equipment) by steaming at 121°C for 15 minutes.

Bacillus anthracis

Anthrax

Bacillus cereus

Food poisoning

Clostridium botulinum

Botulism

Clostridium difficile

Pseudomembranous colitis

Clostridium perfringens

Gas gangrene

Clostridium tetani

Tetanus

Main features of exotoxins and endotoxins

PROPERTY	Exotoxin	Endotoxin
SOURCE	Certain species of gram ⊕ and gram ⊖ 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 μg)	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)	Stable at 100°C for 1 hr
TYPICAL DISEASES	Tetanus, botulism, diphtheria	Meningococemia; sepsis by gram ⊖ rods

Bugs with exotoxins

BACTERIA	TOXIN	MECHANISM	MANIFESTATION
Inhibit protein synthesis			
<i>Corynebacterium diphtheriae</i>	Diphtheria toxin ^a	Inactivate elongation factor (EF-2)	Pharyngitis with pseudomembranes in throat and severe lymphadenopathy (bull neck)
<i>Pseudomonas aeruginosa</i>	Exotoxin A ^a		Host cell death
<i>Shigella</i> spp.	Shiga toxin (ST) ^a	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> (EHEC)	Shiga-like toxin (SLT) ^a		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> (ETEC)	Heat-labile toxin (LT) ^a	Overactivates adenylate cyclase (↑ cAMP) → ↑ Cl ⁻ secretion in gut and H ₂ O efflux	Watery diarrhea: “ labile in the A ir (A denylate cyclase), stable on the G round (G uanylate cyclase)”
	Heat-stable toxin (ST)	Overactivates guanylate cyclase (↑ cGMP) → ↓ resorption of NaCl and H ₂ O in gut	
<i>Bacillus anthracis</i>	Edema toxin ^a	Mimics the adenylate cyclase enzyme (↑ cAMP)	Likely responsible for characteristic edematous borders of black eschar in cutaneous anthrax
<i>Vibrio cholerae</i>	Cholera toxin ^a	Overactivates adenylate cyclase (↑ cAMP) by permanently activating G _s → ↑ Cl ⁻ secretion in gut and H ₂ O efflux	Voluminous “rice-water” diarrhea
Inhibit phagocytic ability			
<i>Bordetella pertussis</i>	Pertussis toxin ^a	Overactivates adenylate cyclase (↑ cAMP) by disabling G _i , impairing phagocytosis to permit survival of microbe	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 neurotransmitter			
<i>Clostridium tetani</i>	Tetanospasmin ^a	Both are proteases that cleave SNARE (soluble NSF attachment protein receptor), a set of proteins required for neurotransmitter release via vesicular fusion	Spastic paralysis, risus sardonicus, and “lockjaw”; toxin prevents release of inhibitory (GABA and glycine) neurotransmitters from Renshaw cells in spinal cord
<i>Clostridium botulinum</i>	Botulinum toxin ^a		Flaccid paralysis, floppy baby; toxin prevents release of stimulatory (ACh) signals at neuromuscular junctions → flaccid paralysis

^aAn 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.

Bugs with exotoxins (continued)

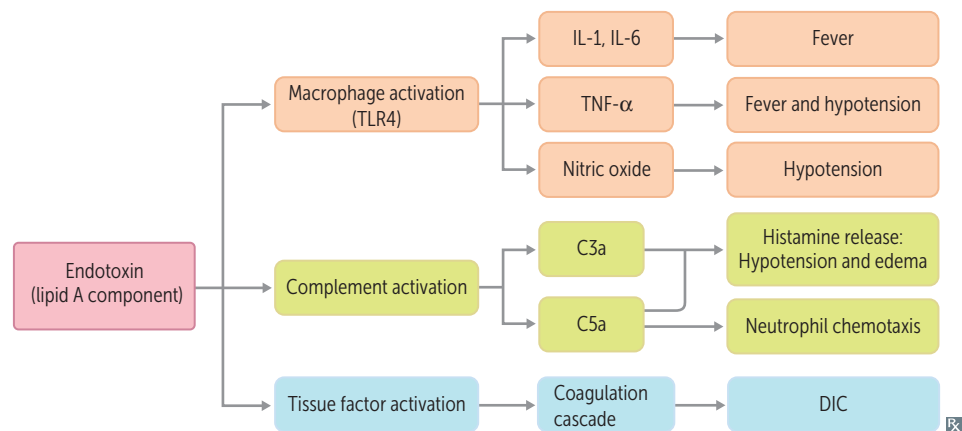
BACTERIA	TOXIN	MECHANISM	MANIFESTATION
Lyse cell membranes			
<i>Clostridium perfringens</i>	Alpha toxin	Phospholipase (lecithinase) that degrades tissue and cell membranes	Degradation of phospholipids → myonecrosis (“gas gangrene”) and hemolysis (“double zone” of hemolysis on blood agar)
<i>Streptococcus pyogenes</i>	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			
<i>Staphylococcus aureus</i>	Toxic shock syndrome toxin (TSST-1)	Binds to MHC II and TCR outside of antigen binding site to cause overwhelming release of IL-1, IL-2, IFN-γ, and TNF-α	Toxic shock syndrome: fever, rash, shock; other toxins cause scalded skin syndrome (exfoliative toxin) and food poisoning (enterotoxin)
<i>Streptococcus pyogenes</i>	Exotoxin A	→ shock	Toxic shock syndrome: fever, rash, shock

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), complement activation, and tissue factor activation.

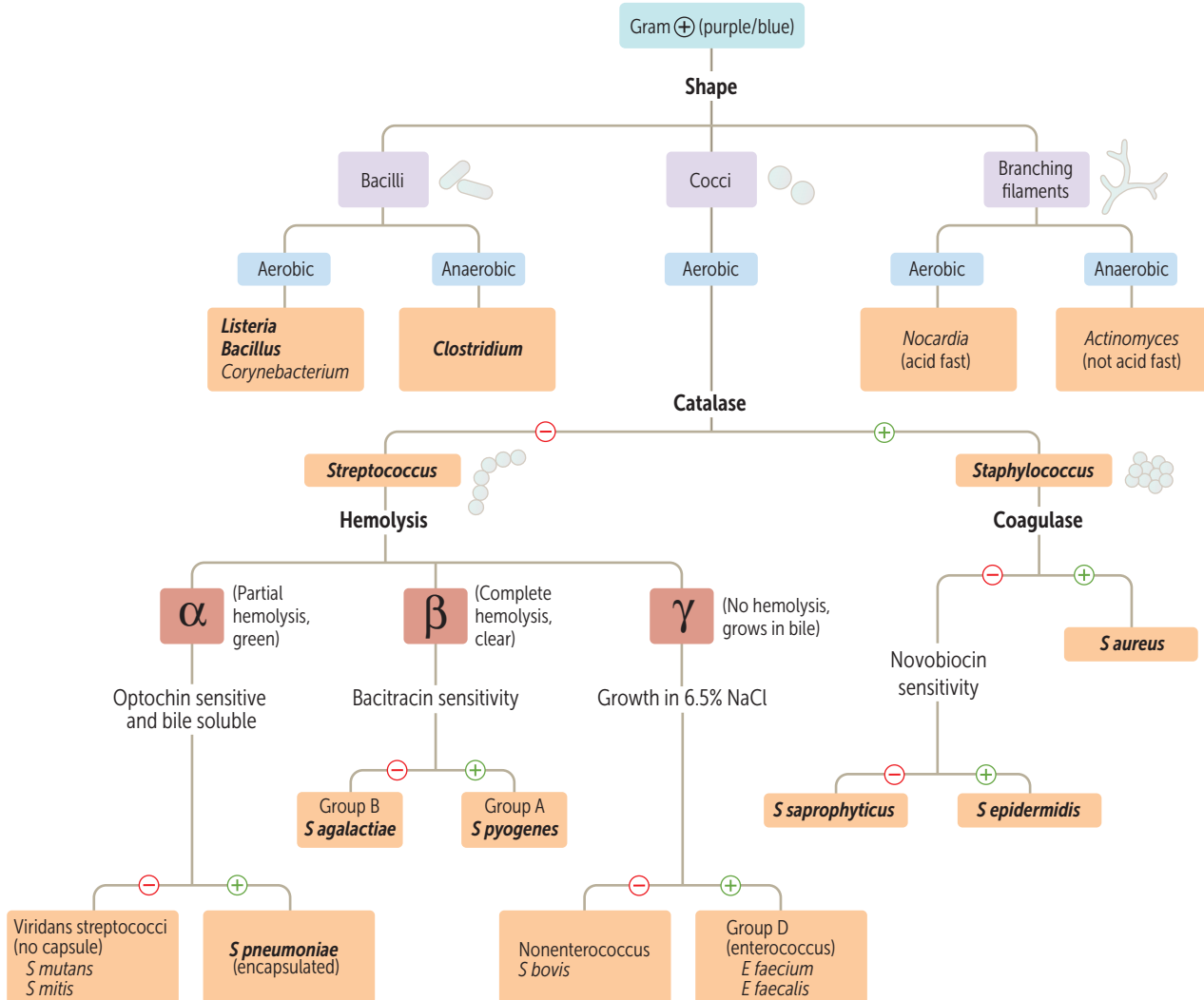
ENDOTOXINS:

- 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



▶ MICROBIOLOGY—CLINICAL BACTERIOLOGY

Gram-positive lab algorithm



Important **tests** are in **bold**. Important **pathogens** are in **bold italics**.
 Note: Enterococcus is either α- or γ-hemolytic.



Gram-positive cocci antibiotic tests

Staphylococci

NOvobiocin—*Saprophyticus* is **R**esistant;
Epidermidis is **S**ensitive.

On the office's "**staph**" retreat, there was
NO StRESs.

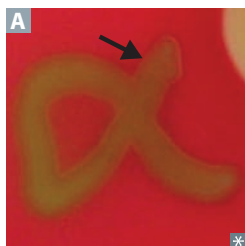
Streptococci

Optochin—*Viridans* is **R**esistant; *Pneumoniae* is
Sensitive.

OVRPS (overpass).

Bacitracin—group **B** strep are **R**esistant; group
A strep are **S**ensitive.

B-BRAS.

α -hemolytic bacteria

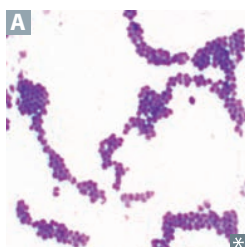
Gram \oplus cocci. Partial reduction of hemoglobin causes greenish or brownish color without clearing around growth on blood agar **A**. Include the following organisms:

- *Streptococcus pneumoniae* (catalase \ominus and optochin sensitive)
- Viridans streptococci (catalase \ominus and optochin resistant)

 β -hemolytic bacteria

Gram \oplus cocci. Complete lysis of RBCs \rightarrow clear area surrounding colony on blood agar **A**. Include the following organisms:

- *Staphylococcus aureus* (catalase and coagulase \oplus)
- *Streptococcus pyogenes*—group A strep (catalase \ominus and bacitracin sensitive)
- *Streptococcus agalactiae*—group B strep (catalase \ominus and bacitracin resistant)

Staphylococcus aureus

Gram \oplus , β -hemolytic, catalase \oplus , coagulase \oplus cocci in clusters **A**. Protein A (virulence factor) binds Fc-IgG, inhibiting complement activation and phagocytosis. Commonly colonizes the nares.

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 *S aureus*) infection—important cause of serious nosocomial and community-acquired infections; resistant to methicillin and nafcillin because of altered penicillin-binding protein.

TSST-1 is a superantigen that binds to MHC II and T-cell receptor, resulting in polyclonal T-cell activation.

Staphylococcal toxic shock syndrome (TSS) presents as fever, vomiting, rash, desquamation, shock, end-organ failure. TSS results in \uparrow AST, \uparrow ALT, \uparrow 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 \rightarrow short incubation period (2–6 hr) followed by nonbloody diarrhea and emesis. Enterotoxin is heat stable \rightarrow not destroyed by cooking.

Staph make catalase because they have more “staff.” Bad staph (*aureus*) make coagulase and toxins. Forms fibrin clot around self \rightarrow abscess.

Staphylococcus epidermidis

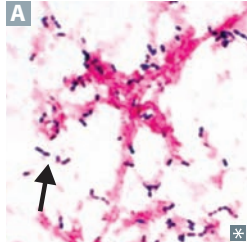
Gram \oplus , catalase \oplus , coagulase \ominus , urease \oplus cocci in clusters. Novobiocin sensitive.

Normal flora of skin; contaminates blood cultures.

Infects prosthetic devices (eg, hip implant, heart valve) and IV catheters by producing adherent biofilms.

Staphylococcus saprophyticus

Gram ⊕, catalase ⊕, coagulase ⊖, urease ⊕ 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 cause is *E coli*).

Streptococcus pneumoniae

Gram ⊕, lancet-shaped diplococci **A**.
Encapsulated. IgA protease. Optochin sensitive. Most common cause of:

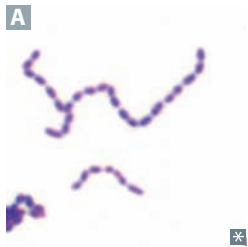
- Meningitis
- Otitis media (in children)
- Pneumonia
- Sinusitis

Pneumococcus is associated with “rusty” sputum, sepsis in patients with sickle cell disease and splenectomy.
No virulence without capsule.

Viridans group streptococci

Gram ⊕, α-hemolytic cocci. They are normal flora of the oropharynx that cause dental caries (*Streptococcus mutans* and *S mitis*) and subacute bacterial endocarditis at damaged **heart** valves (*S sanguinis*). Resistant to optochin, differentiating them from *S pneumoniae*, which is α-hemolytic but is optochin sensitive.

Sanguinis = **blood**. Think, “there is lots of **blood** in the **heart**” (endocarditis). *S sanguinis* makes dextrans, which bind to fibrin-platelet aggregates on damaged heart valves.
Viridans group strep live in the mouth because they are not afraid **of-the-chin** (**op-to-chin** resistant).

***Streptococcus pyogenes* (group A streptococci)**

Gram ⊕ cocci. Group A strep **A** cause:

- Pyogenic—pharyngitis, cellulitis, impetigo, erysipelas
- Toxigenic—scarlet fever, toxic shock–like syndrome, necrotizing fasciitis
- Immunologic—rheumatic fever, glomerulonephritis

Bacitracin sensitive, β-hemolytic, pyrrolidonyl arylamidase (PYR) ⊕. Antibodies to M protein enhance host defenses against *S pyogenes* but can give rise to rheumatic fever.

ASO titer detects recent *S pyogenes* infection.

JONES (major criteria for acute rheumatic fever):

- J**oints—polyarthriti**s**
- ♥**—carditi**s**
- N**odules (subcutaneous)
- E**rythema marginatum
- S**ydenham chorea

Pharyngitis can result in rheumatic “**p**hever” and glomerulonephritis.

Impetigo usually precedes glomerulonephritis.
Scarlet fever—blanching, sandpaper-like body rash, strawberry tongue, and circumoral pallor in the setting of group A streptococcal pharyngitis (erythrogenic toxin ⊕).

***Streptococcus agalactiae* (group B streptococci)**

Gram \oplus cocci, bacitracin resistant, β -hemolytic, Group **B** for **B**abies!
 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 \oplus . PYR \ominus .
 Screen pregnant women at 35–37 weeks of gestation. Patients with \oplus culture receive intrapartum penicillin prophylaxis.

Streptococcus bovis

Gram \oplus cocci, colonizes the gut. *S gallolyticus* (*S bovis* biotype 1) can cause bacteremia and subacute endocarditis and is associated with colon cancer. **B**ovis in the **b**lood = **c**ancer in the **c**olon.

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, hardier than nonenterococcal group D, 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. The only bacterium with a polypeptide capsule (contains D-glutamate).

Cutaneous anthrax

Painless papule surrounded by vesicles \rightarrow ulcer with black eschar (**A**) (painless, necrotic)
 \rightarrow uncommonly progresses to bacteremia and death.

**Pulmonary anthrax**

Inhalation of spores \rightarrow flu-like symptoms that rapidly progress to fever, pulmonary hemorrhage, mediastinitis, and shock. Also known as woolsorter's disease

Bacillus cereus

Gram ⊕ rod. Causes food poisoning.
Spores survive cooking rice. Keeping rice warm results in germination of spores and enterotoxin formation.
Emetic type usually seen with rice and pasta. Nausea and vomiting within 1–5 hr. Caused by cereulide, a preformed toxin.
Diarrheal type causes watery, nonbloody diarrhea and GI pain within 8–18 hr.

Reheated rice syndrome.

Clostridia (with exotoxins)

Gram ⊕, spore-forming, obligate anaerobic rods.

C tetani

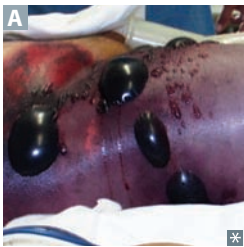
Produces tetanospasmin, an exotoxin causing tetanus. Tetanus toxin (and botulinum toxin) are proteases that cleave SNARE proteins for neurotransmitters. Blocks release of inhibitory neurotransmitters, GABA and glycine, from Renshaw cells in spinal cord.
Causes spastic paralysis, trismus (lockjaw), risus sardonicus (raised eyebrows and open grin).
Prevent with tetanus vaccine. Treat with antitoxin +/- vaccine booster, diazepam (for muscle spasms), and wound debridement.

Tetanus is tetanic paralysis.

C 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 antitoxin.

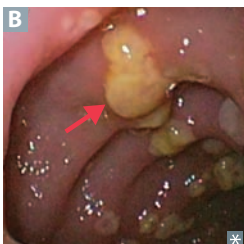
Botulinum is from bad bottles of food, juice, and honey (causes a descending flaccid paralysis). Local botox injections used to treat focal dystonia, achalasia, and muscle spasms. Also used for cosmetic reduction of facial wrinkles.

C perfringens

Produces α toxin (lecithinase, a phospholipase) that can cause myonecrosis (gas gangrene **A**) and hemolysis.

Perfringens perforates a gangrenous leg.

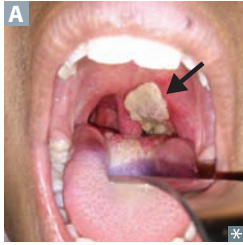
Spores can survive in undercooked food; when ingested, bacteria release heat-labile enterotoxin → food poisoning.

C difficile

Produces 2 toxins. Toxin A, enterotoxin, binds to the brush border of the gut. Toxin B, cytotoxin, causes cytoskeletal disruption via actin depolymerization → diarrhea → pseudomembranous colitis **B**. Often 2° to antibiotic use, especially clindamycin or ampicillin; associated with PPI use. Diagnosed by detecting one or both toxins in stool by PCR.

Difficile causes diarrhea. Treatment: metronidazole or oral vancomycin. For recurrent cases, consider repeating prior regimen, fidaxomicin, or fecal microbiota transplant.

Corynebacterium diphtheriae



Gram ⊕ rod. Causes diphtheria via exotoxin encoded by β-prophage. Potent exotoxin inhibits protein synthesis via ADP-ribosylation of EF-2.

Symptoms include pseudomembranous pharyngitis (grayish-white membrane **A**) with lymphadenopathy, myocarditis, and arrhythmias.

Lab diagnosis based on gram ⊕ rods with metachromatic (blue and red) granules and ⊕ Elek test for toxin.

Toxoid vaccine prevents diphtheria.

Coryne = club shaped.

Black colonies on cystine-tellurite agar.

ABCDEFGF:

ADP-ribosylation

β-prophage

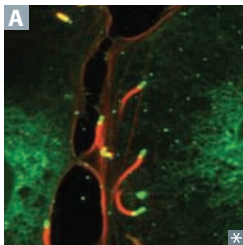
Corynebacterium

Diphtheriae

Elongation Factor 2

Granules

Listeria monocytogenes



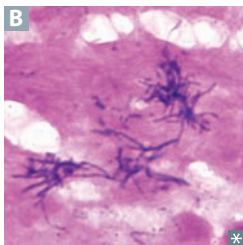
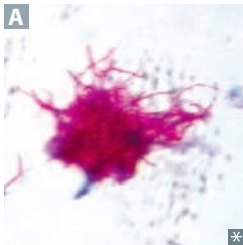
Gram ⊕, facultative intracellular rod; acquired by ingestion of unpasteurized dairy products and cold deli meats, via transplacental transmission, or by vaginal transmission during birth.

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; neonatal meningitis; meningitis in immunocompromised patients; mild, self-limited gastroenteritis in healthy individuals.

Treatment: ampicillin in infants, immunocompromised, and the elderly as empirical treatment of meningitis.

Nocardia vs Actinomyces



Both are gram ⊕ and form long, branching filaments resembling fungi.

Nocardia

Aerobe

Acid fast (weak) **A**

Found in soil

Causes pulmonary infections in immunocompromised (can mimic TB but with ⊖ PPD); cutaneous infections after trauma in immunocompetent

Treat with sulfonamides (TMP-SMX)

Treatment is a **SNAP**: Sulfonamides—*Nocardia*; *Actinomyces*—Penicillin

Actinomyces

Anaerobe

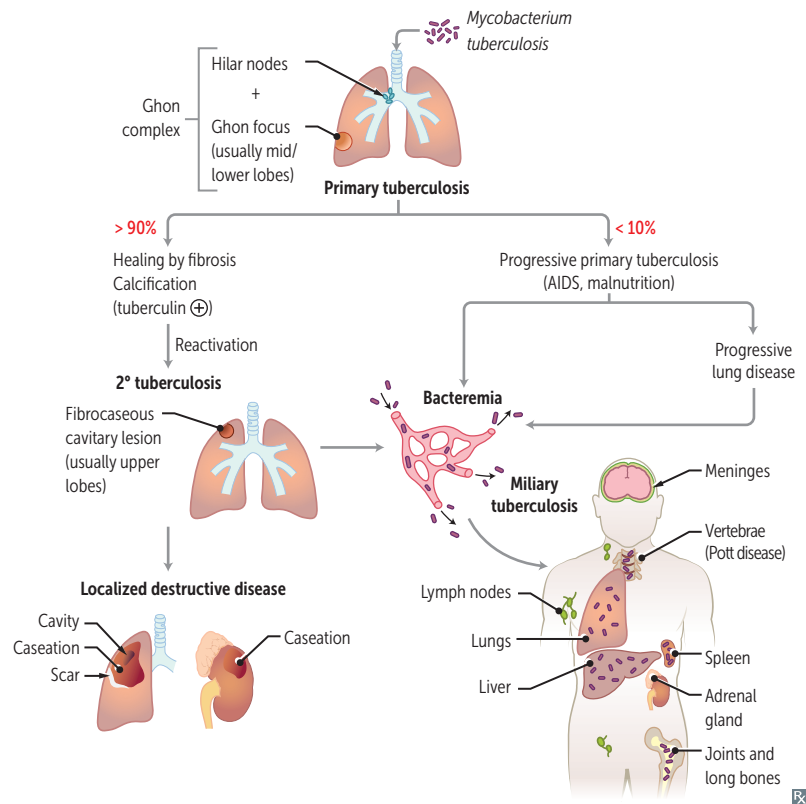
Not acid fast **B**

Normal oral, reproductive, and GI flora

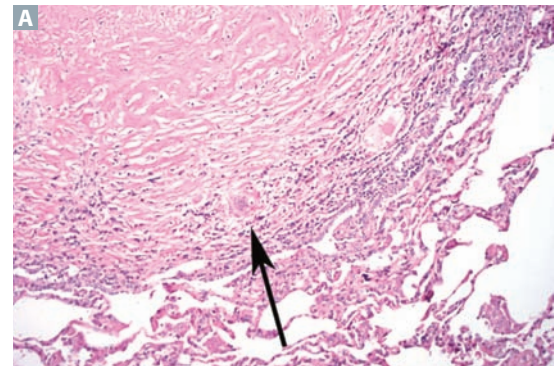
Causes oral/facial abscesses that drain through sinus tracts, forms yellow “sulfur granules;” can also cause PID with IUDs

Treat with penicillin

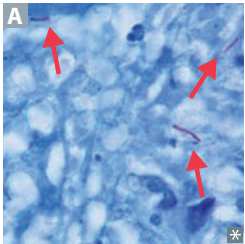
Primary and secondary tuberculosis



PPD ⊕ if current infection or past exposure.
 PPD ⊖ if no infection and in sarcoidosis.
 Interferon- γ release assay (IGRA) has fewer false positives from BCG vaccination.
 Caseating granulomas **A** with central necrosis (upper left) and Langerhans giant cells (arrow) are characteristic of 2° tuberculosis.



Mycobacteria



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/mm³.

M. scrofulaceum (cervical lymphadenitis in children).

M. marinum (hand infection in aquarium handlers).

All mycobacteria are acid-fast organisms (pink rods; arrows in **A**).

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; inhibits macrophage maturation and induces release of TNF- α . Sulfatides (surface glycolipids) inhibit phagolysosomal fusion.

Leprosy (Hansen disease)



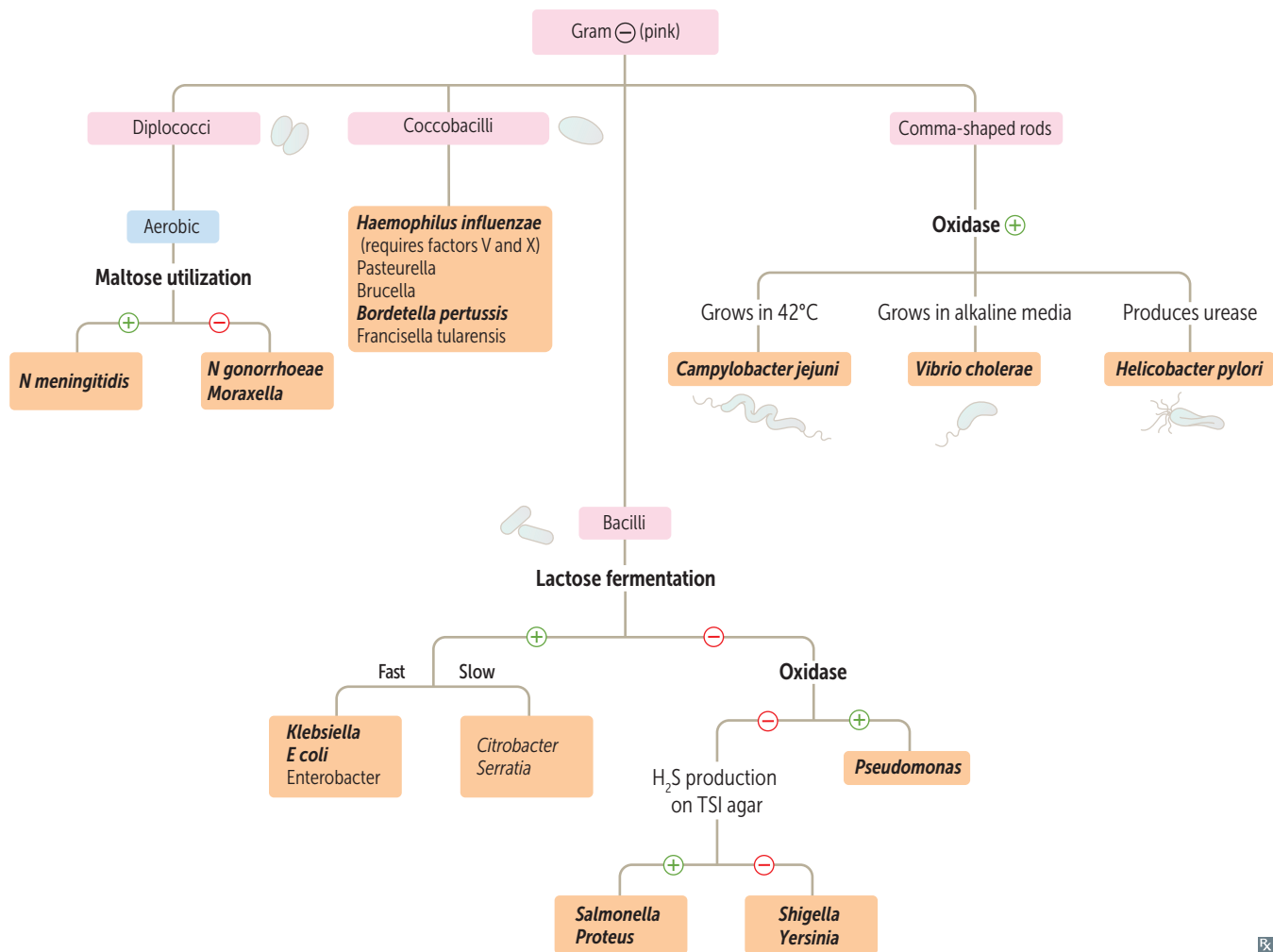
Caused by *Mycobacterium leprae*, an acid-fast bacillus that likes cool temperatures (infects skin and superficial nerves—“glove and stocking” loss of sensation **A**) and cannot be grown in vitro. Reservoir in United States: armadillos.

Hansen disease has 2 forms:

- **Lepromatous**—presents diffusely over the skin, with leonine (lion-like) facies **B**, and is communicable; characterized by low cell-mediated immunity with a humoral Th2 response. Lepromatous form can be lethal.
- **Tuberculoid**—limited to a few hypoesthetic, hairless skin plaques; characterized by high cell-mediated immunity with a largely Th1-type immune response.

Treatment: dapsone and rifampin for tuberculoid form; clofazimine is added for lepromatous form.

Gram-negative lab algorithm



Important tests are in bold. Important pathogens are in bold italics.



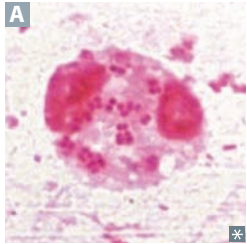
Lactose-fermenting enteric bacteria

Fermentation of **lactose** → pink colonies on MacCon**key** agar. Examples include **Klebsiella**, **E coli**, **Enterobacter**, and **Serratia** (weak fermenter). *E coli* produces β -galactosidase, which breaks down lactose into glucose and galactose.

Lactose is key.

Test with MacCon**KEE'S** agar.

EMB agar—lactose fermenters grow as purple/black colonies. *E coli* grows colonies with a green sheen.

Neisseria

Gram \ominus diplococci. Metabolize glucose and produce IgA proteases. *N gonorrhoeae* is often intracellular (within neutrophils) **A**.

MeninGococci ferment **M**altose and **G**lucose.

Gonococci ferment **G**lucose.

Gonococci

No polysaccharide capsule

No maltose metabolized

No vaccine due to antigenic variation of pilus proteins

Sexually or perinatally transmitted

Causes gonorrhea, septic arthritis, neonatal conjunctivitis, pelvic inflammatory disease (PID), and Fitz-Hugh–Curtis syndrome

Condoms ↓ sexual transmission, erythromycin eye ointment prevents neonatal blindness

Treatment: ceftriaxone + (azithromycin or doxycycline) for possible chlamydial coinfection

Meningococci

Polysaccharide capsule

Maltose fermentation

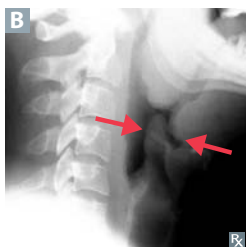
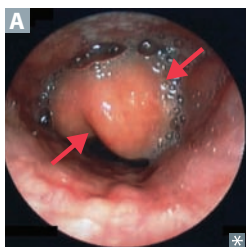
Vaccine (type B vaccine not widely available)

Transmitted via respiratory and oral secretions

Causes meningococemia with petechial hemorrhages and gangrene of toes **B**, meningitis, Waterhouse-Friderichsen syndrome (adrenal insufficiency, fever, DIC, shock) syndrome

Rifampin, ciprofloxacin, or ceftriaxone prophylaxis in close contacts

Treatment: ceftriaxone or penicillin G

Haemophilus influenzae

Small gram \ominus (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 through the hemolysis of RBCs. **HaEMOPhilus** causes **E**piglottitis (endoscopic appearance in **A**), can be “cherry red” in children; “thumbprint sign” on x-ray **B**), **M**eningitis, **O**titis media, and **P**neumonia.

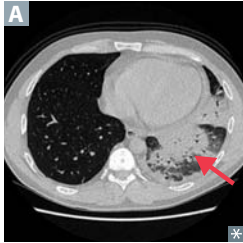
Treatment: amoxicillin +/- clavulanate for mucosal infections; ceftriaxone for meningitis; rifampin prophylaxis for close contacts.

Vaccine contains type b capsular polysaccharide and PRP (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).

Bordetella pertussis

Gram \ominus , aerobic coccobacillus. Virulence factors include pertussis toxin (disables G_i) and tracheal cytotoxin. Causes whooping cough. Prevented by Tdap, DTaP vaccines. May be mistaken as viral infection due to lymphocytic infiltrate resulting from immune response.

Legionella pneumophila

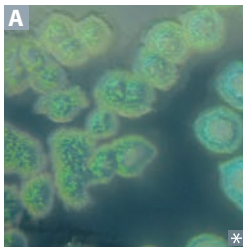
Gram \ominus rod. Gram stains poorly—use **silver** stain. Grow on **charcoal** yeast extract medium with **iron** and **cysteine**. Detected by presence of antigen in urine. Labs may show hyponatremia. Aerosol transmission from environmental water source habitat (eg, air conditioning systems, hot water tanks). No person-to-person transmission.

Treatment: macrolide or quinolone.

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.

Think of a French **legionnaire** (soldier) with his **silver** helmet, sitting around a campfire (**charcoal**) with his **iron** dagger—he is no **sissey** (cysteine).

Pseudomonas aeruginosa

Aerobic, motile, gram \ominus rod. Non-lactose fermenting, oxidase \oplus . Produces pyocyanin (blue-green pigment **A**); has a grape-like odor. Produces endotoxin (fever, shock), exotoxin A (inactivates EF-2), phospholipase C (degrades cell membranes), and pyocyanin (generates reactive oxygen species).

PSEUDOMONAS is associated with:

- **P**neumonia, pyocyanin
- **S**epsis
- **E**cthyma gangrenosum
- **U**TI
- **D**iabetes, drug use
- **O**steomyelitis (eg, puncture wounds)
- **M**ucoid polysaccharide capsule
- **O**titis externa (swimmer's ear)
- **N**osocomial infections (catheters, equipment)
- exotoxin **A**
- **S**kin infections (hot tub folliculitis)

Treatments include “**CAMPFIRE**” drugs:

- **C**arbapenems
- **A**minoglycosides
- **M**onobactams
- **P**olymyxins (eg, polymyxin B, colistin)
- **F**luoroquinolones (eg, ciprofloxacin, levofloxacin)
- **T**h**IR**d- and fourth-generation cephalosporins (eg, ceftazidime, cefepime)
- **E**xtended-spectrum penicillins (eg, piperacillin, ticarcillin)

Aeruginosa—**aerobic**.

Mucoid polysaccharide capsule may contribute to chronic pneumonia in cystic fibrosis patients due to biofilm formation.

Can cause wound infection in burn victims.

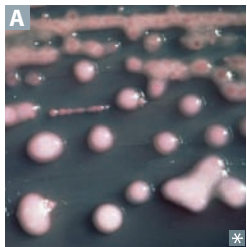
Frequently found in water → hot tub folliculitis.

Ecthyma gangrenosum—rapidly progressive, necrotic cutaneous lesion **B** caused by *Pseudomonas* bacteremia. Typically seen in immunocompromised patients.

E coli

Gram \ominus 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
EIEC	Microbe invades intestinal mucosa and causes necrosis and inflammation.	I nvasive; dysentery. Clinical manifestations similar to <i>Shigella</i> .
ETEC	Produces heat-labile and heat-stable enterotoxins. No inflammation or invasion.	T ravelers' diarrhea (watery).
EPEC	No toxin produced. Adheres to apical surface, flattens villi, prevents absorption.	Diarrhea, usually in children (P ediatrics).
EHEC	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 renal failure 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 (distinguishes EHEC from other <i>E coli</i>). H emorrhagic, H amburgers, H emolytic-uremic syndrome.

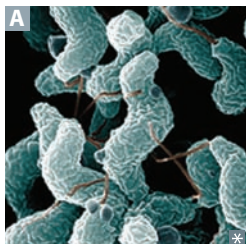
Klebsiella

Gram \ominus 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.

4 A's of *Klebsiella*:

- A**spirations pneumonia
- A**bscess in lungs and liver
- A**lcoholics
- di-**A**-betics

Campylobacter jejuni

Gram \ominus , comma or S shaped (with polar flagella) **A**, oxidase \oplus , 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.

Salmonella vs Shigella

Both *Salmonella* and *Shigella* are gram \ominus rods, non-lactose fermenters, oxidase \ominus , and can invade the GI tract via M cells of Peyer patches.

	<i>Salmonella typhi</i>	<i>Salmonella</i> spp. (except <i>S typhi</i>)	<i>Shigella</i>
RESERVOIRS	Humans only	Humans and animals	Humans only
SPREAD	Can disseminate hematogenously	Can disseminate hematogenously	Cell to cell; no hematogenous spread
H ₂ 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 ₅₀)	High—large inoculum required because organism inactivated by gastric acids	High	Low—very small inoculum required; 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
GI MANIFESTATIONS	Constipation, followed by diarrhea	Diarrhea (possibly bloody)	Bloody diarrhea (bacillary dysentery)
VACCINE	Oral vaccine contains live attenuated <i>S typhi</i> IM vaccine contains Vi capsular polysaccharide	No vaccine	No vaccine
UNIQUE PROPERTIES	<ul style="list-style-type: none"> Causes typhoid fever (rose spots on abdomen, constipation, abdominal pain, fever); treat with ceftriaxone or fluoroquinolone Carrier state with gallbladder colonization 	<ul style="list-style-type: none"> Poultry, eggs, pets, and turtles are common sources Antibiotics not indicated Gastroenteritis is usually caused by non-typhoidal <i>Salmonella</i> 	<ul style="list-style-type: none"> Four F's: Fingers, Flies, Food, Feces In order of decreasing severity (less toxin produced): <i>S dysenteriae</i>, <i>S flexneri</i>, <i>S boydii</i>, <i>S sonnei</i> Invasion is the key to pathogenicity; organisms that produce little toxin can cause disease due to invasion

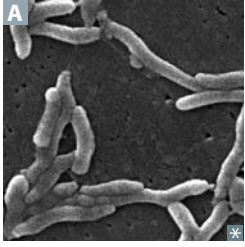
Vibrio cholerae



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 ID₅₀) unless host has \downarrow gastric acidity. Prompt oral rehydration is necessary.

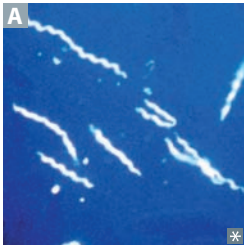
Yersinia enterocolitica

Gram \ominus rod. Usually transmitted from pet feces (eg, puppies), contaminated milk, or pork. Causes acute diarrhea or pseudoappendicitis (right lower abdominal pain due to mesenteric adenitis and/or terminal ileitis).

Helicobacter pylori

Curved, terminally flagellated, gram \ominus rod **A** that is **triple** \oplus : catalase \oplus , oxidase \oplus , and urease \oplus (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: **A**moxicillin (metronidazole if penicillin allergy) + **C**larithromycin + **P**roton pump inhibitor; **A**ntibiotics **C**ure **P**ylori.

Spirochetes

Spiral-shaped bacteria **A** with axial filaments. Includes **B**orrelia (big size), **L**eptospira, and **T**reponema. 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.

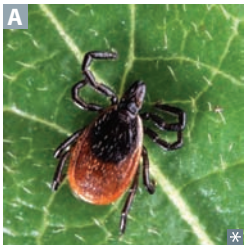
BLT.

Borrelia is Big.

Leptospira interrogans

Spirochete found in water contaminated with animal urine, causes **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.

Lyme disease

Caused by *Borrelia burgdorferi*, which is transmitted by the *Ixodes* deer tick **A** (also vector for *Anaplasma* spp. and protozoa *Babesia*). Natural reservoir is the mouse.

Mice are important to tick life cycle.

Common in northeastern United States.

Stage 1—early localized: erythema migrans **B**, flu-like symptoms.

Stage 2—early disseminated: secondary lesions, carditis, AV block, facial nerve (Bell) palsy, migratory myalgias/transient arthritis.

Stage 3—late disseminated: encephalopathies, chronic arthritis.

A Key **Lyme** pie to the **FACE**:

Facial nerve palsy (typically bilateral)

Arthritis

Cardiac block

Erythema migrans



Syphilis

Caused by spirochete *Treponema pallidum*.

Primary syphilis

Localized disease presenting with **painless chancre** **A**. If available, use dark-field microscopy to visualize treponemes in fluid from chancre **B**. VDRL ⊕ in ~ 80%.

Secondary syphilis

Disseminated disease with constitutional symptoms, maculopapular rash **C** (including palms **D** and soles), condylomata lata **E** (smooth, moist, 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 **G**), snuffles (nasal discharge, red arrow in **G**), saddle nose, notched (Hutchinson) teeth **H**, 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.

**VDRL false positives**

VDRL detects nonspecific antibody that reacts with beef cardiolipin. Inexpensive, widely available test for syphilis, quantitative, sensitive but not specific.

False-positive results on **VDRL** with:
Viral infection (eg, EBV, hepatitis)
Drugs
Rheumatic fever
Lupus and leprosy

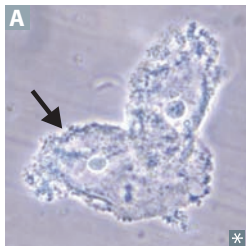
Jarisch-Herxheimer reaction

Flu-like syndrome (fever, chills, headache, myalgia) after antibiotics are started; due to killed bacteria (usually spirochetes) releasing toxins.

Zoonotic bacteria

Zoonosis: infectious disease transmitted between animals and humans.

SPECIES	DISEASE	TRANSMISSION AND SOURCE
<i>Anaplasma</i> spp.	Anaplasmosis	<i>Ixodes</i> ticks (live on deer and mice)
<i>Bartonella</i> spp.	Cat scratch disease, bacillary angiomatosis	Cat scratch
<i>Borrelia burgdorferi</i>	Lyme disease	<i>Ixodes</i> ticks (live on deer and mice)
<i>Borrelia recurrentis</i>	Relapsing fever	Louse (recurrent due to variable surface antigens)
<i>Brucella</i> spp.	Brucellosis/ undulant fever	Un pasteurized dairy
<i>Campylobacter</i>	Bloody diarrhea	Feces from infected pets/animals; contaminated meats/foods/hands
<i>Chlamydophila psittaci</i>	Psittacosis	Parrots, other birds
<i>Coxiella burnetii</i>	Q fever	Aerosols of cattle/sheep amniotic fluid
<i>Ehrlichia chaffeensis</i>	Ehrlichiosis	<i>Amblyomma</i> (Lone Star tick)
<i>Francisella tularensis</i>	Tularemia	Ticks, rabbits, deer flies
<i>Leptospira</i> spp.	Leptospirosis	Animal urine in water; recreational water use
<i>Mycobacterium leprae</i>	Leprosy	Humans with lepromatous leprosy; armadillo (rare)
<i>Pasteurella multocida</i>	Cellulitis, osteomyelitis	Animal bite, cats, dogs
<i>Rickettsia prowazekii</i>	Epidemic typhus	Human to human via human body louse
<i>Rickettsia rickettsii</i>	Rocky Mountain spotted fever	<i>Dermacentor</i> (dog tick)
<i>Rickettsia typhi</i>	Endemic typhus	Fleas
<i>Salmonella</i> spp. (except <i>S typhi</i>)	Diarrhea (which may be bloody), vomiting, fever, abdominal cramps	Reptiles and poultry
<i>Yersinia pestis</i>	Plague	Fleas (rats and prairie dogs are reservoirs)

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. **Clue** cells (vaginal epithelial cells covered with *Gardnerella*) have stippled appearance along outer margin (arrow in **A**).

Treatment: metronidazole or clindamycin.

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.

Rickettsial diseases and vector-borne illnesses

Treatment for all: 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 **C**oxsackievirus **A** infection (hand, foot, and mouth disease), **R**ocky Mountain spotted fever, and 2° **S**yphilis (you drive **CARS** using your **palms** and **soles**).

Typhus

Endemic (fleas)—*R typhi*.
Epidemic (human body louse)—*R prowazekii*.
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. **M**onocytes with morulae **B** (mul**berry**-like inclusions) in cytoplasm.

MEGA berry—
Monocytes = **E**hrlichiosis
Granulocytes = **A**naplasmosis

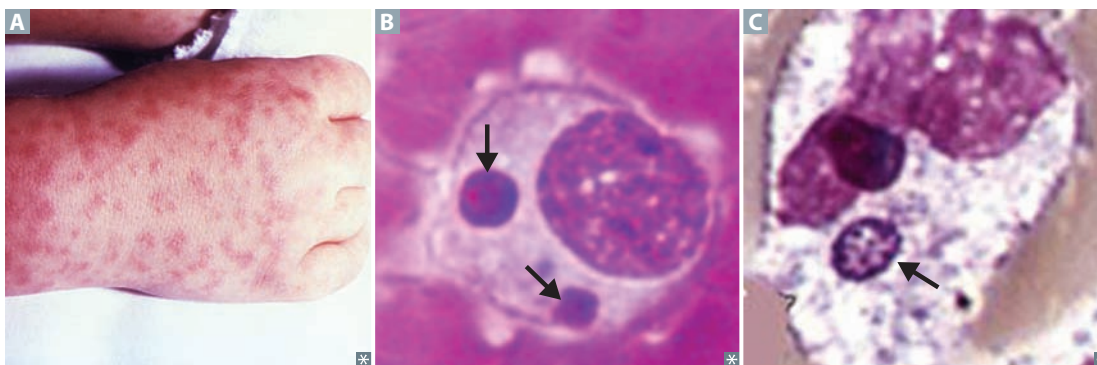
Anaplasmosis

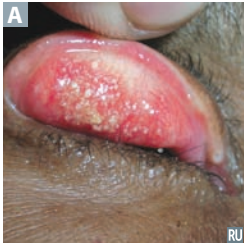
Anaplasma, vector is tick. **G**ranulocytes with morulae **C** in cytoplasm.

Q fever

Coxiella burnetii, no arthropod vector. Spores inhaled as aerosols from cattle/sheep amniotic fluid. Presents as pneumonia. Most common cause of culture ⊖ endocarditis.

Q fever is **Q**ueer because it has no rash or vector and its causative organism can survive outside in its endospore form. Not in the *Rickettsia* genus, but closely related.



Chlamydiae

Chlamydiae cannot make their own ATP. They are obligate intracellular organisms that cause mucosal infections. 2 forms:

- **E**lementary body (small, dense) is “**E**nfectious” and **E**nters cell via **E**ndocytosis; transforms into reticulate body.
- **R**eticulate body **R**eplicates in cell by fission; **R**eorganizes into elementary bodies.

Chlamydia trachomatis causes reactive arthritis (Reiter syndrome), follicular conjunctivitis **A**, nongonococcal urethritis, and PID.

Chlamydophila pneumoniae and *Chlamydophila psittaci* cause atypical pneumonia; transmitted by aerosol.

Treatment: azithromycin (favored because one-time treatment) or doxycycline.

Chlamys = cloak (intracellular).

C psittaci—has an avian reservoir (**p**arrots), causes atypical **p**neumonia.

Lab diagnosis: cytoplasmic inclusions seen on Giemsa or fluorescent antibody–stained smear. The chlamydial cell wall lacks classic peptidoglycan (due to reduced muramic acid), rendering β -lactam antibiotics less effective.

Chlamydia trachomatis serotypes**Types A, B, and C**

Chronic infection, cause blindness due to follicular conjunctivitis in Africa.

ABC = **A**frica, **B**lindness, **C**hronic infection.

Types D–K

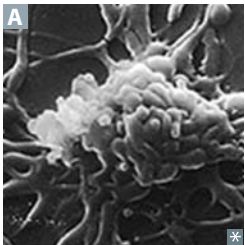
Urethritis/PID, ectopic pregnancy, neonatal pneumonia (staccato cough) with eosinophilia, neonatal conjunctivitis.

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.

Mycoplasma pneumoniae

Classic cause of atypical “walking” pneumonia (insidious onset, headache, nonproductive cough, patchy or diffuse interstitial infiltrate). X-ray looks worse than patient. High titer of **c**old agglutinins (IgM), which can agglutinate or lyse RBCs. Grown on Eaton agar.

Treatment: macrolides, doxycycline, or fluoroquinolone (penicillin ineffective since *Mycoplasma* have no cell wall).

No cell wall. Not seen on Gram stain.

Pleomorphic **A**.

Bacterial membrane contains sterols for stability.

Mycoplasma pneumoniae is more common in patients < 30 years old.

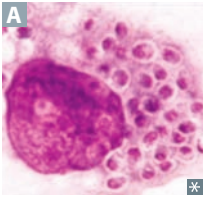
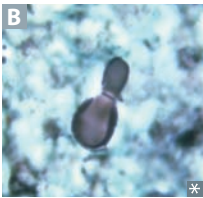
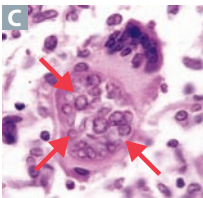
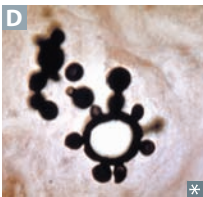
Frequent outbreaks in military recruits and prisons.

Mycoplasma gets **c**old without a **c**oat (cell wall).

▶ 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**. The only exception is coccidioidomycosis, which is a spherule (not yeast) in tissue. Treatment: fluconazole or itraconazole for **local** infection; amphotericin B for **systemic** infection. Systemic mycoses can form granulomas (like TB) but cannot be transmitted person-to-person (unlike TB).

DISEASE	ENDEMIC LOCATION AND PATHOLOGIC FEATURES	NOTES
<p>Histoplasmosis</p> 	<p>Mississippi and Ohio River valleys. Macrophage filled with <i>Histoplasma</i> (smaller than RBC) A.</p>	<p>Histo hides (within macrophages). Bird (eg, starlings) or bat droppings.</p>
<p>Blastomycosis</p> 	<p>Eastern United States and Central America. Causes inflammatory lung disease and can disseminate to skin and bone. Forms granulomatous nodules. Broad-base budding (same size as RBC) B.</p>	<p>Blasto buds broadly.</p>
<p>Coccidioidomycosis</p> 	<p>Southwestern United States, California. Causes pneumonia and meningitis; can disseminate to skin and bone. Case rate ↑ after earthquakes (spores in dust thrown into air → inhaled → spherules in lung). Spherule (much larger than RBC) filled with endospores C.</p>	<p>Coccidio crowds endospores. “(San Joaquin) Valley fever” “Desert bumps” = erythema nodosum “Desert rheumatism” = arthralgias</p>
<p>Paracoccidioidomycosis</p> 	<p>Latin America. Budding yeast with “captain’s wheel” formation (much larger than RBC) D.</p>	<p>Paracoccidio parasails with the captain’s wheel all the way to Latin America.</p>

Cutaneous mycoses

Tinea (dermatophytes)	Tinea is the clinical name given to 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 .
Tinea capitis	Occurs on head, scalp. Associated with lymphadenopathy, alopecia, scaling B .
Tinea corporis	Occurs on torso. Characterized by erythematous scaling rings (“ringworm”) and central clearing C . Can be acquired from contact with an infected cat or dog.
Tinea cruris	Occurs in inguinal area D . Often does not show the central clearing seen in tinea corporis.
Tinea pedis	Three varieties: <ul style="list-style-type: none"> ▪ Interdigital E; most common ▪ Moccasin distribution F ▪ 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 damage melanocytes and cause hypopigmented G and/or pink patches. 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.



Opportunistic fungal infections***Candida albicans***

alba = white. Dimorphic; forms pseudohyphae and budding yeasts at 20°C **A**, germ tubes at 37°C **B**.

Systemic or superficial fungal infection. Causes oral **C** and esophageal thrush in immunocompromised (neonates, steroids, diabetes, AIDS), vulvovaginitis (diabetes, use of antibiotics), diaper rash, endocarditis (IV drug users), disseminated candidiasis (to any organ), chronic mucocutaneous candidiasis.

Treatment: topical azole for vaginal; nystatin, fluconazole, or caspofungin for oral/esophageal; fluconazole, caspofungin, or amphotericin B for systemic.

Aspergillus fumigatus

Septate hyphae that branch at 45° Acute Angle **D**. Produces conidia in radiating chains at end of conidiophore **E**.

Causes invasive aspergillosis, especially in immunocompromised and those with chronic granulomatous disease.

Can cause aspergillomas in pre-existing lung cavities, especially after TB infection.

Some species of *Aspergillus* produce **A**flatoxins, which are associated with hepatocellular carcinoma.

Allergic bronchopulmonary aspergillosis (ABPA): hypersensitivity response 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. Culture on Sabouraud agar. Highlighted with India ink (clear halo **F**) and mucicarmine (red inner capsule **G**). Latex agglutination test detects polysaccharide capsular antigen and is more specific.

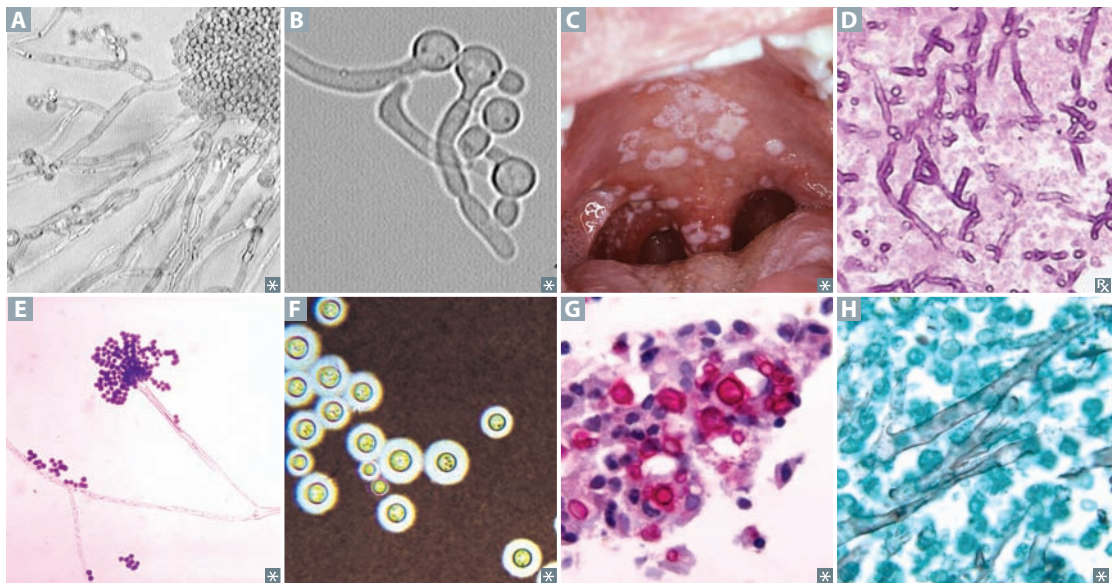
Causes cryptococcosis, cryptococcal meningitis, cryptococcal encephalitis (“soap bubble” lesions in brain), primarily in immunocompromised.

***Mucor and Rhizopus* spp.**

Irregular, broad, nonseptate hyphae branching at wide angles **H**.

Mucormycosis. Causes disease mostly in ketoacidotic diabetic and/or neutropenic patients (eg, leukemia). 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; may have cranial nerve involvement.

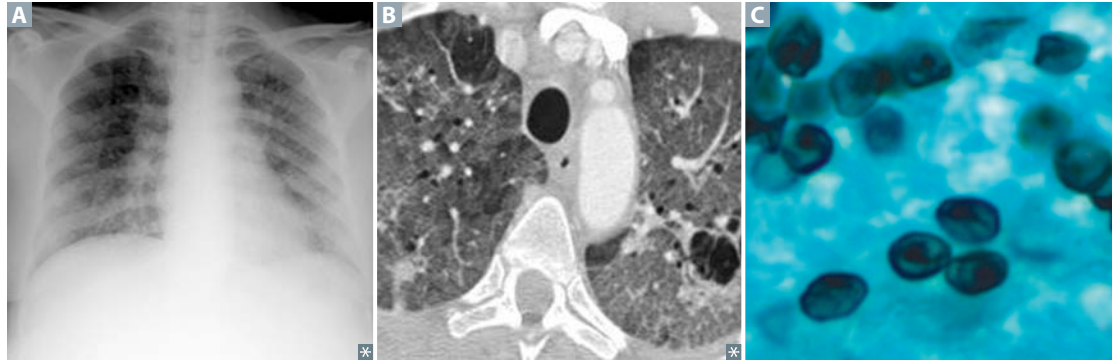
Treatment: surgical debridement, amphotericin B.



Pneumocystis jirovecii

Causes *Pneumocystis* pneumonia (PCP), a diffuse interstitial pneumonia **A**. Yeast-like fungus (originally classified as protozoan). Inhaled. Most infections are asymptomatic. Immunosuppression (eg, AIDS) predisposes to disease. Diffuse, bilateral ground-glass opacities on CXR/CT **B**. Diagnosed by lung biopsy or lavage. Disc-shaped yeast seen on methenamine silver stain of lung tissue **C**.

Treatment/prophylaxis: TMP-SMX, pentamidine, dapsone (prophylaxis only), atovaquone. Start prophylaxis when CD4+ count drops to < 200 cells/mm³ in HIV patients.

***Sporothrix schenckii***

Sporotrichosis. Dimorphic, cigar-shaped budding yeast that grows in branching hyphae with **rosettes** of 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 **A** with nodules along draining lymphatics (ascending lymphangitis). Disseminated disease possible in immunocompromised host.

Treatment: itraconazole or **potassium iodide**.

“Plant a **rose** in the **pot**.”

▶ MICROBIOLOGY—PARASITOLOGY

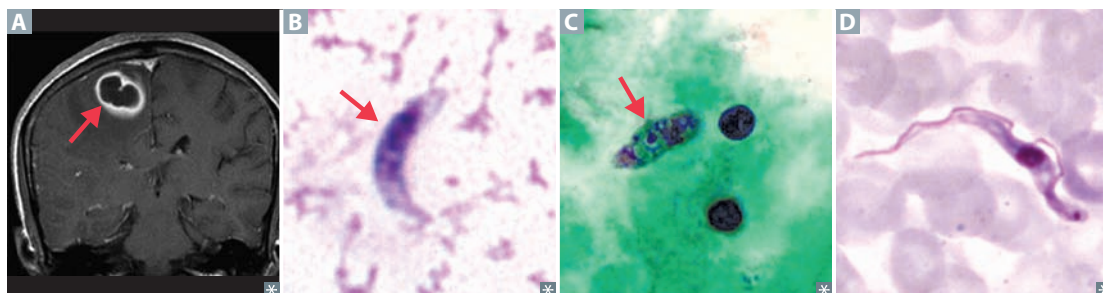
Protozoa—GI infections

ORGANISM	DISEASE	TRANSMISSION	DIAGNOSIS	TREATMENT
<i>Giardia lamblia</i>	Giardiasis —bloating, flatulence, foul-smelling, fatty diarrhea (often seen in campers/hikers)—think fat-rich Ghirardelli chocolates for fatty stools of <i>Giardia</i>	Cysts in water	Multinucleated trophozoites A or cysts B in stool	Metronidazole
<i>Entamoeba histolytica</i>	Amebiasis —bloody diarrhea (dysentery), liver abscess (“anchovy paste” exudate), RUQ pain; histology shows flask-shaped ulcer	Cysts in water	Serology and/or trophozoites (with engulfed RBCs C in the cytoplasm) or cysts with up to 4 nuclei D in stool	Metronidazole; iodoquinol for asymptomatic cyst passers
<i>Cryptosporidium</i>	Severe diarrhea in AIDS Mild disease (watery diarrhea) in immunocompetent hosts	Oocysts in water	Oocysts on acid-fast stain E	Prevention (by filtering city water supplies); nitazoxanide in immunocompetent hosts

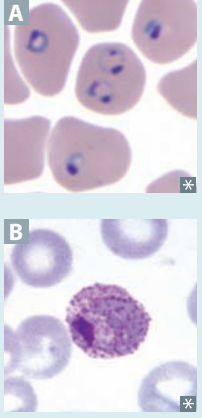
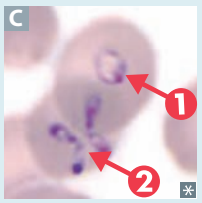


Protozoa—CNS infections

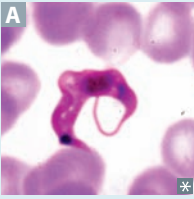
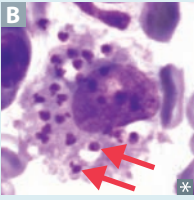

ORGANISM	DISEASE	TRANSMISSION	DIAGNOSIS	TREATMENT
<i>Toxoplasma gondii</i>	Congenital toxoplasmosis = classic triad of chorioretinitis, hydrocephalus, and intracranial calcifications; reactivation in AIDS → brain abscess seen as ring-enhancing lesions on MRI A	Cysts in meat (most common); oocysts in cat feces; crosses placenta (pregnant women should avoid cats)	Serology, biopsy (tachyzoite) B	Sulfadiazine + pyrimethamine
<i>Naegleria fowleri</i>	Rapidly fatal meningoencephalitis	Swimming in freshwater lakes (think Nalgene bottle filled with fresh water containing Naegleria); enters via cribriform plate	Amoebas in spinal fluid C	Amphotericin B has been effective for a few survivors
<i>Trypanosoma brucei</i>	African sleeping sickness —enlarged lymph nodes, recurring fever (due to antigenic variation), somnolence, coma Two subspecies: <i>Trypanosoma brucei rhodesiense</i> , <i>Trypanosoma brucei gambiense</i>	Tsetse fly, a painful bite	Trypomastigote in blood smear D	Suramin for blood-borne disease or melarsoprol for CNS penetration (“it sure is nice to go to sleep”; melatonin helps with sleep)



Protozoa—hematologic infections

ORGANISM	DISEASE	TRANSMISSION	DIAGNOSIS	TREATMENT
<p>Plasmodium <i>P vivax/ovale</i> <i>P falciparum</i> <i>P malariae</i></p> 	<p>Malaria—fever, headache, anemia, splenomegaly <i>P vivax/ovale</i>—48-hr cycle (tertian; includes fever on first day and third day, thus fevers are actually 48 hr apart); dormant form (hypnozoite) in liver <i>P falciparum</i>—severe; irregular fever patterns; parasitized RBCs occlude capillaries in brain (cerebral malaria), kidneys, lungs <i>P malariae</i>—72-hr cycle (quartan)</p>	<p><i>Anopheles</i> mosquito</p>	<p>Blood smear: trophozoite ring form within RBC A, schizont containing merozoites; red granules (Schüffner stippling) B throughout RBC cytoplasm seen with <i>P vivax/ovale</i></p>	<p>Chloroquine (for sensitive species), which blocks <i>Plasmodium</i> heme polymerase; 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)</p>
<p>Babesia</p> 	<p>Babesiosis—fever and hemolytic anemia; predominantly in northeastern United States; asplenia ↑ risk of severe disease</p>	<p><i>Ixodes</i> tick (same as <i>Borrelia burgdorferi</i> of Lyme disease; may often coinfect humans)</p>	<p>Blood smear: ring form C1, “Maltese cross” C2; PCR</p>	<p>Atovaquone + azithromycin</p>

Protozoa—others

ORGANISM	DISEASE	TRANSMISSION	DIAGNOSIS	TREATMENT
Visceral infections				
<i>Trypanosoma cruzi</i> 	Chagas disease —dilated cardiomyopathy with apical atrophy, megacolon, megaesophagus; predominantly in South America Unilateral periorbital swelling (Romaña sign) characteristic of acute stage	Reduviid bug (“kissing bug”) feces, deposited in a painless bite (much like a kiss)	Trypomastigote in blood smear A	Benznidazole or nifurtimox; Cruzing in my Benz , with a fur coat on
<i>Leishmania donovani</i> 	Visceral leishmaniasis (kala-azar) —spiking fevers, hepatosplenomegaly, pancytopenia Cutaneous leishmaniasis —skin ulcers	Sandfly	Macrophages containing amastigotes B	Amphotericin B, sodium stibogluconate
Sexually transmitted infections				
<i>Trichomonas vaginalis</i> 	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) C on wet mount; “strawberry cervix”	Metronidazole for patient and partner (prophylaxis)
Nematode routes of infection	Ingested— <i>Enterobius</i> , <i>Ascaris</i> , <i>Toxocara</i> , <i>Trichinella</i> Cutaneous— <i>Strongyloides</i> , <i>Ancylostoma</i> , <i>Necator</i> Bites— <i>Loa loa</i> , <i>Onchocerca volvulus</i> , <i>Wuchereria bancrofti</i>	You’ll get sick if you EATT these! These get into your feet from the SANd . Lay LOW to avoid getting bitten.		
Immune response to helminths	Eosinophils act by type I and type II hypersensitivity reactions in responding to helminths. Type I—neutralization of histamine and leukotrienes. Type II—eosinophils attach to surface of helminths via IgE and release cytotoxins (eg, major basic protein) contained in their granules.			

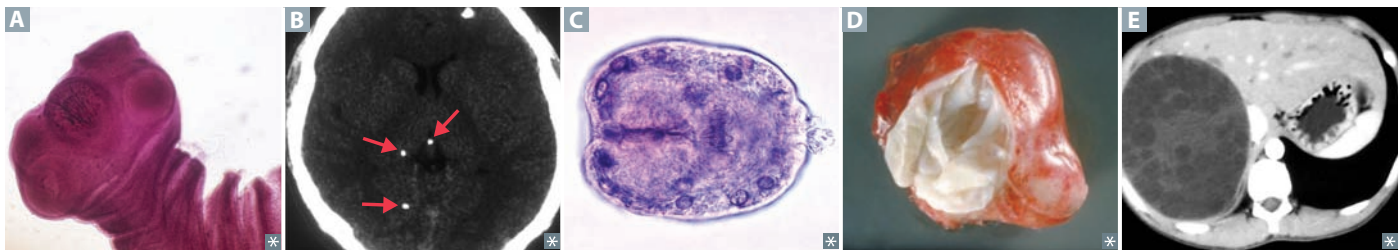
Nematodes (roundworms)

ORGANISM	DISEASE	TRANSMISSION	TREATMENT
Intestinal			
<i>Enterobius vermicularis</i> (pinworm)	Intestinal infection causing anal pruritus (diagnosed by seeing egg A via the tape test)	Fecal-oral	Bendazoles (because worms are bendy)
<i>Ascaris lumbricoides</i> (giant roundworm)	Intestinal infection with possible obstruction at ileocecal valve	Fecal-oral; eggs visible in feces under microscope B	Bendazoles
<i>Strongyloides stercoralis</i> (threadworm)	Intestinal infection causing vomiting, diarrhea, epigastric pain (may mimic peptic ulcer)	Larvae in soil penetrate the skin	Ivermectin or bendazoles
<i>Ancylostoma duodenale, Necator americanus</i> (hookworms)	Intestinal infection causing 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
<i>Trichinella spiralis</i>	Intestinal infection; larvae enter bloodstream and encyst in striated muscle cells → inflammation of muscle. Trichinosis —fever, vomiting, nausea, periorbital edema, myalgia.	Fecal-oral; undercooked meat (especially pork)	Bendazoles
Tissue			
<i>Toxocara canis</i>	Visceral larva migrans —nematodes migrate to blood through intestinal wall causing inflammation and damage. Organs frequently affected include the heart (myocarditis), liver, and CNS (seizures, coma).	Fecal-oral	Bendazoles
<i>Onchocerca volvulus</i>	Skin changes, loss of elastic fibers, and river blindness (black flies, black skin nodules, “black sight”); allergic reaction to microfilaria possible.	Female blackfly	Ivermectin (ivermectin for river blindness)
<i>Loa loa</i>	Swelling in skin, worm in conjunctiva	Deer fly, horse fly, mango fly	Diethylcarbamazine
<i>Wuchereria bancrofti</i>	Elephantiasis —worms invade lymph nodes and cause inflammation, which can block lymphatic vessels C , takes 9 mo–1 yr after bite to become symptomatic.	Female mosquito	Diethylcarbamazine



Cestodes (tapeworms)

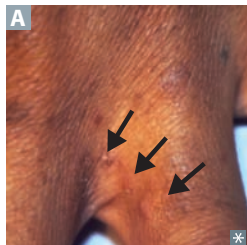
ORGANISM	DISEASE	TRANSMISSION	TREATMENT
<i>Taenia solium</i> A	Intestinal tapeworm	Ingestion of larvae encysted in undercooked pork	Praziquantel
	Cysticercosis, neurocysticercosis B	Ingestion of eggs contaminated with human feces	Praziquantel; albendazole for neurocysticercosis
<i>Diphyllobothrium latum</i>	Vitamin B ₁₂ deficiency (tapeworm competes for B ₁₂ in intestine) → megaloblastic anemia	Ingestion of larvae from raw freshwater fish	Praziquantel
<i>Echinococcus granulosus</i> C	Hydatid cysts D in liver E , causing anaphylaxis if antigens released (hydatid cyst injected with ethanol or hypertonic saline to kill daughter cysts before removal)	Ingestion of eggs from dog feces Sheep are an intermediate host	Albendazole

**Trematodes (flukes)**

ORGANISM	DISEASE	TRANSMISSION	TREATMENT
<i>Schistosoma</i>	Liver and spleen enlargement (<i>S. mansoni</i> , egg with lateral spine A), fibrosis, and inflammation	Snails are host; cercariae penetrate skin of humans	Praziquantel
	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		
<i>Clonorchis sinensis</i>	Biliary tract inflammation → pigmented gallstones Associated with cholangiocarcinoma	Undercooked fish	Praziquantel

Parasite hints

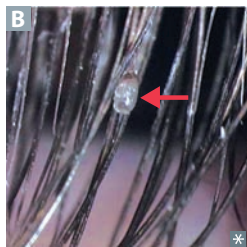
ASSOCIATIONS	ORGANISM
Biliary tract disease, cholangiocarcinoma	<i>Clonorchis sinensis</i>
Brain cysts, seizures	<i>Taenia solium</i> (neurocysticercosis)
Hematuria, squamous cell bladder cancer	<i>Schistosoma haematobium</i>
Liver (hydatid) cysts	<i>Echinococcus granulosus</i>
Microcytic anemia	<i>Ancylostoma</i> , <i>Necator</i>
Myalgias, periorbital edema	<i>Trichinella spiralis</i>
Perianal pruritus	<i>Enterobius</i>
Portal hypertension	<i>Schistosoma mansoni</i> , <i>Schistosoma japonicum</i>
Vitamin B ₁₂ deficiency	<i>Diphyllobothrium latum</i>

Ectoparasites**Scabies**
(*Sarcoptes scabiei*)

Mites that burrow into the stratum corneum and cause pruritis. Causes serpiginous burrows (lines) in webspace of hands and feet **A**.

Common in children, crowded populations (jails, nursing homes); transmission through fomites.

Treatment: permethrin cream, washing/drying all clothing/bedding, treat close contacts.

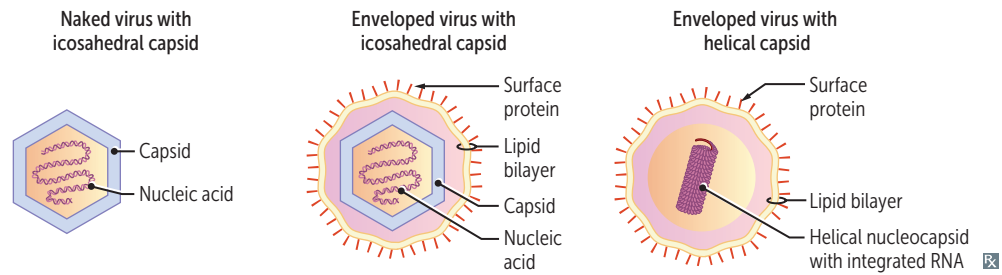
Lice
(*Pediculus humanus/Phthirus pubis*)

Blood-sucking insects that prefer to live on clothing. Cause intense pruritis, pink macules and papules commonly in intertriginous regions.

Can transmit *Rickettsia prowazekii* (typhus), *Borrelia recurrentis* (relapsing fever), *Bartonella quintana* (trench fever).

Treatment includes pyrethroids, malathion, or ivermectin lotion, and nit **B** combing. Children with head lice can be treated at home without interrupting school.

▶ 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. 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. However, the progeny from this infection have a type A coat that is encoded by its type A genetic material.

Viral vaccines**Live attenuated
vaccines**

Induce humoral and cell-mediated immunity but have reverted to virulence on rare occasions.

Live attenuated: **smallpox**, **yellow fever**, **rotavirus**, **chickenpox** (VZV), **Sabin** polio virus, **MMR**, **Influenza** (intranasal).

No booster needed for live attenuated vaccines. Dangerous to give live vaccines to immunocompromised patients. Close contacts may be vaccinated with live vaccines (except live polio or influenza).

“**Live!** One night only! See **small yellow rotating chickens** get vaccinated with **Sabin** and **MMR!** It’s incredible!”

MMR = measles, mumps, rubella; live attenuated vaccine that can be given to HIV ⊕ patients who do not show signs of immunodeficiency.

Killed

Rabies, **Influenza** (injected), Salk **Polio**, and **HAV** vaccines. Killed/inactivated vaccines induce only humoral immunity but are stable.

SalK = Killed.
RIP Always.

Subunit

HBV (antigen = HBsAg), HPV (types 6, 11, 16, and 18).

DNA viral genomes All DNA viruses except the Parvoviridae are dsDNA. 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 except Reoviridae are ssRNA. ⊕ 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 (like our mRNA), except “**repeato-virus**” (**reovirus**) is dsRNA.

Naked viral genome infectivity Purified nucleic acids of most dsDNA (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 replication

DNA viruses All replicate in the nucleus (except poxvirus).

RNA viruses All replicate in the cytoplasm (except influenza virus and retroviruses).


Viral envelopes **Naked** (nonenveloped) viruses include **P**apillomavirus, **A**denovirus, **P**arvovirus, **P**olyomavirus, **C**alicivirus, **P**icornavirus, **R**eovirus, and **H**epevirus. Give **PAPP** smears and **CPR** to a **naked hippie** (**hepevirus**). DNA = **PAPP**; RNA = **CPR** and **hepevirus**. Generally, enveloped viruses acquire their envelopes from plasma membrane when they exit from cell. Exceptions include herpesviruses, which acquire envelopes from nuclear membrane.

DNA virus characteristics

Some general rules—all DNA viruses:

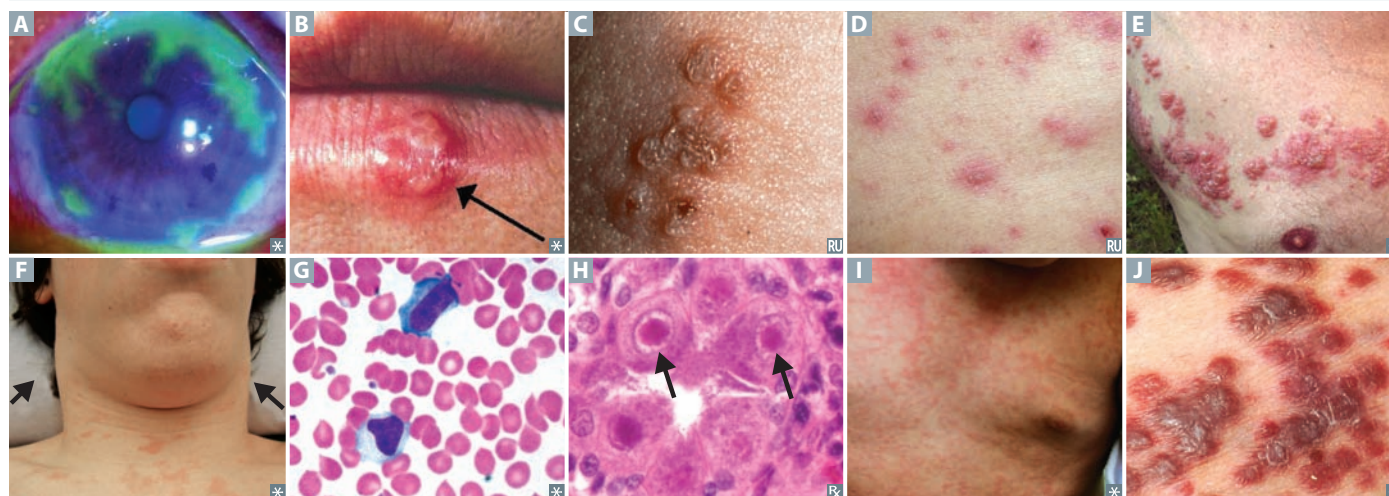
GENERAL RULE	COMMENTS
Are HHAPPPY viruses	H epadna, H erpes, A deno, P ox, P arvo, P apilloma, P olyoma.
Are double stranded	Except parvo (single stranded).
Have linear genomes	Except papilloma and polyoma (circular, supercoiled) and hepadna (circular, incomplete).
Are icosahedral	Except pox (complex).
Replicate in the nucleus	Except pox (carries own DNA-dependent RNA polymerase).

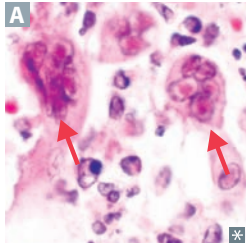
DNA viruses

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	HBV: <ul style="list-style-type: none"> ▪ Acute or chronic hepatitis ▪ Not a retrovirus but has reverse transcriptase
Adenovirus	No	DS and linear	Febrile pharyngitis A —sore throat Acute hemorrhagic cystitis Pneumonia Conjunctivitis—“pink eye”
			
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: J unky C erebrum; BK: B ad K idney
Parvovirus	No	SS and linear (smallest DNA virus)	B19 virus—aplastic crises in sickle cell disease, “slapped cheeks” rash in children (erythema infectiosum, or fifth disease) RBC destruction in fetus leads to hydrops fetalis and death, in adults leads to pure RBC aplasia and rheumatoid arthritis–like symptoms

Herpesviruses Enveloped, DS and linear viruses

VIRUS	ROUTE OF TRANSMISSION	CLINICAL SIGNIFICANCE	NOTES
Herpes simplex virus-1	Respiratory secretions, saliva	Gingivostomatitis, keratoconjunctivitis A , herpes labialis B , herpetic whitlow on finger, temporal lobe encephalitis.	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 C , neonatal herpes.	Latent in sacral ganglia. Viral meningitis more common with HSV-2 than with HSV-1.
Varicella-Zoster virus (HHV-3)	Respiratory secretions	Varicella-zoster (chickenpox D , shingles E), encephalitis, pneumonia. Most common complication of shingles is post-herpetic neuralgia.	Latent in dorsal root or trigeminal ganglia.
Epstein-Barr virus (HHV-4)	Respiratory secretions, saliva; aka “kissing disease,” (common in teens, young adults)	Mononucleosis—fever, hepatosplenomegaly, pharyngitis, and lymphadenopathy (especially posterior cervical nodes F). Avoid contact sports until resolution due to risk of splenic rupture. Associated with lymphomas (eg, endemic Burkitt lymphoma), nasopharyngeal carcinoma.	Infects B cells through CD21. Atypical lymphocytes on peripheral blood smear G —not infected B cells but reactive cytotoxic T cells. ⊕ Monospot test—heterophile antibodies detected by agglutination of sheep or horse RBCs.
Cytomegalovirus (HHV-5)	Congenital transfusion, sexual contact, saliva, urine, transplant	Mononucleosis (⊖ Monospot) in immunocompetent patients; infection in immunocompromised patients, especially pneumonia in transplant patients; AIDS retinitis (“ sight omegalovirus”): hemorrhage, cotton-wool exudates, vision loss. Congenital CMV	Infected cells have characteristic “owl eye” inclusions H . Latent in mononuclear cells.
Human herpesviruses 6 and 7	Saliva	Roseola infantum (exanthem subitum): high fevers for several days that can cause seizures, followed by diffuse macular rash I . 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 J representing vascular proliferations.	Can also affect GI and lungs.



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.

Intranuclear inclusions also seen with HSV-1, HSV-2, VZV.

Tzanck heavens I do not have herpes.

Receptors used by viruses

VIRUS	RECEPTORS
CMV	Integrins (heparan sulfate)
EBV	CD21
HIV	CD4, CXCR4, CCR5
Rabies	Nicotinic AChR
Rhinovirus	ICAM-1

RNA viruses

VIRAL FAMILY	ENVELOPE	RNA STRUCTURE	CAPSID SYMMETRY	MEDICAL IMPORTANCE
Reoviruses	No	DS linear 10–12 segments	Icosahedral (double)	Coltivirus ^a —Colorado tick fever Rotavirus—#1 cause of fatal diarrhea in children
Picornaviruses	No	SS ⊕ linear	Icosahedral	P oliovirus—polio-Salk/Sabin vaccines—IPV/OPV E chovirus—aseptic meningitis R hinovirus—“common cold” C oxsackievirus—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 ^a Dengue ^a St. Louis encephalitis ^a West Nile virus ^a
Togaviruses	Yes	SS ⊕ linear	Icosahedral	Rubella Eastern equine encephalitis ^a Western equine encephalitis ^a
Retroviruses	Yes	SS ⊕ linear 2 copies	Icosahedral (HTLV), complex and conical (HIV)	Have reverse transcriptase 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 : P arainfluenza—croup RSV —bronchiolitis in babies; Rx —ribavirin M easles, M umps
Rhabdoviruses	Yes	SS ⊖ linear	Helical	Rabies
Filoviruses	Yes	SS ⊖ linear	Helical	Ebola/Marburg hemorrhagic fever—often fatal!
Arenaviruses	Yes	SS ⊕ or ⊖ circular 2 segments	Helical	LCMV—lymphocytic choriomeningitis virus Lassa fever encephalitis—spread by rodents
Bunyaviruses	Yes	SS ⊖ circular 3 segments	Helical	California encephalitis ^a Sandfly/Rift Valley fevers ^a Crimean-Congo hemorrhagic fever ^a Hantavirus—hemorrhagic fever, pneumonia
Delta virus	Yes	SS ⊖ circular	Uncertain	HDV is a “defective” virus that requires the presence of HBV to replicate

SS, single-stranded; DS, double-stranded; ⊕, positive sense; ⊖, negative sense; ^a= **arbovirus**, **arthropod borne** (mosquitoes, ticks).

Negative-stranded viruses

Must transcribe \ominus strand to \oplus . Virion brings its own RNA-dependent RNA polymerase. They include **A**renaviruses, **B**unyaviruses, **P**aramyxoviruses, **O**rthomyxoviruses, **F**iloviruses, and **R**habdoviruses.

Always **B**ring **P**olymerase **O**r **F**ail **R**eplication.

Segmented viruses

All are RNA viruses. They include **B**unyaviruses, **O**rthomyxoviruses (influenza viruses), **A**renaviruses, and **R**eoviruses.

BOAR.

Picornavirus

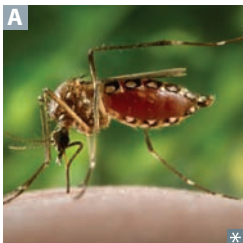
Includes **P**oliovirus, **E**chovirus, **R**hinovirus, **C**oxsackievirus, and **H**AV. RNA is translated into 1 large polypeptide that is cleaved by proteases into functional viral proteins. Can cause aseptic (viral) meningitis (except rhinovirus and HAV). All are enteroviruses (fecal-oral spread) except rhinovirus.

Pico**R**NA**v**irus = small **R**NA virus. **P**ER**C**H on a “**p**eak” (**p**ico).

Rhinovirus

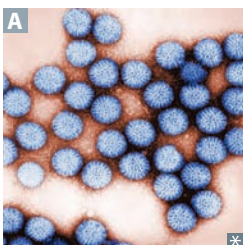
A picornavirus. Nonenveloped RNA virus. Cause of common cold; > 100 serologic types. Acid labile—destroyed by stomach acid; therefore, does not infect the GI tract (unlike the other picornaviruses).

Rhino has a runny **n**ose.

Yellow fever virus

A flavivirus (also an arbovirus) transmitted by *Aedes* mosquitoes **A**. 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

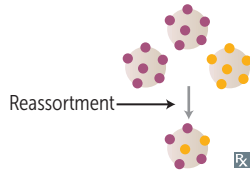
Rotavirus **A**, the most important global cause of infantile gastroenteritis, is a segmented dsRNA virus (a reovirus). Major cause of acute diarrhea in the United States during winter, especially in day care centers, kindergartens. Villous destruction with atrophy leads to ↓ absorption of Na^+ and loss of K^+ .

ROTAvirus = **R**ight **O**ut **T**he **A**nus. CDC recommends routine vaccination of all infants.

Influenza viruses

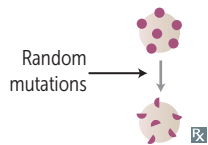
Orthomyxoviruses. Enveloped, \ominus ssRNA viruses with 8-segment genome. Contain hemagglutinin (promotes viral entry) and neuraminidase (promotes progeny virion release) antigens. Patients at risk for fatal bacterial superinfection, most commonly *S aureus*, *S pneumoniae*, and *H influenzae*.

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.

**Genetic shift/
antigenic shift**

Causes pandemics. Reassortment of viral genome segments, such as when segments of human flu A virus reassort with swine flu A virus.

Sudden shift is more deadly than gradual drift.

**Genetic drift/
antigenic drift**

Causes epidemics. Minor (antigenic drift) changes based on random mutation in hemagglutinin or neuraminidase genes.

Rubella virus

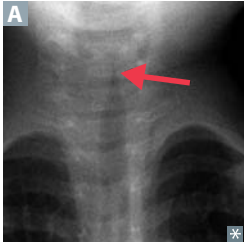
A togavirus. Causes rubella, once known as German (3-day) measles. Fever, postauricular and other lymphadenopathy, arthralgias, and fine, confluent rash that starts on face and spreads centrifugally to involve trunk and extremities **A**. Causes mild disease in children but serious congenital disease (a ToRCHeS 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: seal-like barking cough), mumps, and measles as well as RSV, 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.

Croup (acute laryngo-tracheobronchitis)

Caused by parainfluenza viruses (paramyxovirus). 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.

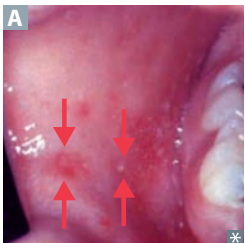
**Measles (rubeola) virus**

A paramyxovirus that causes measles. 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. SSPE (subacute sclerosing panencephalitis, occurring years later), encephalitis (1:2000), and giant cell pneumonia (rarely, in immunosuppressed) are possible sequelae.

3 C's of measles:

- C**ough
- C**oryza
- C**onjunctivitis

Vitamin A supplementation can reduce morbidity and mortality from measles, particularly in malnourished children.

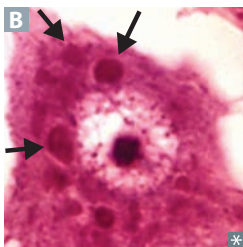
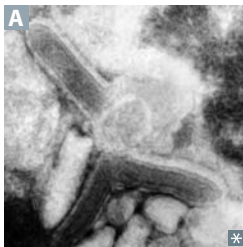


Mumps virus

A paramyxovirus that causes mumps, uncommon due to effectiveness of MMR vaccine.

Symptoms: **P**arotitis **A**, **O**rchitis (inflammation of testes), aseptic **M**eningitis, and **P**ancreatitis. Can cause sterility (especially after puberty).

Mumps makes your parotid glands and testes as big as **POM-Poms**.

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 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.

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**.

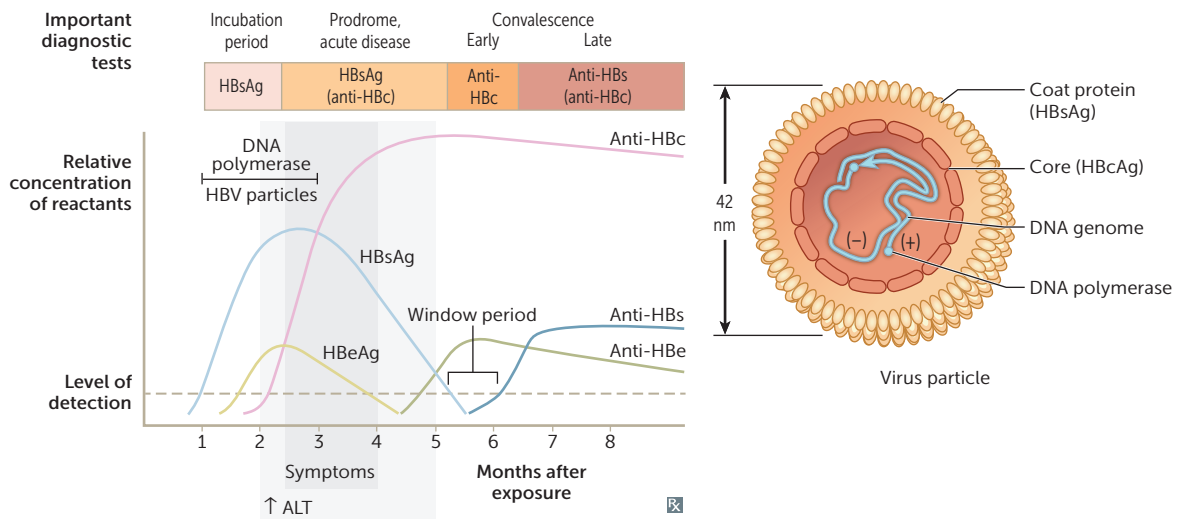
HBV DNA polymerase has DNA- and RNA-dependent activities. Upon entry into nucleus, the polymerase completes the partial dsDNA. Host RNA polymerase transcribes mRNA from viral DNA to make viral proteins. The DNA polymerase then reverse transcribes viral RNA to DNA, which is the genome of the progeny virus.

HCV lacks 3'-5' exonuclease activity → variation in antigenic structures of HCV envelope proteins. Host antibody production lags behind production of new mutant strains of HCV.

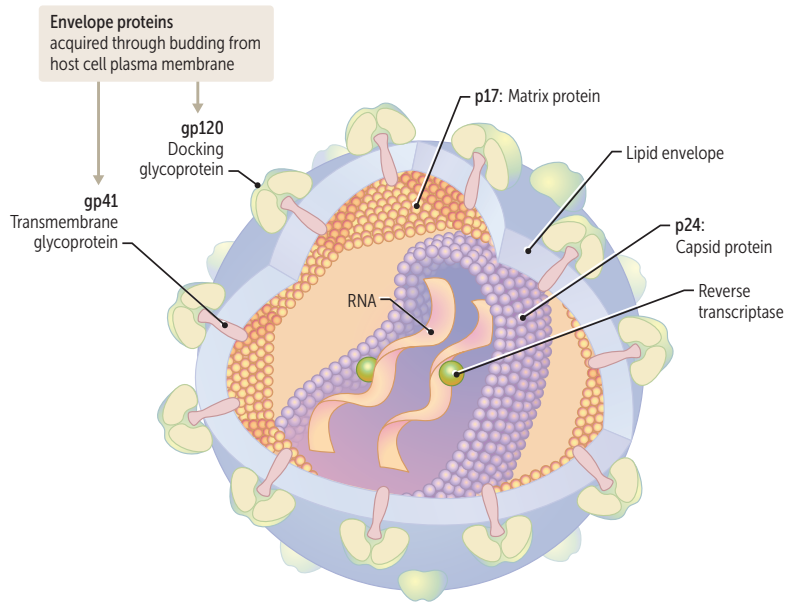
Virus	HAV	HBV	HCV	HDV	HEV
FAMILY	RNA picornavirus	DNA hepadnavirus	RNA flavivirus	RNA deltavirus	RNA hepevirus
TRANSMISSION	Fecal-oral (shellfish, travelers, day care)	Parenteral (B lood), sexual (B aby-making), perinatal (B irthing)	Primarily blood (IVDU, post-transfusion)	Parenteral, sexual, perinatal	Fecal-oral, especially waterborne
INCUBATION	Short (weeks)	Long (months)	Long	Superinfection (HDV after HBV) = short Coinfection (HDV with HBV) = long	Short
CLINICAL COURSE	A symptomatic (usually), A cute	Initially like serum sickness (fever, arthralgias, rash); may progress to carcinoma	May progress to C irrhosis or C arcinoma	Similar to HBV	Fulminant hepatitis in E xpectant (pregnant) women
PROGNOSIS	Good	Most adults have full resolution, minority have chronic infection	Majority develop stable, C hronic 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 (“ A lone”)	Carrier state common	Carrier state common	D efective virus, D epends on HBV	E nteric, E pidemic, no carrier state

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.
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 ⊕ 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.
Anti-HBe	Antibody to HBeAg; indicates low transmissibility.



	HBsAg	Anti-HBs	HBeAg	Anti-HBe	Anti-HBc
Acute HBV	✓		✓		IgM
Window				✓	IgM
Chronic HBV (high infectivity)	✓		✓		IgG
Chronic HBV (low infectivity)	✓			✓	IgG
Recovery		✓		✓	IgG
Immunized		✓			

HIV

Diploid genome (2 molecules of RNA).

The 3 structural genes (protein coded for):

- *env* (gp120 and gp41):
 - Formed from cleavage of gp160 to form envelope glycoproteins.
 - gp120—attachment to host CD4+ T cell.
 - gp41—fusion and entry.
- *gag* (p24 and p17—capsid and matrix proteins, respectively).
- *pol*—reverse transcriptase, aspartate protease, integrase.

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

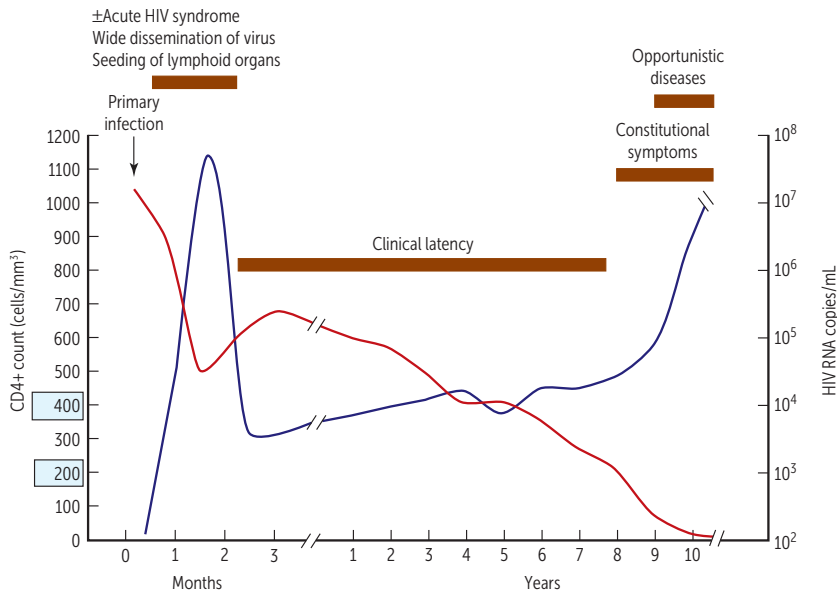
Presumptive diagnosis made with ELISA (sensitive, high false ⊕ rate and low threshold, **rule out** test); ⊕ results are then confirmed with Western blot assay (specific, low false ⊕ rate and high threshold, **rule in** test).

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.

AIDS diagnosis ≤ 200 CD4+ cells/mm³ (normal: 500–1500 cells/mm³). HIV⊕ with AIDS-defining condition (eg, *Pneumocystis pneumonia*) or CD4+ percentage < 14%.

ELISA/Western blot tests look for antibodies to viral proteins; these tests often are falsely ⊖ in the first 1–2 months of HIV infection and falsely ⊕ initially in babies born to infected mothers (anti-gp120 crosses placenta).

Time course of untreated HIV infection



Four stages of untreated infection:

1. **F**lu-like (acute)
2. **F**eeling fine (latent)
3. **F**alling count
4. **F**inal crisis

During latent phase, virus replicates in lymph nodes.

Red line = CD4+ T cell count (cells/mm³); blue line = HIV RNA copies/mL plasma.

Blue boxes on vertical CD4+ count axis indicate moderate immunocompromise (< 400 CD4+ cells/mm³) and when AIDS-defining illnesses emerge (< 200 CD4+ cells/mm³).

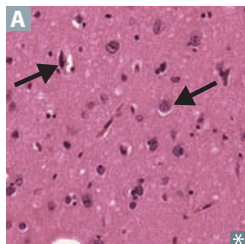
Most patients who do not receive treatment eventually die of complications of HIV infection.

Common diseases of HIV-positive adults

As CD4+ cell count ↓, risks of 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		
<i>Candida albicans</i>	Oral thrush	Scrapable white plaque, pseudohyphae on microscopy
EBV	Oral hairy leukoplakia	Unscrapable white plaque on lateral tongue
<i>Bartonella henselae</i>	Bacillary angiomatosis	Biopsy with neutrophilic inflammation
HHV-8	Kaposi sarcoma	Biopsy with lymphocytic inflammation
<i>Cryptosporidium</i> spp.	Chronic, watery diarrhea	Acid-fast oocysts in stool
HPV	Squamous cell carcinoma, commonly of anus (men who have sex with men) or cervix (women)	
CD4+ cell count < 200/mm³		
HIV	Dementia	
JC virus (reactivation)	Progressive multifocal leukoencephalopathy	Nonenhancing areas of demyelination on MRI
<i>Pneumocystis jirovecii</i>	<i>Pneumocystis</i> pneumonia	“Ground-glass” opacities on CXR
CD4+ cell count < 100/mm³		
<i>Aspergillus fumigatus</i>	Hemoptysis, pleuritic pain	Cavitation or infiltrates on chest imaging
<i>Cryptococcus neoformans</i>	Meningitis	Encapsulated yeast on India ink stain or capsular antigen ⊕
<i>Candida albicans</i>	Esophagitis	White plaques on endoscopy; yeast and pseudohyphae on biopsy
CMV	Retinitis, esophagitis, colitis, pneumonitis, encephalitis	Linear ulcers on endoscopy, cotton-wool spots on funduscopy Biopsy reveals cells with intranuclear (owl eye) inclusion bodies
EBV	B-cell lymphoma (eg, non-Hodgkin lymphoma, CNS lymphoma)	CNS lymphoma—ring enhancing, may be solitary (vs <i>Toxoplasma</i>)
<i>Histoplasma capsulatum</i>	Fever, weight loss, fatigue, cough, dyspnea, nausea, vomiting, diarrhea	Oval yeast cells within macrophages
<i>Mycobacterium avium-intracellulare</i> , <i>Mycobacterium avium</i> complex	Nonspecific systemic symptoms (fever, night sweats, weight loss) or focal lymphadenitis	
<i>Toxoplasma gondii</i>	Brain abscesses	Multiple ring-enhancing lesions on MRI

Prions



Prion diseases are caused by the conversion of a normal (predominantly α -helical) protein termed prion protein (PrP^c) to a β -pleated form (PrP^{sc}), which is transmissible via CNS-related tissue (iatrogenic CJD) or food contaminated by BSE-infected animal products (variant CJD). PrP^{sc} resists protease degradation and facilitates the conversion of still more PrP^c to PrP^{sc}. Resistant to standard sterilizing procedures, including standard autoclaving. Accumulation of PrP^{sc} results in spongiform encephalopathy **A** and dementia, ataxia, and death.

Creutzfeldt-Jakob disease—rapidly progressive dementia, typically sporadic (some familial forms).

Bovine spongiform encephalopathy (BSE)—also known as “mad cow disease.”

Kuru—acquired prion disease noted in tribal populations practicing human cannibalism.

▶ MICROBIOLOGY—SYSTEMS

Normal flora: dominant

LOCATION	MICROORGANISM
Skin	<i>S epidermidis</i>
Nose	<i>S epidermidis</i> ; colonized by <i>S aureus</i>
Oropharynx	Viridans group streptococci
Dental plaque	<i>S mutans</i>
Colon	<i>B fragilis</i> > <i>E coli</i>
Vagina	<i>Lactobacillus</i> , colonized by <i>E coli</i> and group B strep

Neonates delivered by C-section have no flora but are rapidly colonized after birth.

Bugs causing food poisoning

S aureus and *B cereus* food poisoning starts quickly and ends quickly.

MICROORGANISM	SOURCE OF INFECTION
<i>B cereus</i>	Reheated rice. “Food poisoning from reheated rice? Be serious! ” (<i>B cereus</i>)
<i>C botulinum</i>	Improperly canned foods (toxins), raw honey (spores)
<i>C perfringens</i>	Reheated meat
<i>E coli</i> O157:H7	Undercooked meat
<i>Salmonella</i>	Poultry, meat, and eggs
<i>S aureus</i>	Meats, mayonnaise, custard; preformed toxin
<i>V paraahaemolyticus</i> and <i>V vulnificus</i> ^a	Contaminated seafood

^a*V vulnificus* can also cause wound infections from contact with contaminated water or shellfish.

Bugs causing diarrhea

Bloody diarrhea	
<i>Campylobacter</i>	Comma- or S-shaped organisms; growth at 42°C
<i>E histolytica</i>	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
<i>Salmonella</i>	Lactose ⊖; flagellar motility; has animal reservoir, especially poultry and eggs
<i>Shigella</i>	Lactose ⊖; very low ID ₅₀ ; produces Shiga toxin (human reservoir only); bacillary dysentery
<i>Y enterocolitica</i>	Day care outbreaks, pseudoappendicitis
Watery diarrhea	
<i>C difficile</i>	Pseudomembranous colitis; caused by antibiotics; occasionally bloody diarrhea
<i>C perfringens</i>	Also causes gas gangrene
Enterotoxigenic <i>E coli</i>	Travelers' diarrhea; produces heat-labile (LT) and heat-stable (ST) toxins
Protozoa	<i>Giardia</i> , <i>Cryptosporidium</i>
<i>V cholerae</i>	Comma-shaped organisms; rice-water diarrhea; often from infected seafood
Viruses	Rotavirus, norovirus, adenovirus

Common causes of pneumonia

NEONATES (< 4 WK)	CHILDREN (4 WK–18 YR)	ADULTS (18–40 YR)	ADULTS (40–65 YR)	ELDERLY
Group B streptococci	Viruses (RSV)	<i>Mycoplasma</i>	<i>S pneumoniae</i>	<i>S pneumoniae</i>
<i>E coli</i>	Mycoplasma	<i>C pneumoniae</i>	<i>H influenzae</i>	Influenza virus
	C trachomatis	<i>S pneumoniae</i>	Anaerobes	Anaerobes
	(infants–3 yr)	Viruses (eg, influenza)	Viruses	<i>H influenzae</i>
	C pneumoniae		<i>Mycoplasma</i>	Gram ⊖ rods
	(school-aged children)			
	S pneumoniae			
	Runts May Cough			
	Chunky Sputum			

Special groups

Alcoholic	<i>Klebsiella</i> , anaerobes (eg, <i>Peptostreptococcus</i> , <i>Fusobacterium</i> , <i>Prevotella</i> , <i>Bacteroides</i>)
IV drug users	<i>S pneumoniae</i> , <i>S aureus</i>
Aspiration	Anaerobes
Atypical	<i>Mycoplasma</i> , <i>Legionella</i> , <i>Chlamydia</i>
Cystic fibrosis	<i>Pseudomonas</i> , <i>S aureus</i> , <i>S pneumoniae</i> , <i>Burkholderia cepacia</i>
Immunocompromised	<i>S aureus</i> , enteric gram ⊖ rods, fungi, viruses, <i>P jirovecii</i> (with HIV)
Nosocomial (hospital acquired)	<i>S aureus</i> , <i>Pseudomonas</i> , other enteric gram ⊖ rods
Postviral	<i>S pneumoniae</i> , <i>S aureus</i> , <i>H influenzae</i>

Common causes of meningitis

NEWBORN (0–6 MO)	CHILDREN (6 MO–6 YR)	6–60 YR	60 YR +
Group B streptococci	<i>S pneumoniae</i>	<i>S pneumoniae</i>	<i>S pneumoniae</i>
<i>E coli</i>	<i>N meningitidis</i>	<i>N meningitidis</i> (#1 in teens)	Gram ⊖ rods
<i>Listeria</i>	<i>H influenzae</i> type B	Enteroviruses	<i>Listeria</i>
	Enteroviruses	HSV	

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 *H influenzae* meningitis has ↓ greatly with introduction of the conjugate *H influenzae* vaccine in last 10–15 years. Today, cases are usually seen in unimmunized children.

CSF findings in meningitis

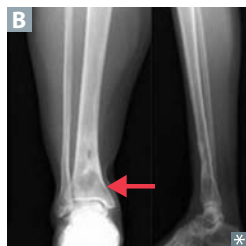
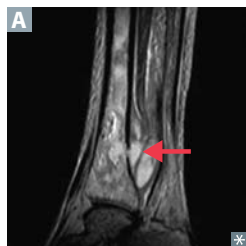
	OPENING PRESSURE	CELL TYPE	PROTEIN	SUGAR
Bacterial	↑	↑ PMNs	↑	↓
Fungal/TB	↑	↑ lymphocytes	↑	↓
Viral	Normal/↑	↑ lymphocytes	Normal/↑	Normal

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



RISK FACTOR	ASSOCIATED INFECTION
Assume if no other information is available	<i>S aureus</i> (most common overall)
Sexually active	<i>Neisseria gonorrhoeae</i> (rare), septic arthritis more common
Sickle cell disease	<i>Salmonella</i> and <i>S aureus</i>
Prosthetic joint replacement	<i>S aureus</i> and <i>S epidermidis</i>
Vertebral involvement	<i>S aureus</i> , <i>Mycobacterium tuberculosis</i> (Pott disease)
Cat and dog bites	<i>Pasteurella multocida</i>
IV drug abuse	<i>Pseudomonas</i> , <i>Candida</i> , <i>S aureus</i> are most common

Elevated C-reactive protein (CRP) and erythrocyte sedimentation rate common but nonspecific. MRI is best for detecting acute infection and detailing anatomic involvement **A**. Radiographs are insensitive early but can be useful in chronic osteomyelitis **B**.

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. Males—infants with congenital defects, vesicoureteral reflux. Elderly—enlarged prostate. Ascension to kidney results in pyelonephritis, which presents with fever, chills, flank pain, costovertebral angle tenderness, hematuria, and WBC casts.

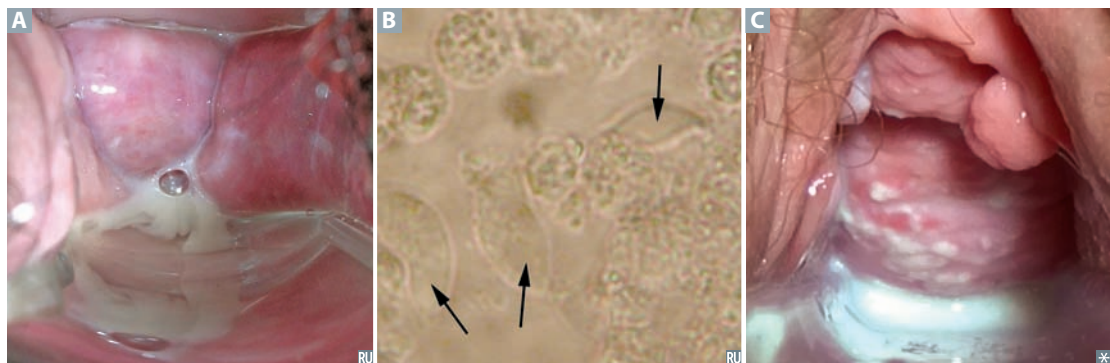
Ten times more common in women (shorter urethras colonized by fecal flora). Other predisposing factors: obstruction, kidney surgery, catheterization, GU malformation, diabetes, pregnancy.

UTI bugs

SPECIES	FEATURES	COMMENTS
<i>Escherichia coli</i>	Leading cause of UTI. Colonies show green metallic sheen on EMB agar.	Diagnostic markers: ⊕ Leukocyte esterase = evidence of WBC activity. ⊕ Nitrite test = reduction of urinary nitrates by bacterial species (eg, <i>E coli</i>). ⊕ Urease test = urease-producing bugs (eg, <i>Proteus</i> , <i>Klebsiella</i>).
<i>Staphylococcus saprophyticus</i>	2nd leading cause of UTI in sexually active women.	
<i>Klebsiella pneumoniae</i>	3rd leading cause of UTI. Large mucoid capsule and viscous colonies.	
<i>Serratia marcescens</i>	Some strains produce a red pigment; often nosocomial and drug resistant.	
<i>Enterococcus</i>	Often nosocomial and drug resistant.	
<i>Proteus mirabilis</i>	Motility causes “swarming” on agar; produces urease; associated with struvite stones.	
<i>Pseudomonas aeruginosa</i>	Blue-green pigment and fruity odor; usually nosocomial and drug resistant.	

Common vaginal infections


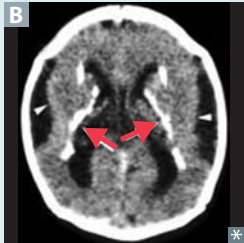
	Bacterial vaginosis	<i>Trichomonas vaginitis</i>	<i>Candida vulvovaginitis</i>
SIGNS AND SYMPTOMS	No inflammation Thin, white discharge A with fishy odor	Inflammation (“strawberry cervix”) Frothy, yellow-green, foul-smelling discharge	Inflammation Thick, white, “cottage cheese” discharge C
LAB FINDINGS	Clue cells pH > 4.5	Motile trichomonads B pH > 4.5	Pseudohyphae pH normal (4.0–4.5)
TREATMENT	Metronidazole	Metronidazole Treat sexual partner(s)	-azoles



ToRCHeS 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 **ToRCHeS** 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
<i>Toxoplasma gondii</i> 	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, polyarthrits, polyarthralgia	Classic triad: abnormalities of eye (cataract) 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, periventricular calcifications 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	Encephalitis, 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

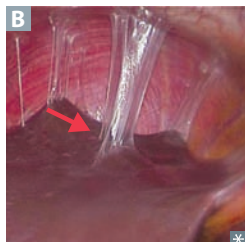
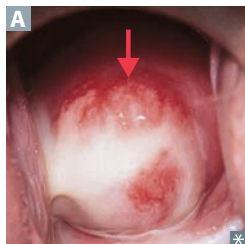
Red rashes of childhood

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
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)	Beginning at head and moving down; rash is 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 (can cause hydrops fetalis in pregnant women)
Rubella virus	Rubella (German measles)	Pink coalescing macules begin at head and move down → fine desquamating truncal rash; postauricular lymphadenopathy
<i>Streptococcus pyogenes</i>	Scarlet fever	Erythematous, sandpaper-like rash C with fever and sore throat
Varicella-Zoster virus	Chickenpox	Vesicular rash begins on trunk; spreads to face and extremities with lesions of different stages



Sexually transmitted infections

DISEASE	CLINICAL FEATURES	ORGANISM
AIDS	Opportunistic infections, Kaposi sarcoma, lymphoma	HIV
Chancroid	Painful genital ulcer with exudate, inguinal adenopathy	<i>Haemophilus ducreyi</i> (it's so painful, you “do cry”)
Chlamydia	Urethritis, cervicitis, epididymitis, conjunctivitis, reactive arthritis, PID	<i>Chlamydia trachomatis</i> (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	<i>Neisseria gonorrhoeae</i>
Hepatitis B	Jaundice	HBV
Lymphogranuloma venereum	Infection of lymphatics; painless genital ulcers, painful lymphadenopathy (ie, buboes)	<i>C trachomatis</i> (L1–L3)
Primary syphilis	Painless chancre	<i>Treponema pallidum</i>
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	<i>Trichomonas vaginalis</i>

Pelvic inflammatory disease

Top bugs—*Chlamydia trachomatis* (subacute, often undiagnosed), *Neisseria gonorrhoeae* (acute). *C trachomatis*—most common bacterial STI in the United States. Cervical motion tenderness (chandelier sign), 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 **Fitz-Hugh–Curtis syndrome**—infection of the liver capsule and “violin string” adhesions of peritoneum to liver **B**.

Nosocomial infections *E coli* (UTI) and *S aureus* (wound infection) are the two most common causes.

RISK FACTOR	PATHOGEN	UNIQUE SIGNS/SYMPTOMS
Antibiotic use	<i>Clostridium difficile</i>	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	<i>S aureus</i> (including MRSA), gram ⊖ anaerobes (<i>Bacteroides</i> , <i>Prevotella</i> , <i>Fusobacterium</i>)	Erythema, tenderness, induration, drainage from surgical wound sites
Intravascular catheters	<i>S aureus</i> (including MRSA), <i>S epidermidis</i> (long term), <i>Enterobacter</i>	Erythema, induration, tenderness, drainage from access sites
Mechanical ventilation, endotracheal intubation	Late onset: <i>P aeruginosa</i> , <i>Klebsiella</i> , <i>Acinetobacter</i> , <i>S aureus</i>	New infiltrate on CXR, ↑ sputum production; sweet odor (<i>Pseudomonas</i>)
Renal dialysis unit, needlestick	HBV	
Urinary catheterization	<i>E coli</i> , <i>Klebsiella</i> , <i>Proteus</i> spp.	Dysuria, leukocytosis, flank pain or costovertebral angle tenderness
Water aerosols	<i>Legionella</i>	Signs of pneumonia, GI symptoms (nausea, vomiting), neurologic abnormalities

Bugs affecting unvaccinated children

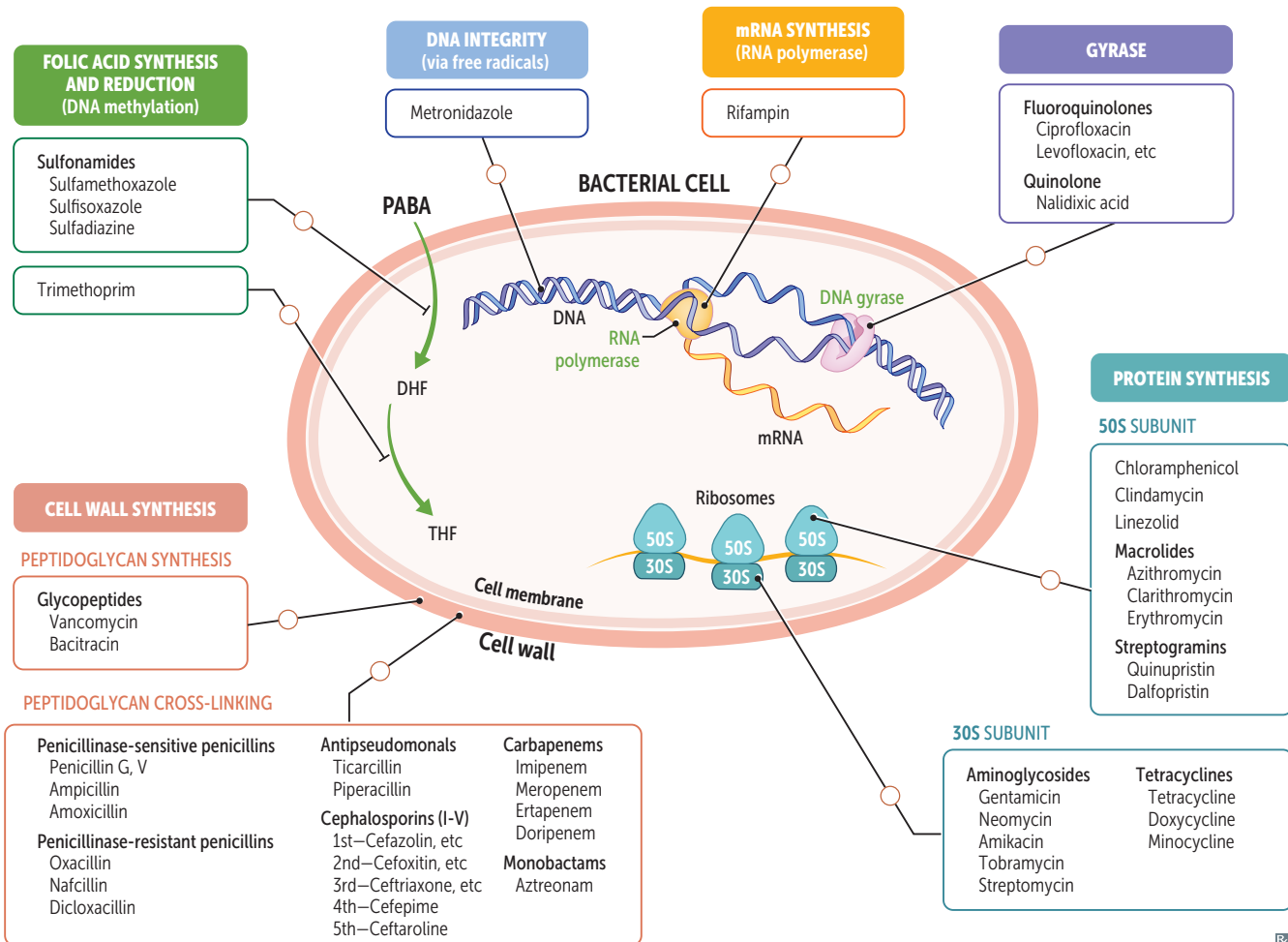
CLINICAL PRESENTATION	FINDINGS/LABS	PATHOGEN
Dermatologic		
Rash	Beginning at head and moving down with postauricular lymphadenopathy	Rubella virus
	Beginning at head and moving down; rash preceded by cough, coryza, conjunctivitis, and blue-white (Koplik) spots on buccal mucosa	Measles virus
Neurologic		
Meningitis	Microbe colonizes nasopharynx	<i>H influenzae</i> type B
	Can also lead to myalgia and paralysis	Poliovirus
Respiratory		
Epiglottitis	Fever with dysphagia, drooling, and difficulty breathing due to edematous “cherry red” epiglottis; “thumbprint sign” on x-ray	<i>H influenzae</i> type B (also capable of causing epiglottitis in fully immunized children)
Pharyngitis	Grayish oropharyngeal exudate (“pseudomembranes” may obstruct airway); painful throat	<i>Corynebacterium diphtheriae</i> (elaborates toxin that causes necrosis in pharynx, cardiac, and CNS tissue)

Bug hints (if all else fails)

CHARACTERISTIC	ORGANISM
Asplenic patient (due to surgical splenectomy or autosplenectomy, eg, chronic sickle cell disease)	Encapsulated microbes, especially SHiN (<i>S pneumoniae</i> >> <i>H influenzae</i> type B > <i>N meningitidis</i>)
Branching rods in oral infection, sulfur granules	<i>Actinomyces israelii</i>
Chronic granulomatous disease	Catalase ⊕ microbes, especially <i>S aureus</i>
“Currant jelly” sputum	<i>Klebsiella</i>
Dog or cat bite	<i>Pasteurella multocida</i>
Facial nerve palsy	<i>Borrelia burgdorferi</i> (Lyme disease)
Fungal infection in diabetic or immunocompromised patient	<i>Mucor</i> or <i>Rhizopus</i> spp.
Health care provider	HBV (from needlestick)
Neutropenic patients	<i>Candida albicans</i> (systemic), <i>Aspergillus</i>
Organ transplant recipient	CMV
PAS ⊕	<i>Tropheryma whipplei</i> (Whipple disease)
Pediatric infection	<i>Haemophilus influenzae</i> (including epiglottitis)
Pneumonia in cystic fibrosis, burn infection	<i>Pseudomonas aeruginosa</i>
Pus, empyema, abscess	<i>S aureus</i>
Rash on hands and feet	Coxsackie A virus, <i>Treponema pallidum</i> , <i>Rickettsia rickettsii</i>
Sepsis/meningitis in newborn	Group B strep
Surgical wound	<i>S aureus</i>
Traumatic open wound	<i>Clostridium perfringens</i>

▶ MICROBIOLOGY—ANTIMICROBIALS

Antimicrobial therapy

**Penicillin G, V**

Penicillin G (IV and IM form), penicillin V (oral). Prototype β -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 (*S pneumoniae*, *S pyogenes*, *Actinomyces*). Also used for gram \ominus cocci (mainly *N meningitidis*) and spirochetes (namely *T pallidum*). Bactericidal for gram \oplus cocci, gram \oplus rods, gram \ominus cocci, and spirochetes. Penicillinase sensitive.

ADVERSE EFFECTS

Hypersensitivity reactions, direct Coombs \oplus hemolytic anemia.

RESISTANCE

Penicillinase in bacteria (a type of β -lactamase) cleaves β -lactam ring.

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 AMP ed-up penicillin. Am O xicillin has greater O ral bioavailability than ampicillin.
CLINICAL USE	Extended-spectrum penicillin— H influenzae, H pylori, E coli, L isteria monocytogenes, P roteus mirabilis, S almonella, S higella, enterococci.	Coverage: ampicillin/amoxicillin HHELPSS kill enterococci.
ADVERSE EFFECTS	Hypersensitivity reactions; rash; pseudomembranous colitis.	
MECHANISM OF RESISTANCE	Penicillinase in bacteria (a type of β -lactamase) cleaves β -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	<i>S aureus</i> (except MRSA; resistant because of altered penicillin-binding protein target site).	“Use naf (nafcillin) for staph .”
ADVERSE EFFECTS	Hypersensitivity reactions, interstitial nephritis.	
Antipseudomonal penicillins	Piperacillin, ticarcillin.	
MECHANISM	Same as penicillin. Extended spectrum.	
CLINICAL USE	<i>Pseudomonas</i> spp. and gram \ominus rods; susceptible to penicillinase; use with β -lactamase inhibitors.	
ADVERSE EFFECTS	Hypersensitivity reactions.	
β-lactamase inhibitors	Include C lavulanic A cid, S ulbactam, T azobactam. Often added to penicillin antibiotics to protect the antibiotic from destruction by β -lactamase (penicillinase).	CAST .

Cephalosporins (generations I–V)

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 : L isteria, A typicals (<i>Chlamydia</i> , <i>Mycoplasma</i>), M RSA, and E nterococci. Exception: ceftaroline (5th generation cephalosporin) covers MRSA.
CLINICAL USE	<p>1st generation (cefazolin, cephalexin)—gram ⊕ cocci, <i>Proteus mirabilis</i>, <i>E coli</i>, <i>Klebsiella pneumoniae</i>. Cefazolin used prior to surgery to prevent <i>S aureus</i> wound infections.</p> <p>2nd generation (cefaclor, cefoxitin, cefuroxime)—gram ⊕ cocci, <i>H influenzae</i>, <i>Enterobacter aerogenes</i>, <i>Neisseria</i> spp., <i>Serratia marcescens</i>, <i>Proteus mirabilis</i>, <i>E coli</i>, <i>Klebsiella pneumoniae</i>.</p> <p>3rd generation (ceftriaxone, cefotaxime, ceftazidime)—serious gram ⊖ infections resistant to other β-lactams.</p> <p>4th generation (cefepime)—gram ⊖ organisms, with ↑ activity against <i>Pseudomonas</i> and gram ⊕ organisms.</p> <p>5th generation (ceftaroline)—broad gram ⊕ and gram ⊖ organism coverage, including MRSA; does not cover <i>Pseudomonas</i>.</p>	<p>1st generation—PEcK.</p> <p>Fake fox fur.</p> <p>2nd generation—HENS PEcK.</p> <p>Ceftriaxone—meningitis, gonorrhea, disseminated Lyme disease.</p> <p>Ceftazidime—<i>Pseudomonas</i>.</p>
ADVERSE EFFECTS	Hypersensitivity reactions, autoimmune hemolytic anemia, disulfiram-like reaction, vitamin K deficiency. Exhibit cross-reactivity with penicillins. ↑ nephrotoxicity of aminoglycosides.	
MECHANISM OF RESISTANCE	Structural change in penicillin-binding proteins (transpeptidases).	

Carbapenems

Imipenem, meropenem, ertapenem, doripenem.

MECHANISM

Imipenem is a broad-spectrum, β -lactamase-resistant carbapenem. Always administered with cilastatin (inhibitor of renal dehydropeptidase I) to \downarrow 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 \oplus cocci, gram \ominus rods, and anaerobes. Wide spectrum, but significant side effects limit use to life-threatening infections or after other drugs have failed. Meropenem has a \downarrow risk of seizures and is stable to dehydropeptidase I.

ADVERSE EFFECTS

GI distress, skin rash, and CNS toxicity (seizures) at high plasma levels.

Monobactams

Aztreonam

MECHANISM

Less susceptible to β -lactamases. Prevents peptidoglycan cross-linking by binding to penicillin-binding protein 3. Synergistic with aminoglycosides. No cross-allergenicity with penicillins.

CLINICAL USE

Gram \ominus rods only—no activity against gram \oplus 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 *C difficile*). Not susceptible to β -lactamases.

CLINICAL USE

Gram \oplus bugs only—serious, multidrug-resistant organisms, including MRSA, *S epidermidis*, sensitive *Enterococcus* species, and *Clostridium difficile* (oral dose for pseudomembranous colitis).

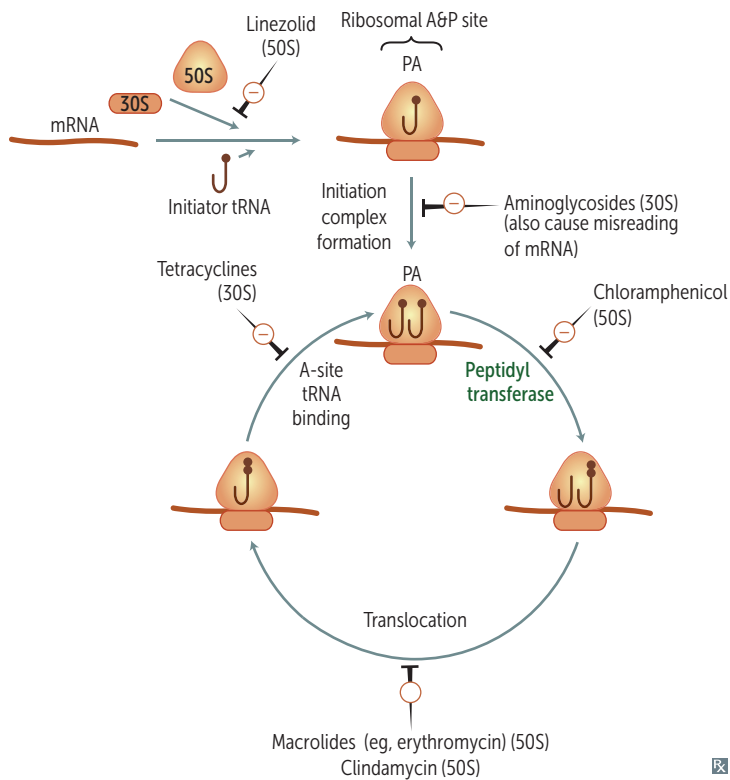
ADVERSE EFFECTS

Well tolerated in general—but **NOT** trouble free. **N**ephrotoxicity, **O**totoxicity, **T**hrombophlebitis, diffuse flushing—**red man syndrome** **A** (can largely prevent by pretreatment with antihistamines and slow infusion rate).

**MECHANISM OF RESISTANCE**

Occurs in bacteria via amino acid modification of **D-ala D-ala** to D-ala D-lac. “Pay back **2 D-als** (dollars) for **v**andalizing (**van**comycin).”

Protein synthesis inhibitors



Specifically target smaller bacterial ribosome (70S, made of 30S and 50S subunits), leaving human ribosome (80S) unaffected.

30S inhibitors

A = Aminoglycosides [bactericidal]

T = Tetracyclines [bacteriostatic]

50S inhibitors

C = Chloramphenicol, Clindamycin [bacteriostatic]

E = Erythromycin (macrolides) [bacteriostatic]

L = Linezolid [variable]

“Buy **AT 30**, **CCEL** (sell) at **50**.”

Aminoglycosides

Gentamicin, Neomycin, Amikacin, Tobramycin, Streptomycin.

“**Mean**” (aminoglycoside) **GNATS** ca**NNOT** kill anaerobes.

MECHANISM

Bactericidal; irreversible inhibition of initiation complex through binding of the 30S subunit. Can cause misreading of mRNA. Also block translocation. Require O₂ 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, Ototoxicity (especially when used with loop diuretics). Teratogen.

MECHANISM OF RESISTANCE

Bacterial transferase enzymes inactivate the drug by acetylation, phosphorylation, or adenylation.

Tetracyclines

Tetracycline, doxycycline, minocycline.

MECHANISM	Bacteriostatic; bind to 30S and prevent attachment of aminoacyl-tRNA; limited CNS penetration. Doxycycline is fecally eliminated and can be used in patients with renal failure. Do not take tetracyclines with milk (Ca^{2+}), antacids (Ca^{2+} or Mg^{2+}), or iron-containing preparations because divalent cations inhibit drugs' absorption in the gut.
CLINICAL USE	<i>Borrelia burgdorferi</i> , <i>M pneumoniae</i> . Drugs' ability to accumulate intracellularly makes them very effective against <i>Rickettsia</i> and <i>Chlamydia</i> . Also used to treat acne.
ADVERSE EFFECTS	GI distress, discoloration of teeth and inhibition of bone growth in children, photosensitivity. Contraindicated in pregnancy.
MECHANISM OF RESISTANCE	↓ uptake or ↑ efflux out of bacterial cells by plasmid-encoded transport pumps.

Chloramphenicol

MECHANISM	Blocks peptidyltransferase at 50S ribosomal subunit. Bacteriostatic.
CLINICAL USE	Meningitis (<i>Haemophilus influenzae</i> , <i>Neisseria meningitidis</i> , <i>Streptococcus pneumoniae</i>) and Rocky Mountain spotted fever (<i>Rickettsia rickettsii</i>). Limited use owing to toxicities but often still used in developing countries because of low cost.
ADVERSE EFFECTS	Anemia (dose dependent), aplastic anemia (dose independent), gray baby syndrome (in premature infants because they lack liver UDP-glucuronyl transferase).
MECHANISM OF RESISTANCE	Plasmid-encoded acetyltransferase inactivates the 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 above the diaphragm vs metronidazole (anaerobic infections below diaphragm).
ADVERSE EFFECTS	Pseudomembranous colitis (<i>C difficile</i> overgrowth), fever, diarrhea.

Oxazolidinones	Linezolid.
MECHANISM	Inhibit 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.
MECHANISM OF RESISTANCE	Point mutation of ribosomal RNA.
Macrolides	Azithromycin, clarithromycin, erythromycin.
MECHANISM	Inhibit protein synthesis by blocking translocation (“macro slides ”); 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 M otility issues, A rrhythmia caused by prolonged Q T interval, acute C holestatic hepatitis, R ash, e Osinophilia. 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.

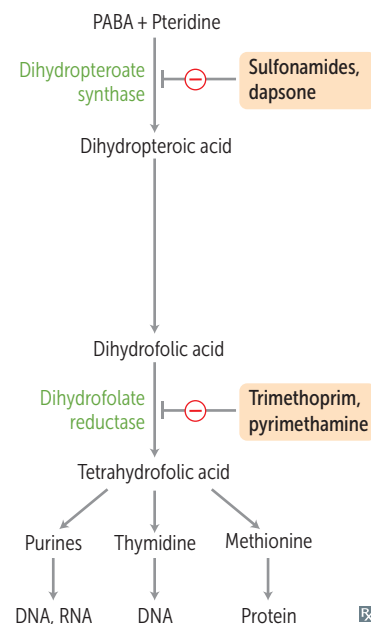
Sulfonamides	
	Sulfamethoxazole (SMX), sulfisoxazole, sulfadiazine.
MECHANISM	Inhibit dihydropteroate synthase, thus inhibiting folate synthesis. Bacteriostatic (bactericidal when combined with trimethoprim).
CLINICAL USE	Gram-⊕, gram ⊖, <i>Nocardia</i> , <i>Chlamydia</i> . SMX for simple UTI.
ADVERSE EFFECTS	Hypersensitivity reactions, hemolysis if G6PD deficient, nephrotoxicity (tubulointerstitial nephritis), photosensitivity, 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.
ADVERSE EFFECTS	Hemolysis if G6PD deficient.

Trimethoprim

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, <i>Shigella</i> , <i>Salmonella</i> , <i>Pneumocystis jirovecii</i> pneumonia treatment and prophylaxis, toxoplasmosis prophylaxis.
ADVERSE EFFECTS	Megaloblastic anemia, leukopenia, granulocytopenia. (May alleviate with supplemental folinic acid). TMP Treats M arrow P oorly.



Fluoroquinolones	
	Ciprofloxacin, norfloxacin, levofloxacin, ofloxacin, moxifloxacin, gemifloxacin, enoxacin.
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>), <i>Neisseria</i> , some gram \oplus organisms.
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. Fluoroquinolones hurt attachments to your bones.
MECHANISM OF RESISTANCE	Chromosome-encoded mutation in DNA gyrase, plasmid-mediated resistance, efflux pumps.

Daptomycin

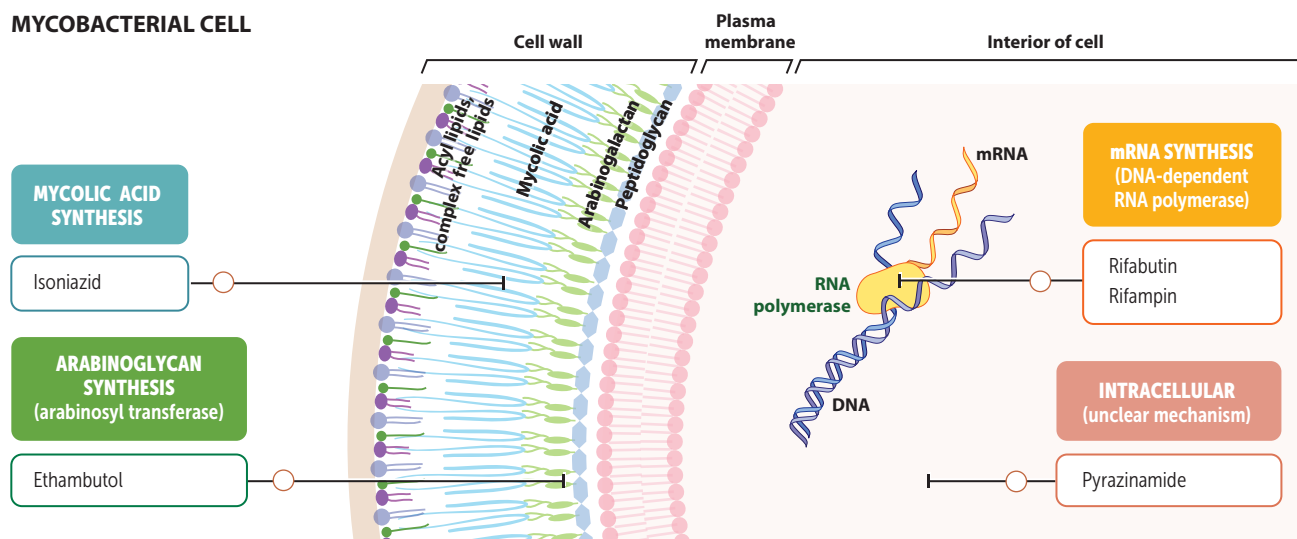
MECHANISM	Lipopeptide that disrupts cell membrane of gram \oplus cocci.
CLINICAL USE	<i>S aureus</i> skin infections (especially MRSA), bacteremia, endocarditis, VRE. Not used for pneumonia (avidly binds to and is inactivated by surfactant).
ADVERSE EFFECTS	Myopathy, rhabdomyolysis.

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> , Anaerobes (<i>Bacteroides</i> , <i>C difficile</i>). Used with a proton pump inhibitor and clarithromycin for “triple therapy” against <i>H Pylori</i> . 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.

Antimycobacterial drugs

BACTERIUM	PROPHYLAXIS	TREATMENT
<i>M tuberculosis</i>	Isoniazid	Rifampin, Isoniazid, Pyrazinamide, Ethambutol (RIPE for treatment)
<i>M avium–intracellulare</i>	Azithromycin, rifabutin	More drug resistant than <i>M tuberculosis</i> . Azithromycin or clarithromycin + ethambutol. Can add rifabutin or ciprofloxacin.
<i>M leprae</i>	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.	<p>Rifampin's 4 R's:</p> <ul style="list-style-type: none"> RNA polymerase inhibitor Ramps up microsomal cytochrome P-450 Red/orange body fluids Rapid resistance if used alone <p>Rifampin ramps up cytochrome P-450, but rifabutin does not.</p>
CLINICAL USE	<i>Mycobacterium tuberculosis</i> ; delay resistance to dapsone when used for leprosy. Used for meningococcal prophylaxis and chemoprophylaxis in contacts of children with <i>Haemophilus influenzae</i> type B.	
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.	
MECHANISM OF RESISTANCE	Mutations reduce drug binding to RNA polymerase. Monotherapy rapidly leads to resistance.	

Isoniazid

MECHANISM	↓ synthesis of mycolic acids. Bacterial catalase-peroxidase (encoded by KatG) needed to convert INH to active metabolite.	
CLINICAL USE	<i>Mycobacterium tuberculosis</i> . 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, P-450 inhibition, drug-induced SLE, vitamin B ₆ deficiency (peripheral neuropathy, sideroblastic anemia). Administer with pyridoxine (B ₆).	INH Injures Neurons and Hepatocytes.
MECHANISM OF RESISTANCE	Mutations leading to underexpression of KatG.	

Pyrazinamide

MECHANISM	Mechanism uncertain. Pyrazinamide is a prodrug that is converted to the active compound pyrazinoic acid. Works best at acidic pH (eg, in host phagolysosomes).	
CLINICAL USE	<i>Mycobacterium tuberculosis</i> .	
ADVERSE EFFECTS	Hyperuricemia, hepatotoxicity.	

Ethambutol

MECHANISM	↓ carbohydrate polymerization of mycobacterium cell wall by blocking arabinosyltransferase.	
CLINICAL USE	<i>Mycobacterium tuberculosis</i> .	
ADVERSE EFFECTS	Optic neuropathy (red-green color blindness). Pronounce “ ey thambutol.”	

Streptomycin

MECHANISM	Interferes with 30S component of ribosome.	
CLINICAL USE	<i>Mycobacterium tuberculosis</i> (2nd line).	
ADVERSE EFFECTS	Tinnitus, vertigo, ataxia, nephrotoxicity.	

Antimicrobial prophylaxis

CLINICAL SCENARIO	MEDICATION
High risk for endocarditis and undergoing surgical or dental procedures	Amoxicillin
Exposure to gonorrhea	Ceftriaxone
History of recurrent UTIs	TMP-SMX
Exposure to meningococcal infection	Ceftriaxone, ciprofloxacin, or rifampin
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 <i>S aureus</i>	Cefazolin
Prophylaxis of strep pharyngitis in child with prior rheumatic fever	Benzathine penicillin G or oral penicillin V
Exposure to syphilis	Benzathine penicillin G

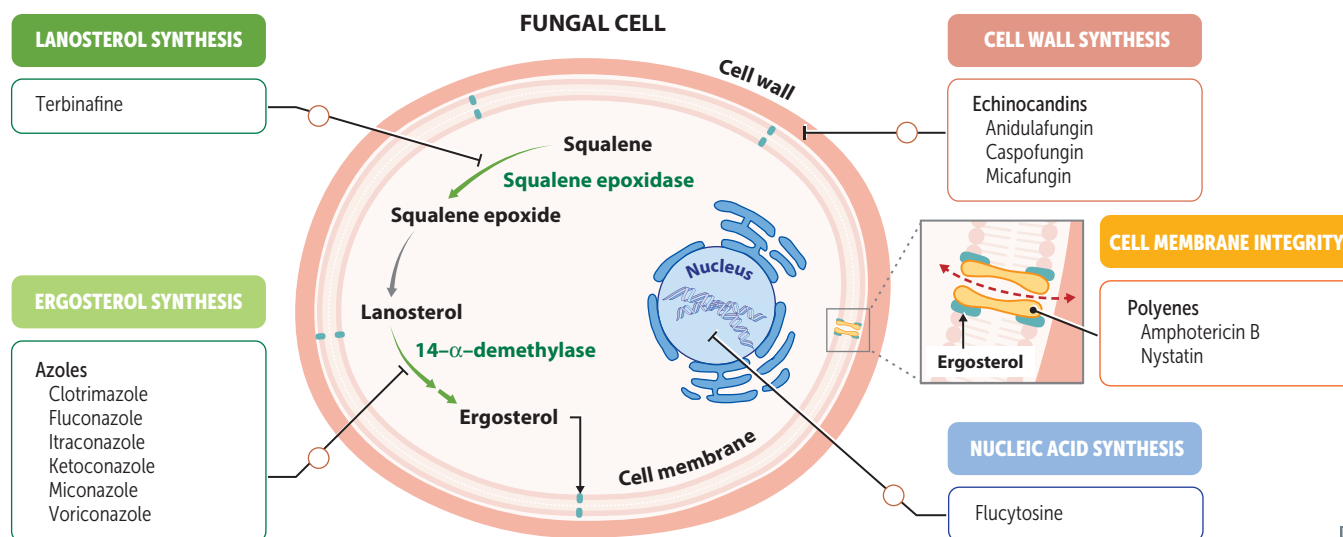
Prophylaxis in HIV patients

CELL COUNT	PROPHYLAXIS	INFECTION
CD4 < 200 cells/mm ³	TMP-SMX	<i>Pneumocystis pneumonia</i>
CD4 < 100 cells/mm ³	TMP-SMX	<i>Pneumocystis pneumonia</i> and toxoplasmosis
CD4 < 50 cells/mm ³	Azithromycin or clarithromycin	<i>Mycobacterium avium</i> complex

Treatment of highly resistant bacteria

MRSA: vancomycin, daptomycin, linezolid, tigecycline, ceftaroline.
 VRE: linezolid and streptogramins (quinupristin, dalfopristin).
 Multidrug-resistant *P aeruginosa*, multidrug-resistant *Acinetobacter baumannii*: polymyxins B and E (colistin).

Antifungal therapy



Amphotericin B

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 fungal meningitis. Supplement K ⁺ and Mg ²⁺ 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 caused by <i>Cryptococcus</i>) in combination with amphotericin B.
ADVERSE EFFECTS	Bone marrow suppression.

Azoles

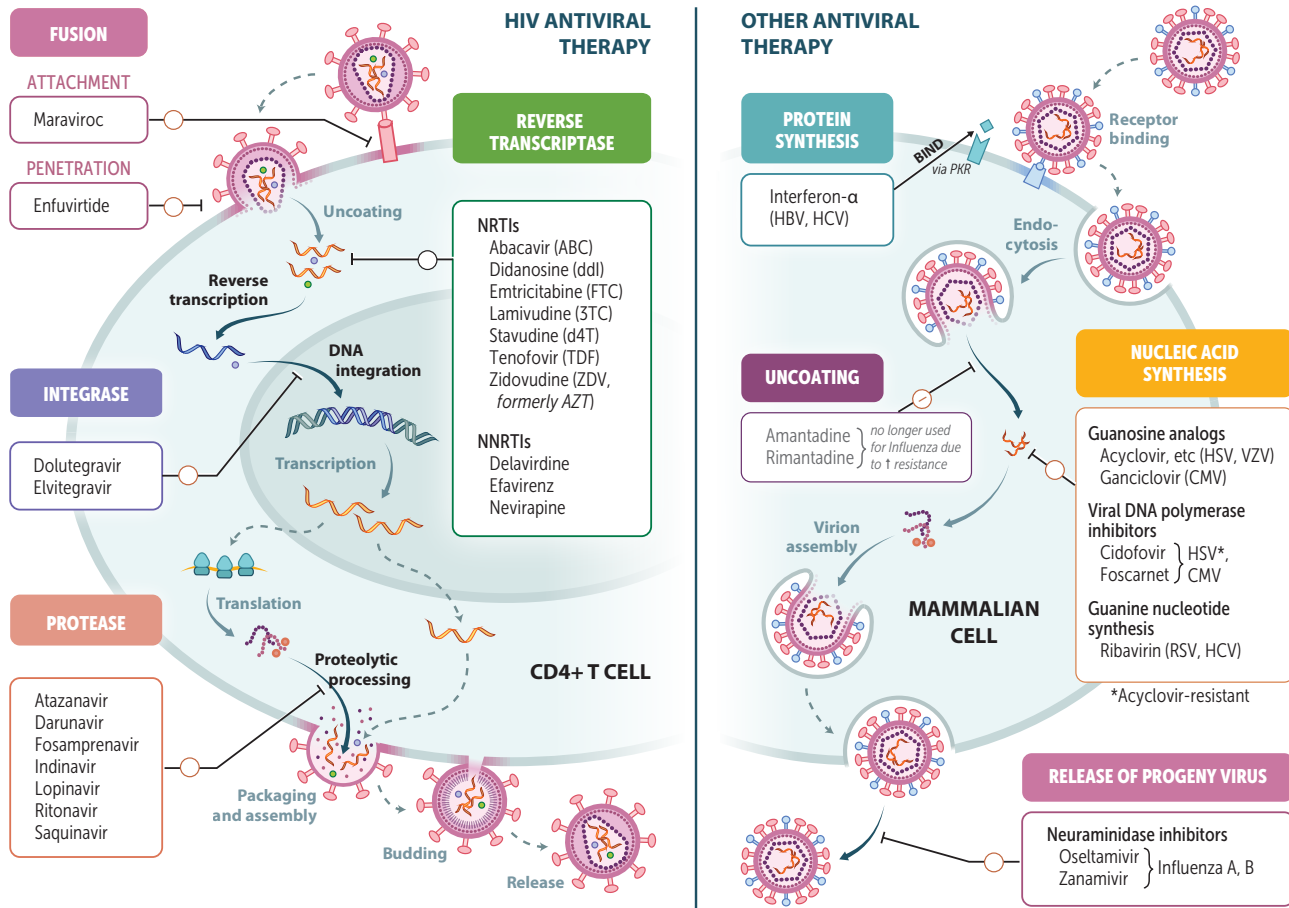
	Clotrimazole, fluconazole, itraconazole, ketoconazole, miconazole, voriconazole.
MECHANISM	Inhibit fungal sterol (ergosterol) synthesis by inhibiting the cytochrome P-450 enzyme that converts lanosterol to ergosterol.
CLINICAL USE	Local and less serious systemic mycoses. Fluconazole for chronic suppression of cryptococcal meningitis in AIDS patients and candidal infections of all types. Itraconazole for <i>Blastomyces</i> , <i>Coccidioides</i> , <i>Histoplasma</i> . Clotrimazole and miconazole for topical fungal infections.
ADVERSE EFFECTS	Testosterone synthesis inhibition (gynecomastia, especially with ketoconazole), liver dysfunction (inhibits cytochrome P-450).

Terbinafine

MECHANISM	Inhibits the fungal enzyme squalene epoxidase.
CLINICAL USE	Dermatophytoses (especially onychomycosis—fungal infection of finger or toe nails).
ADVERSE EFFECTS	GI upset, headaches, hepatotoxicity, taste disturbance.

Echinocandins	Anidulafungin, caspofungin, micafungin.	
MECHANISM	Inhibit cell wall synthesis by inhibiting synthesis of β -glucan.	
CLINICAL USE	Invasive aspergillosis, <i>Candida</i> .	
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, \uparrow cytochrome P-450 and warfarin metabolism.	
Antiprotozoan therapy	Pyrimethamine (toxoplasmosis), suramin and melarsoprol (<i>Trypanosoma brucei</i>), nifurtimox (<i>T cruzi</i>), sodium stibogluconate (leishmaniasis).	
Anti-mite/louse therapy	Permethrin (blocks Na^+ channels \rightarrow neurotoxicity), malathion (acetylcholinesterase inhibitor), lindane (blocks GABA channels \rightarrow neurotoxicity). Used to treat scabies (<i>Sarcoptes scabiei</i>) and lice (<i>Pediculus</i> and <i>Pthirus</i>).	Treat PML (Pesty M ites and L ice) with PML (Permethrin, M alathion, L indane), because they NAG you (N a, AChE , GABA blockade).
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 \downarrow 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).	
Anthelmintic therapy	Mebendazole (microtubule inhibitor), pyrantel pamoate, ivermectin, diethylcarbamazine, praziquantel.	

Antiviral therapy



Oseltamivir, zanamivir

MECHANISM	Inhibit influenza neuraminidase → ↓ release of progeny virus.
CLINICAL USE	Treatment and prevention of both influenza A and B.

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 renal failure if not adequately hydrated.
MECHANISM OF RESISTANCE	Mutated viral thymidine kinase.

Ganciclovir

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 = pyro fos phate 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 and IV saline to ↓ toxicity).

HIV therapy

Highly active antiretroviral therapy (HAART): often initiated at the time of HIV diagnosis. Strongest indication for patients presenting with AIDS-defining illness, low CD4+ cell counts (< 500 cells/mm³), or high viral load. Regimen consists of 3 drugs to prevent resistance: 2 NRTIs and preferably an integrase inhibitor.

DRUG	MECHANISM	TOXICITY
NRTIs		
Abacavir (ABC) Didanosine (ddI) 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). T enofovir is a nucleotide; the others are nucleosides and need to be phosphorylated to be active. ZDV can be used for general prophylaxis and during pregnancy to ↓ 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.
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. Delavirdine and efavirenz are contraindicated in pregnancy.
Protease inhibitors		
Atazanavir Darunavir Fosamprenavir Indinavir Lopinavir Ritonavir Saquinavir	Assembly of virions depends on HIV-1 protease (<i>pol</i> 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. All protease inhibitors end in <i>-navir</i> . Navir (never) tease a protease .	Hyperglycemia, GI intolerance (nausea, diarrhea), lipodystrophy (Cushing-like syndrome). Nephropathy, hematuria (indinavir). Rifampin (a potent CYP/UGT inducer) contraindicated with protease inhibitors because it can decrease protease inhibitor concentration.
Integrase inhibitors		
Raltegravir Elvitegravir Dolutegravir	Inhibits HIV genome integration into host cell chromosome by reversibly inhibiting HIV integrase.	↑ creatine kinase.
Fusion inhibitors		
Enfuvirtide Maraviroc	Binds gp41, inhibiting viral entry. Binds CCR-5 on surface of T cells/monocytes, inhibiting interaction with gp120.	Skin reaction at injection sites.

Interferons

MECHANISM	Glycoproteins normally synthesized by virus-infected cells, exhibiting a wide range of antiviral and antitumoral properties.
CLINICAL USE	IFN- α : chronic hepatitis B and C, Kaposi sarcoma, hairy cell leukemia, condyloma acuminatum, renal cell carcinoma, malignant melanoma. IFN- β : multiple sclerosis. IFN- γ : chronic granulomatous disease.
ADVERSE EFFECTS	Flu-like symptoms, depression, neutropenia, myopathy.

Hepatitis C therapy

DRUG	MECHANISM	CLINICAL USE
Ribavirin	Inhibits synthesis of guanine nucleotides by competitively inhibiting inosine monophosphate dehydrogenase.	Chronic HCV; also used in RSV (palivizumab preferred in children) Adverse effects: hemolytic anemia; severe teratogen.
Sofosbuvir	Inhibits HCV RNA-dependent RNA polymerase acting as a chain terminator.	Chronic HCV in combination with ribavirin, +/- peginterferon alfa. Do not use as monotherapy. Adverse effects: fatigue, headache, nausea.
Simeprevir	HCV protease inhibitor; prevents viral replication.	Chronic HCV in combination with ledipasvir (NS5A inhibitor). Do not use as monotherapy. Adverse effects: photosensitivity reactions, rash.

Infection control techniques

	Goals include the reduction of pathogenic organism counts to safe levels (disinfection) and the inactivation of self-propagating biological entities (sterilization).
Autoclave	Pressurized steam at > 120°C. May be sporicidal.
Alcohols	Denature proteins and disrupt cell membranes. Not sporicidal.
Chlorhexidine	Denatures proteins and disrupts cell membranes. Not sporicidal.
Hydrogen peroxide	Free radical oxidation. Sporicidal.
Iodine and iodophors	Halogenation of DNA, RNA, and proteins. May be sporicidal.

Antimicrobials to avoid in pregnancy

ANTIMICROBIAL	ADVERSE EFFECT
Sulfonamides	Kernicterus
Aminoglycosides	Ototoxicity
Fluoroquinolones	Cartilage damage
Clarithromycin	Embryotoxic
Tetracyclines	Discolored teeth, inhibition of bone growth
Ribavirin	Teratogenic
Griseofulvin	Teratogenic
Chloramphenicol	Gray baby syndrome

SAFE Children **T**ake **R**eally **G**ood **C**are.

Immunology

“I hate to disappoint you, but my rubber lips are immune to your charms.”

—Batman & Robin

“No State shall make or enforce any law which shall abridge the privileges or immunities of citizens of the United States . . .”

—The United States Constitution

Mastery of the basic principles and facts in the immunology section will be useful for the Step 1 exam. Cell surface markers are important to know because they are clinically useful (eg, in identifying specific types of immunodeficiency or cancer) and are functionally critical to the jobs immune cells carry out. By spending a little extra effort here, it is possible to turn a traditionally difficult subject into one that is high yield.

▶ Lymphoid Structures 190

▶ Lymphocytes 192

▶ Immune Responses 198

▶ Immunosuppressants 212

▶ IMMUNOLOGY—LYMPHOID STRUCTURES

Lymph node

A 2° lymphoid organ that has many afferents, 1 or more efferents. Encapsulated, with trabeculae. Functions are nonspecific filtration by macrophages, storage 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 dormant. 2° follicles have pale central germinal centers and are active.

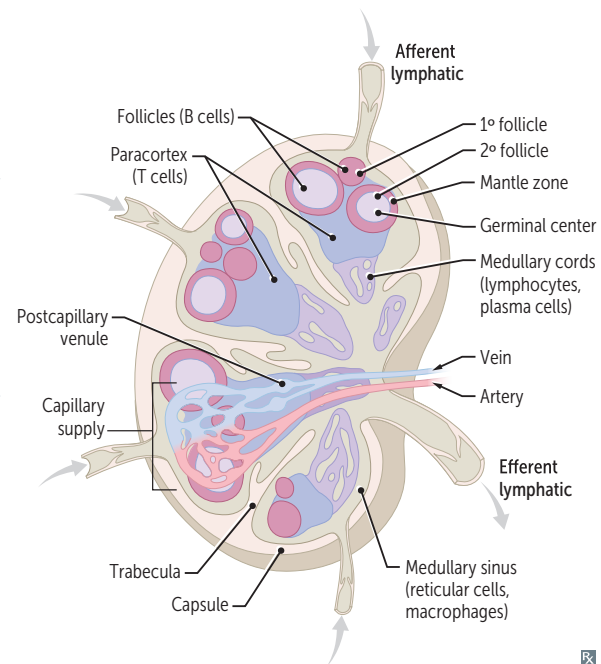
Medulla

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

Houses 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, viral infection).

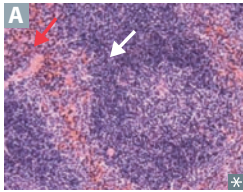
**Lymph drainage**

LYMPH NODE CLUSTER	AREA OF BODY DRAINED
Cervical	Head and neck
Hilar	Lungs
Mediastinal	Trachea and esophagus
Axillary	Upper limb, breast, skin above umbilicus
Celiac	Liver, stomach, spleen, pancreas, upper duodenum
Superior mesenteric	Lower duodenum, jejunum, ileum, colon to splenic flexure
Inferior mesenteric	Colon from splenic flexure to upper rectum
Internal iliac	Lower rectum to anal canal (above pectinate line), bladder, vagina (middle third), cervix, prostate
Para-aortic	Testes, ovaries, kidneys, uterus
Superficial inguinal	Anal canal (below pectinate line), skin below umbilicus (except popliteal area), scrotum, vulva
Popliteal	Dorsolateral foot, posterior calf

Right lymphatic duct drains right side of body above diaphragm.

Thoracic duct drains everything else into junction of left subclavian and internal jugular veins.

Sinusoids of spleen



Long, vascular channels in red pulp (red arrow in **A**) with fenestrated “barrel hoop” basement membrane.

- T cells are found in the periarteriolar lymphatic sheath (PALS) within the white pulp (white arrow 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 antigen-presenting cells (APCs) capture blood-borne antigens for recognition by lymphocytes.

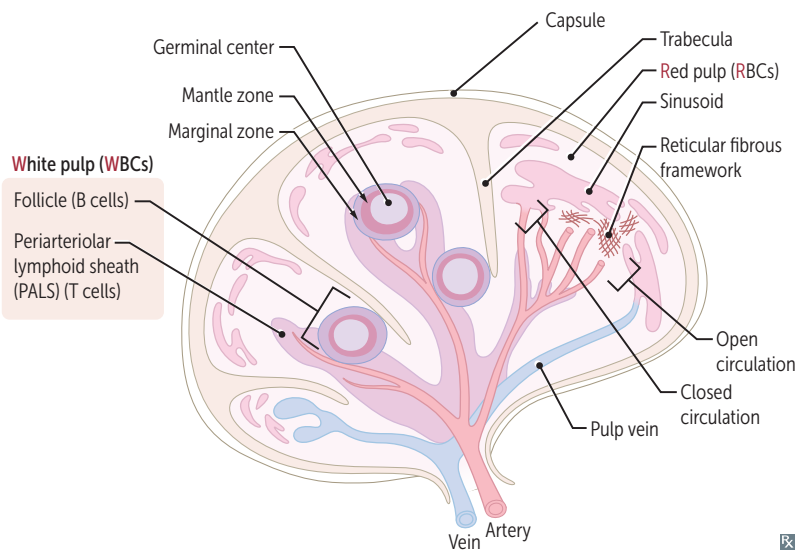
Macrophages found nearby in spleen remove encapsulated bacteria.

Splenic dysfunction (eg, postsplenectomy, sickle cell disease): ↓ IgM → ↓ complement activation → ↓ C3b opsonization → ↑ susceptibility to encapsulated organisms (**Please SHINE my SKiS**):

- *Pseudomonas aeruginosa*
- *Streptococcus pneumoniae*
- *Haemophilus Influenzae* type b
- *Neisseria meningitidis*
- *Escherichia coli*
- *Salmonella* spp.
- *Klebsiella pneumoniae*
- Group B *Streptococci*

Postsplenectomy:

- Howell-Jolly bodies (nuclear remnants)
- Target cells
- Thrombocytosis (loss of sequestration and removal)
- Lymphocytosis (loss of sequestration)



Thymus

Located in the anterosuperior mediastinum. Site of T-cell differentiation and maturation. Encapsulated. **T**hymus is derived from the **T**hird pharyngeal pouch. Lymphocytes of mesenchymal origin. Cortex is dense with immature T cells; medulla is pale with mature T cells and Hassall corpuscles containing epithelial reticular cells.

T cells = **T**hymus

B cells = **B**one marrow

Hypoplastic in DiGeorge syndrome and severe combined immunodeficiency (SCID).

Enlarged in myasthenia gravis.

▶ IMMUNOLOGY—LYMPHOCYTES

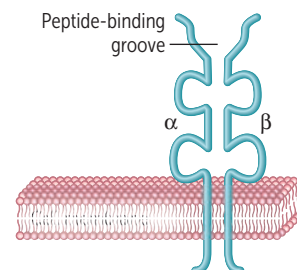
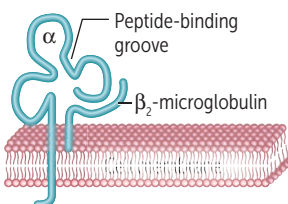
Innate vs adaptive immunity

	Innate immunity	Adaptive immunity
COMPONENTS	Neutrophils, macrophages, monocytes, dendritic cells, natural killer (NK) cells (lymphoid origin), complement	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)	Highly specific, refined over time Develops over long periods; memory response is faster and more robust
PHYSICAL BARRIERS	Epithelial tight junctions, mucus	—
SECRETED PROTEINS	Lysozyme, complement, C-reactive protein (CRP), defensins	Immunoglobulins
KEY FEATURES IN PATHOGEN RECOGNITION	Toll-like receptors (TLRs): pattern recognition receptors that recognize pathogen-associated molecular patterns (PAMPs). Examples of PAMPs include LPS (gram \ominus bacteria), flagellin (bacteria), nucleic acids (viruses).	Memory cells: activated B and T cells; subsequent exposure to a previously encountered antigen \rightarrow stronger, quicker immune response

MHC I and II

MHC encoded by HLA genes. Present antigen fragments to T cells and bind T-cell receptors (TCRs).

	MHC I (1 letter)	MHC II (2 letters)
LOCI	HLA-A, HLA-B, HLA-C	HLA-DP, HLA-DQ, HLA-DR
BINDING	TCR and CD8	TCR and CD4
EXPRESSION	Expressed on all nucleated cells Not expressed on RBCs	Expressed on APCs
FUNCTION	Present endogenously synthesized antigens (eg, viral or cytosolic proteins) to CD8+ cytotoxic T cells	Present exogenously synthesized 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	β_2 -microglobulin	Invariant chain



HLA subtypes associated with diseases

A3	Hemochromatosis.	
B8	Addison disease, myasthenia gravis.	
B27	P soriatic arthritis, A nkylosing spondylitis, I BD-associated arthritis, R eactive arthritis (formerly Reiter syndrome).	PAIR. Also known as seronegative arthropathies.
DQ2/DQ8	Celiac disease.	I ate (8) too (2) much gluten at Dairy Queen.
DR2	Multiple sclerosis, hay fever, SLE, Goodpasture syndrome.	
DR3	Diabetes mellitus type 1, SLE, Graves disease, Hashimoto thyroiditis, Addison disease.	
DR4	R heumatoid arthritis, diabetes mellitus type 1, Addison disease.	There are 4 walls in a “ rheum ” (room).
DR5	Pernicious anemia → vitamin B ₁₂ deficiency, Hashimoto thyroiditis.	

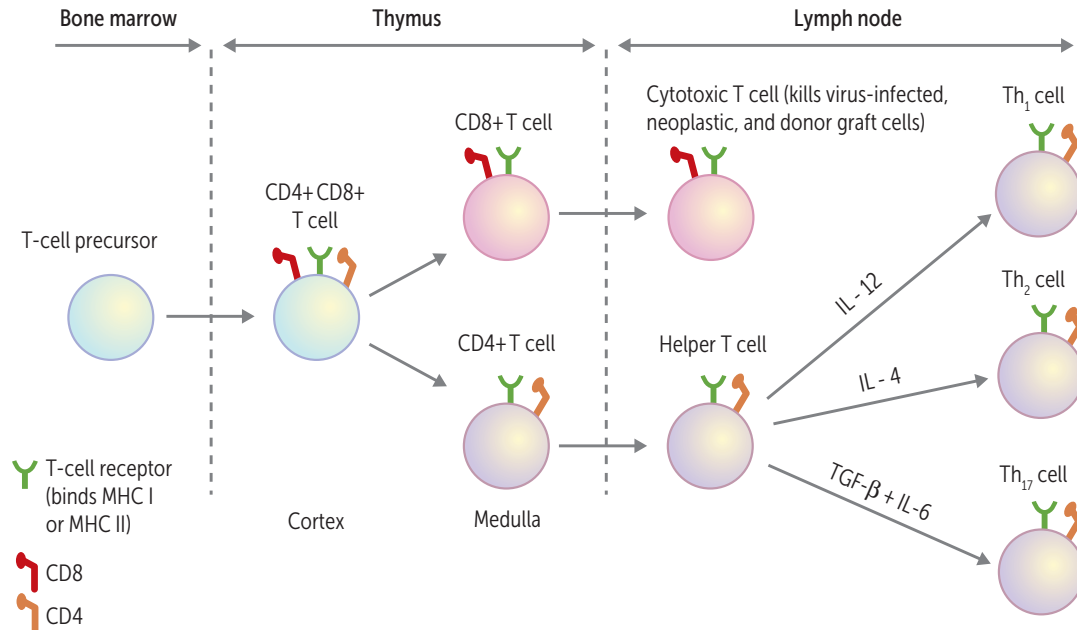
Natural killer cells

Use perforin and granzymes to induce apoptosis of virally infected cells and tumor cells.
 Lymphocyte member of innate immune system.
 Activity enhanced by IL-2, IL-12, IFN- α , and IFN- β .
 Induced to kill when exposed to a nonspecific activation signal on target cell and/or to an absence of class I MHC on target cell surface.
 Also kills via antibody-dependent cell-mediated cytotoxicity (CD16 binds Fc region of bound Ig, activating the NK cell).

Major functions of B and T cells

B-cell functions	Recognize 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-cell functions	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 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.

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. Tissue-restricted self-antigens are expressed in the thymus due to the action of autoimmune regulator (AIRE); deficiency leads to autoimmune polyendocrine syndrome-1.

Helper T cells

Th1 cell

Secretes IFN- γ
 Activates macrophages and cytotoxic T cells
 Differentiation induced by IFN- γ and IL-12
 Inhibited by IL-4 and IL-10 (from Th2 cell)

Th2 cell

Secretes IL-4, IL-5, IL-10, IL-13
 Recruits eosinophils for parasite defense and promotes IgE production by B cells
 Differentiation induced by IL-4
 Inhibited by IFN- γ (from Th1 cell)

Macrophage-lymphocyte interaction—macrophages and other APCs release IL-12, which stimulates T cells to differentiate into Th1 cells. Th1 cells release IFN- γ to stimulate macrophages.

Helper T cells have CD4, which binds to MHC II on APCs.

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 and CD8 T-cell effector functions. Identified by expression of CD3, CD4, CD25, and FOXP3.
 Activated regulatory T cells produce anti-inflammatory cytokines (eg, IL-10, TGF- β).

T- and B-cell activation APCs: B cells, macrophages, dendritic cells.

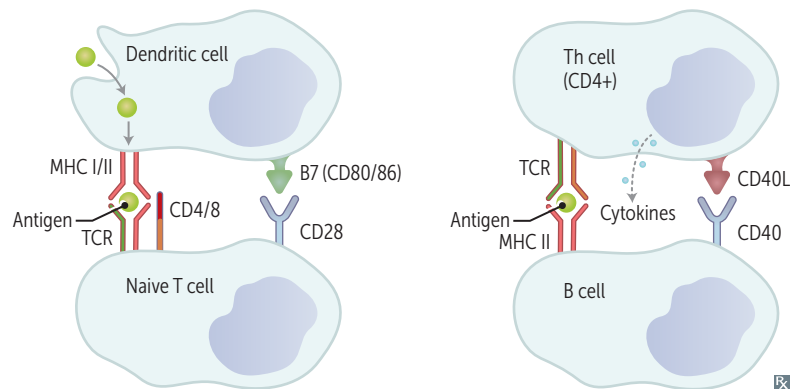
Two signals are required for T-cell activation, B-cell activation, and class switching.

Naive T-cell activation

1. Dendritic cell (specialized APC) samples and processes antigen.
2. Dendritic cell migrates to the draining lymph node.
3. T-cell activation (signal 1): antigen is presented on MHC II and recognized by TCR on Th (CD4+) cell. Endogenous antigen is presented on MHC I to Tc (CD8+) cell.
4. Proliferation and survival (signal 2): costimulatory signal via interaction of B7 proteins (CD80/86) and CD28.
5. Th cell activates and produces cytokines. Tc cell activates and is able to recognize and kill virus-infected cell.

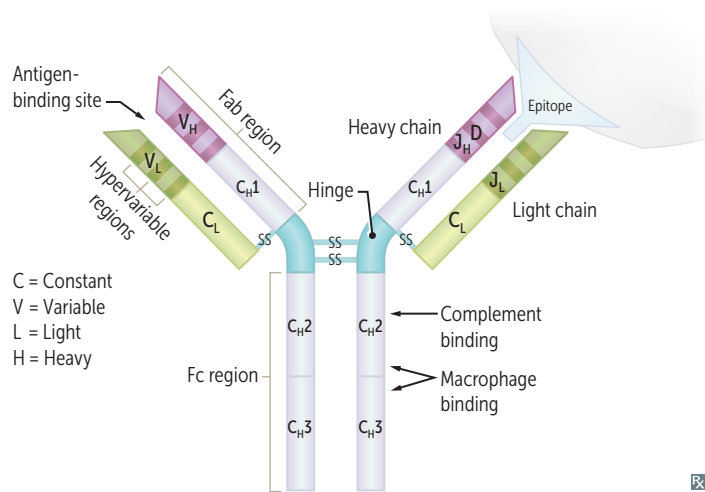
B-cell activation and class switching

1. Th-cell activation as above.
2. B-cell receptor–mediated endocytosis; foreign antigen is presented on MHC II and recognized by TCR on Th cell.
3. CD40 receptor on B cell binds CD40 ligand (CD40L) on Th cell.
4. Th cell secretes cytokines that determine Ig class switching of B cell. B cell activates and undergoes class switching, affinity maturation, and antibody production.



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:

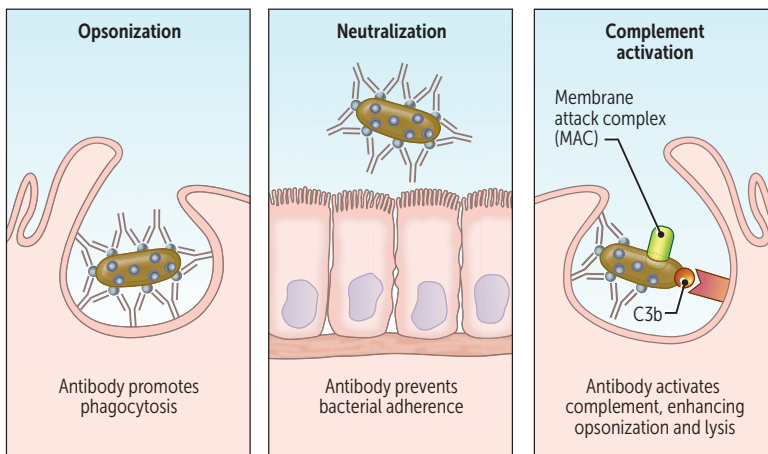
- Constant
- Carboxy terminal
- Complement binding
- Carbohydrate side chains
- Determines isotype (IgM, IgD, etc)

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)

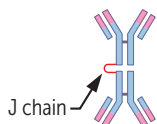


Immunoglobulin isotypes

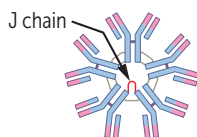
All isotypes can exist as monomers. Mature, naive B cells prior to activation express IgM and IgD on their surfaces. They may differentiate in germinal centers of lymph nodes by isotype switching (gene rearrangement; mediated by cytokines and CD40L) into plasma cells that secrete IgA, IgE, or IgG.

IgG

Main antibody in 2° (**delayed**) response to an antigen. Most abundant isotype in serum. Fixes complement, crosses the placenta (provides infants with passive immunity), opsonizes bacteria, neutralizes bacterial toxins and viruses.

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 but does not cross the placenta. 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. Mediates immunity to worms by activating eosinophils. Lowest concentration in serum.

Antigen type and memory**Thymus-independent antigens**

Antigens lacking a peptide component (eg, lipopolysaccharides from gram \ominus bacteria); cannot be presented by MHC to T cells. Weakly immunogenic; vaccines often require boosters and adjuvants (eg, pneumococcal polysaccharide vaccine).

Thymus-dependent antigens

Antigens containing a protein component (eg, diphtheria vaccine). Class switching and immunologic memory occur as a result of direct contact of B cells with Th cells (CD40–CD40L interaction).

▶ IMMUNOLOGY—IMMUNE RESPONSES

Acute-phase reactants 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.

POSITIVE (UPREGULATED)

C-reactive protein	Opsonin; fixes complement and facilitates phagocytosis. Measured clinically as a sign of ongoing inflammation.
Ferritin	Binds and sequesters iron to inhibit microbial iron scavenging.
Fibrinogen	Coagulation factor; promotes endothelial repair; correlates with ESR.
Hepcidin	↓ iron absorption (by degrading ferroportin) and ↓ iron release (from macrophages) → anemia of chronic disease.
Serum amyloid A	Prolonged elevation can lead to amyloidosis.

NEGATIVE (DOWNREGULATED)

Albumin	Reduction conserves amino acids for positive reactants.
Transferrin	Internalized by macrophages to sequester iron.

Complement

System of hepatically synthesized plasma proteins that play a role in innate immunity and inflammation. Membrane attack complex (MAC) defends against gram \ominus bacteria.

ACTIVATION

Classic pathway—IgG or IgM mediated.

GM makes **classic** cars.

Alternative pathway—microbe surface molecules.

Lectin pathway—mannose or other sugars on microbe surface.

FUNCTIONS

C3b—opsonization.

C3b binds bacteria.

C3a, C4a, C5a—anaphylaxis.

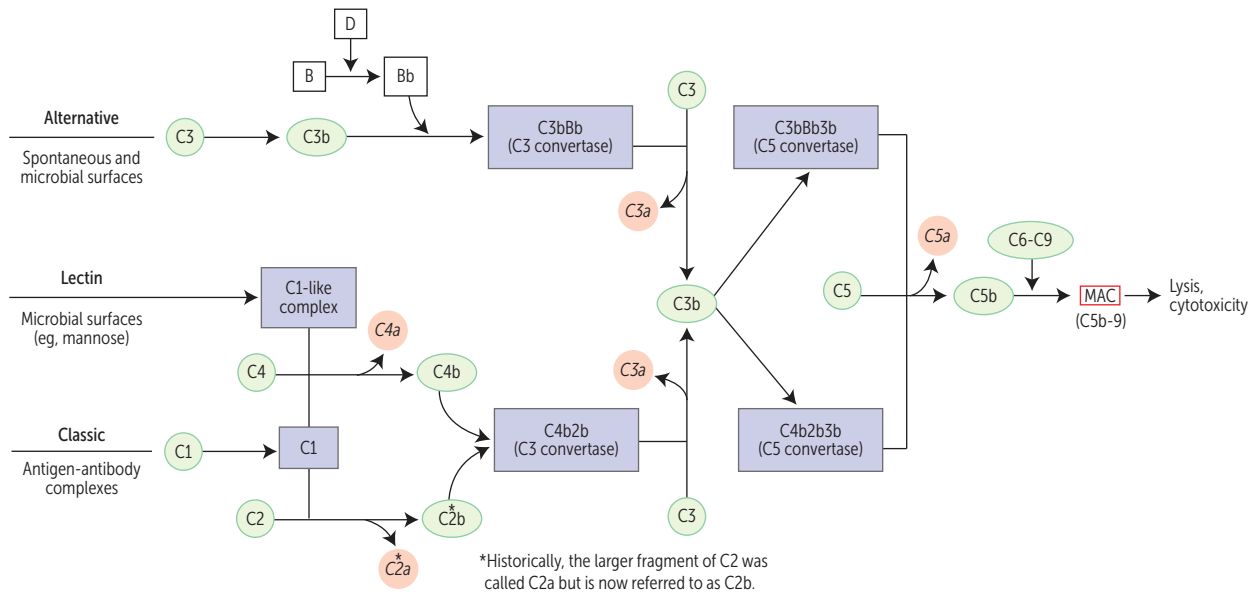
C5a—neutrophil chemotaxis.

C5b-9—cytolysis by MAC.

Opsonins—C3b and IgG are the two 1° opsonins in bacterial defense; enhance phagocytosis. C3b also helps clear immune complexes.

Opsonin (Greek) = to prepare for eating.

Inhibitors—decay-accelerating factor (DAF, aka CD55) and C1 esterase inhibitor help prevent complement activation on self cells (eg, RBCs).



Complement disorders

C1 esterase inhibitor deficiency

Causes hereditary angioedema due to unregulated activation of kallikrein → ↑ bradykinin. ACE inhibitors are contraindicated.

C3 deficiency

Increases risk of severe, recurrent pyogenic sinus and respiratory tract infections; ↑ susceptibility to type III hypersensitivity reactions.

C5–C9 deficiencies

Terminal complement deficiency increases susceptibility to recurrent *Neisseria* bacteremia.

DAF (GPI-anchored enzyme) deficiency

Causes complement-mediated lysis of RBCs and paroxysmal nocturnal hemoglobinuria.

Important cytokines

SECRETED BY MACROPHAGES

IL-1	Also called osteoclast-activating factor. Causes fever, acute inflammation. Activates endothelium to express adhesion molecules. Induces chemokine secretion to recruit WBCs.	“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 aK ute-phase protein production.
IL-6	Causes fever and stimulates production of acute-phase proteins.	
IL-8	Major chemotactic factor for neutrophils.	“Clean up on aisle 8.” Neutrophils are recruited by IL-8 to clear infections.
IL-12	Induces differentiation of T cells into Th1 cells. Activates NK cells.	
TNF-α	Mediates septic shock. Activates endothelium. Causes WBC recruitment, vascular leak.	Causes cachexia in malignancy.

SECRETED BY ALL T CELLS

IL-2	Stimulates growth of helper, cytotoxic, and regulatory T cells, and NK cells.	
IL-3	Supports growth and differentiation of bone marrow stem cells. Functions like GM-CSF.	

FROM Th1 CELLS

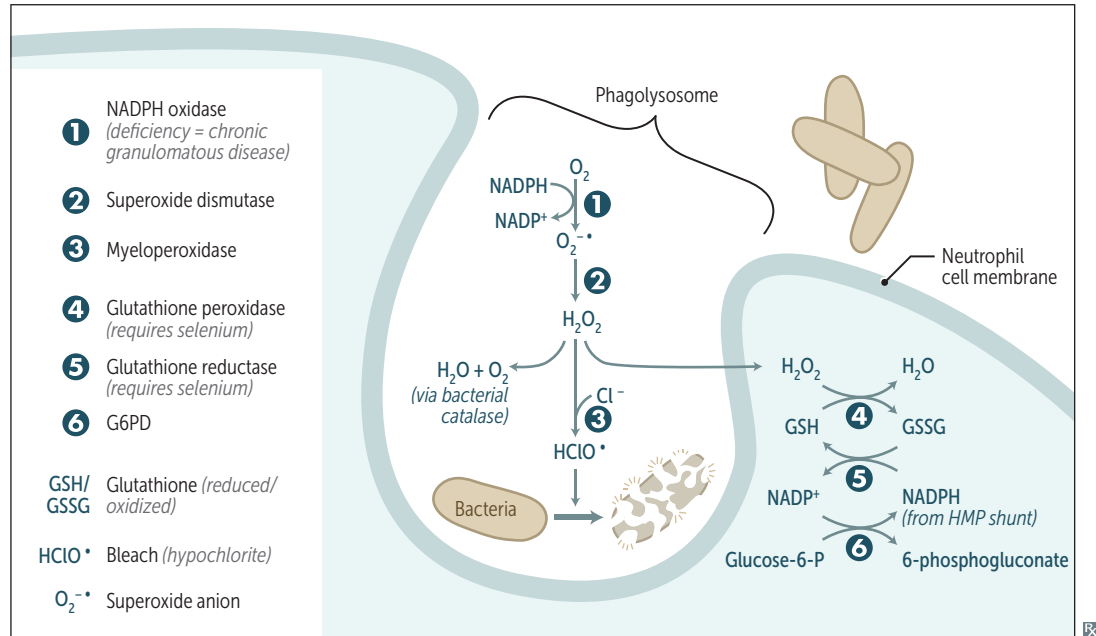
Interferon-γ	Secreted by NK cells and T cells in response to IL-12 from macrophages; stimulates macrophages to kill phagocytosed pathogens. Inhibits differentiation of Th2 cells.	Also activates NK cells to kill virus-infected cells. Increases MHC expression and antigen presentation by all cells.
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FROM Th2 CELLS

IL-4	Induces differentiation of T cells into Th2 cells. Promotes growth of B cells. Enhances class switching to IgE and IgG.	
IL-5	Promotes growth and differentiation of B cells. Enhances class switching to IgA. Stimulates growth and differentiation of eosinophils.	
IL-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- β and IL-10 both attenuate the immune response.

**Respiratory burst
(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 → rapid release of reactive oxygen species (ROS). NADPH plays a role in both the creation and neutralization of ROS. Myeloperoxidase is 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 ⊕ species (eg, *S aureus*, *Aspergillus*) capable of neutralizing their own H_2O_2 , leaving phagocytes without ROS for fighting infections. Pyocyanin of *P aeruginosa* functions to generate ROS to kill competing microbes. Lactoferrin is a protein found in secretory fluids and neutrophils that inhibits microbial growth via iron chelation.

Interferon-α and -β

A part of innate host defense against both RNA and DNA viruses. **Interferons** are glycoproteins synthesized by virus-infected cells that act locally on uninfected cells, “priming them” for viral defense by helping to selectively degrade viral nucleic acid and protein.

Interfere with viruses.

Cell surface proteins	MHC I present on all nucleated cells (ie, not mature RBCs).	
T cells	TCR (binds antigen-MHC complex) CD3 (associated with TCR for signal transduction) CD28 (binds B7 on APC) CXCR4/CCR5 (co-receptors for HIV)	
Helper T cells	CD4, CD40L	
Cytotoxic T cells	CD8 CXCR4/CCR5	
Regulatory T cells	CD4, CD25	
B cells	Ig (binds antigen) CD19, CD20, CD21 (receptor for EBV), CD40 MHC II, B7	You can drink B eer at the B ar when you're 21 : B cells, Epstein- B arr virus, CD21 .
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 (unique marker for NK)	
Hematopoietic stem cells	CD34	

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.

Effects of bacterial toxins Superantigens (*S pyogenes* and *S aureus*)—cross-link the β region of the T-cell receptor to the MHC class II on APCs. Can activate any CD4+ T cell → massive release of cytokines.
Endotoxins/lipopolysaccharide (gram \ominus bacteria)—directly stimulate macrophages by binding to endotoxin receptor TLR4/CD14; Th cells are not involved.

Antigenic variation Classic examples:

- Bacteria—*Salmonella* (2 flagellar variants), *Borrelia recurrentis* (relapsing fever), *N gonorrhoeae* (pilus protein)
- Viruses—influenza, HIV, HCV
- Parasites—trypanosomes

Some mechanisms for variation include DNA rearrangement and RNA segment reassortment (eg, influenza major shift).

Passive vs active immunity

	Passive	Active
MEANS OF ACQUISITION	Receiving preformed antibodies	Exposure to foreign 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
NOTES	After exposure to T etanus toxin, B otulinum toxin, H BV, V aricella, or R abies virus, unvaccinated patients are given preformed antibodies (passive)—“ T o B e H ealed V ery R apidly”	Combined passive and active immunizations can be given for hepatitis B or rabies exposure

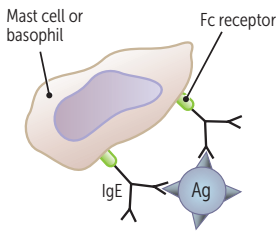
Vaccination

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 cellular and humoral responses . MMR is the only live attenuated vaccine given to persons with HIV.	Pro: induces strong, often lifelong immunity. Con: may revert to virulent form. Often contraindicated in pregnancy and immunodeficiency.	BCCG, influenza (intranasal), measles, mumps, polio (Sabin), rubella, varicella, yellow fever.
Inactivated or killed vaccine	Pathogen is inactivated by heat or chemicals. Maintaining epitope structure on surface antigens is important for immune response. Mainly induces a humoral response .	Pro: safer than live vaccines. Con: weaker immune response; booster shots usually required.	R abies, I nfluenza (injection), P olio (Salk), hepatitis A (“ R.I.P. Always ”).

Hypersensitivity types Four types: **A**naphylactic and **A**topic (type I), **C**ytotoxic (antibody mediated, type II), **I**mmune complex (type III), **D**elayed (cell mediated, type IV) (**ACID**).

Type I



Anaphylactic and atopic—free antigen cross-links IgE on presensitized mast cells and basophils, triggering immediate release of vasoactive amines that act at postcapillary venules (ie, histamine). Reaction develops rapidly after antigen exposure because of preformed antibody. Delayed response follows due to production of arachidonic acid metabolites (eg, leukotrienes).

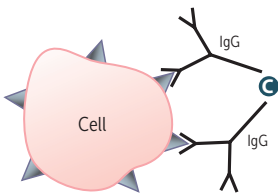
First (type) and **F**ast (anaphylaxis). Types I, II, and III are all antibody mediated.

Test: skin test for specific IgE.

Examples:

- Allergic and atopic disorders (eg, rhinitis, hay fever, eczema, hives, asthma)
- Anaphylaxis (eg, bee sting, some food/drug allergies)

Type II



C = complement

Cytotoxic (antibody mediated)—IgM, IgG bind to fixed antigen on “enemy” cell → cellular destruction.

Antibody and complement lead to MAC.

3 mechanisms:

- Opsonization and phagocytosis
- Complement- and Fc receptor–mediated inflammation
- Antibody-mediated cellular dysfunction

Disease tends to be specific to tissue or site where antigen is found.

Type **II** is **cy-2**-toxic.

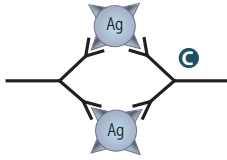
Direct and indirect Coombs' tests:

Direct—detects antibodies that have adhered to patient's RBCs (eg, test an Rh ⊕ infant of an Rh ⊖ mother).

Indirect—detects serum antibodies that can adhere to other RBCs (eg, test an Rh ⊖ woman for Rh ⊕ antibodies).

Examples:

- Acute hemolytic transfusion reactions
- Autoimmune hemolytic anemia
- Bullous pemphigoid
- Erythroblastosis fetalis
- Goodpasture syndrome
- Graves disease
- Guillain-Barré syndrome
- Idiopathic thrombocytopenic purpura
- Myasthenia gravis
- Pemphigus vulgaris
- Pernicious anemia
- Rheumatic fever

Hypersensitivity types (continued)**Type III**

Immune complex—antigen-antibody (IgG) complexes activate complement, which attracts neutrophils; neutrophils release lysosomal enzymes.

Can be associated with vasculitis and systemic manifestations.

Serum sickness—an immune complex disease in which antibodies to foreign proteins are produced (takes 5 days). Immune complexes form and are deposited in membranes, where they fix complement (leads to tissue damage). More common than Arthus reaction.

Arthus reaction—a local subacute antibody-mediated hypersensitivity reaction. Intradermal injection of antigen into a presensitized (has circulating IgG) individual leads to immune complex formation in the skin. Characterized by edema, necrosis, and activation of complement.

In type **III** reaction, imagine an immune complex as **3** things stuck together: antigen-antibody-complement.

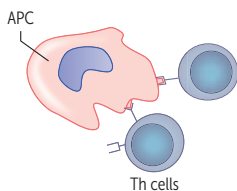
Examples:

- Arthus reaction
- SLE
- Polyarteritis nodosa
- Poststreptococcal glomerulonephritis
- Serum sickness

Most serum sickness is now caused by drugs (not serum) acting as haptens. Fever, urticaria, arthralgia, proteinuria, lymphadenopathy occur 5–10 days after antigen exposure.

Antigen-antibody complexes cause the Arthus reaction.

Test: immunofluorescent staining.

Type IV

Delayed (T-cell-mediated) type—sensitized T cells encounter antigen and then release cytokines (leads to macrophage activation).

Response does **not** involve antibodies (vs types I, II, and III).

4th and **last**—delayed. Cell mediated; therefore, it is not transferable by serum.

4 T's = T cells, **T**ransplant rejections, **T**B skin tests, **T**ouching (contact dermatitis).

Test: patch test, PPD.

Examples:

- Contact dermatitis (eg, poison ivy, nickel allergy)
- Graft-versus-host disease
- Multiple sclerosis

Blood transfusion reactions

TYPE	PATHOGENESIS	CLINICAL PRESENTATION
Allergic reaction	Type I hypersensitivity reaction against plasma proteins in transfused blood.	Urticaria, pruritus, wheezing, fever. Treat with antihistamines.
Anaphylactic reaction	Severe allergic reaction. IgA-deficient individuals must receive blood products without IgA.	Dyspnea, bronchospasm, hypotension, respiratory arrest, shock. Treat with epinephrine.
Febrile nonhemolytic transfusion reaction	Type II hypersensitivity reaction. Host antibodies against donor HLA antigens and WBCs.	Fever, headaches, chills, flushing.
Acute hemolytic transfusion reaction	Type II hypersensitivity reaction. Intravascular hemolysis (ABO blood group incompatibility) or extravascular hemolysis (host antibody reaction against foreign antigen on donor RBCs).	Fever, hypotension, tachypnea, tachycardia, flank pain, hemoglobinuria (intravascular hemolysis), jaundice (extravascular).

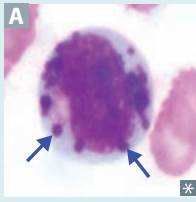
Autoantibodies

AUTOANTIBODY	ASSOCIATED DISORDER
Anti-ACh receptor	Myasthenia gravis
Anti-basement membrane	Goodpasture syndrome
Anticardiolipin, lupus anticoagulant	SLE, antiphospholipid syndrome
Anticentromere	Limited scleroderma (CREST syndrome)
Anti-desmoglein (anti-desmosome)	Pemphigus vulgaris
Anti-dsDNA, anti-Smith	SLE
Anti-glutamic acid decarboxylase (GAD-65)	Type 1 diabetes mellitus
Antihemidesmosome	Bullous pemphigoid
Anti-histone	Drug-induced lupus
Anti-Jo-1, anti-SRP, anti-Mi-2	Polymyositis, dermatomyositis
Antimicrosomal, antithyroglobulin	Hashimoto thyroiditis
Antimitochondrial	1° biliary cirrhosis
Antinuclear (ANA)	SLE, nonspecific
Antiparietal cell	Pernicious anemia
Antiphospholipase A ₂ receptor	1° membranous nephropathy
Anti-Scl-70 (anti-DNA topoisomerase I)	Scleroderma (diffuse)
Anti-smooth muscle	Autoimmune hepatitis type 1
Anti-SSA, anti-SSB (anti-Ro, anti-La)	Sjögren syndrome
Anti-TSH receptor	Graves disease
Anti-U1 RNP (ribonucleoprotein)	Mixed connective tissue disease
Voltage-gated calcium channel antibodies	Lambert-Eaton syndrome
IgA anti-endomysial, IgA anti-tissue transglutaminase	Celiac disease
MPO-ANCA/p-ANCA	Microscopic polyangiitis, eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)
PR3-ANCA/c-ANCA	Granulomatosis with polyangiitis (Wegener)
Rheumatoid factor (IgM antibody that targets IgG Fc region), anti-CCP (more specific)	Rheumatoid arthritis

Immunodeficiencies

DISEASE	DEFECT	PRESENTATION	FINDINGS
B-cell disorders			
X-linked (Bruton) agammaglobulinemia	Defect in BTK , a tyrosine kinase gene → no B -cell maturation. X-linked recessive (↑ in B oys).	Recurrent bacterial and enteroviral infections after 6 months (↓ maternal IgG).	Absent B cells in peripheral blood, ↓ Ig of all classes. Absent/scanty lymph nodes and tonsils.
Selective IgA deficiency	Unknown. Most common 1° immunodeficiency.	Majority A symptomatic. Can see A irway and GI infections, A utoimmune disease, A topy, A naphylaxis to Ig A -containing products.	↓ IgA with normal IgG, IgM levels.
Common variable immunodeficiency	Defect in B-cell differentiation. Many causes.	Can be acquired in 20s–30s; ↑ risk of autoimmune disease, bronchiectasis, lymphoma, sinopulmonary infections.	↓ plasma cells, ↓ immunoglobulins.
T-cell disorders			
Thymic aplasia (DiGeorge syndrome)	22q11 deletion; failure to develop 3rd and 4th pharyngeal pouches → absent thymus and parathyroids.	Tetany (hypocalcemia), recurrent viral/fungal infections (T-cell deficiency), conotruncal abnormalities (eg, tetralogy of Fallot, truncus arteriosus).	↓ T cells, ↓ PTH, ↓ Ca ²⁺ . Absent thymic shadow on CXR. 22q11 deletion detected by FISH.
IL-12 receptor deficiency	↓ Th1 response. Autosomal recessive.	Disseminated mycobacterial and fungal infections; may present after administration of BCG vaccine.	↓ IFN-γ.
Autosomal dominant hyper-IgE syndrome (Job syndrome)	Deficiency of Th17 cells due to STAT3 mutation → impaired recruitment of neutrophils to sites of infection.	FATED : coarse F acies, cold (noninflamed) staphylococcal A bscesses, retained primary T eeth, ↑ IgE , D ermatologic problems (eczema).	↑ IgE, ↓ IFN-γ.
Chronic mucocutaneous candidiasis	T-cell dysfunction. Many causes.	Noninvasive <i>Candida albicans</i> infections of skin and mucous membranes.	Absent in vitro T-cell proliferation in response to <i>Candida</i> antigens. Absent cutaneous reaction to <i>Candida</i> antigens.

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), adenosine deaminase deficiency (autosomal recessive).	Failure to thrive, chronic diarrhea, thrush. Recurrent viral, bacterial, fungal, and protozoal infections. Treatment: bone marrow transplant (no concern for rejection).	↓ 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 <i>ATM</i> gene → failure to repair DNA double strand breaks → cell cycle arrest.	Triad: cerebellar defects (A taxia), spider A ngiomas (telangiectasia), IgA deficiency.	↑ AFP. ↓ IgA, IgG, and IgE. Lymphopenia, cerebellar atrophy.
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.
Wiskott-Aldrich syndrome	Mutation in <i>WAS</i> gene; T cells unable to reorganize actin cytoskeleton. X-linked recessive.	WATER: Wiskott-Aldrich: T hrombocytopenia, E czema, R ecurrent 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.	Recurrent bacterial skin and mucosal infections, absent pus formation, impaired wound healing, delayed separation of umbilical cord (> 30 days).	↑ neutrophils. Absence of neutrophils at infection sites.
Chédiak-Higashi syndrome	Defect in lysosomal trafficking regulator gene (<i>LYST</i>). Microtubule dysfunction in phagosome-lysosome fusion; autosomal recessive.	Recurrent pyogenic infections by staphylococci and streptococci, partial albinism, peripheral neuropathy, progressive neurodegeneration, infiltrative lymphohistiocytosis.	Giant granules (A , 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 recessive most common.	↑ susceptibility to C atalase ⊕ organisms (Cats Need PLACESS to B elch their H airballs): Nocardia , Pseudomonas , Listeria , Aspergillus , Candida , E coli , Staphylococci , Serratia , B cepacia , H pylori	Abnormal dihydrorhodamine (flow cytometry) test (↓ green fluorescence). Nitroblue tetrazolium dye reduction test obsolete.

Infections in immunodeficiency

PATHOGEN	↓ T CELLS	↓ B CELLS	↓ GRANULOCYTES	↓ COMPLEMENT
Bacteria	Sepsis	Encapsulated: <i>Pseudomonas aeruginosa</i> , <i>Streptococcus pneumoniae</i> , <i>Haemophilus Influenzae</i> type B, <i>Neisseria meningitidis</i> , <i>Escherichia coli</i> , <i>Salmonella</i> , <i>Klebsiella pneumoniae</i> , group B Strep (Please SHINE my SKiS)	<i>Staphylococcus</i> , <i>Burkholderia cepacia</i> , <i>Pseudomonas aeruginosa</i> , <i>Serratia</i> , <i>Nocardia</i>	Encapsulated species with early component deficiencies <i>Neisseria</i> with late component (MAC) deficiencies
Viruses	CMV, EBV, JCV, VZV, chronic infection with respiratory/GI viruses	Enteroviral encephalitis, poliovirus (live vaccine contraindicated)	N/A	N/A
Fungi/parasites	<i>Candida</i> (local), PCP	GI giardiasis (no IgA)	<i>Candida</i> (systemic), <i>Aspergillus</i>	N/A

Note: B-cell deficiencies tend to produce recurrent bacterial infections, whereas T-cell deficiencies produce more fungal and viral infections.

Grafts

Autograft	From self.
Syngeneic graft (isograft)	From identical twin or clone.
Allograft	From nonidentical individual of same species.
Xenograft	From different species.

Transplant rejection

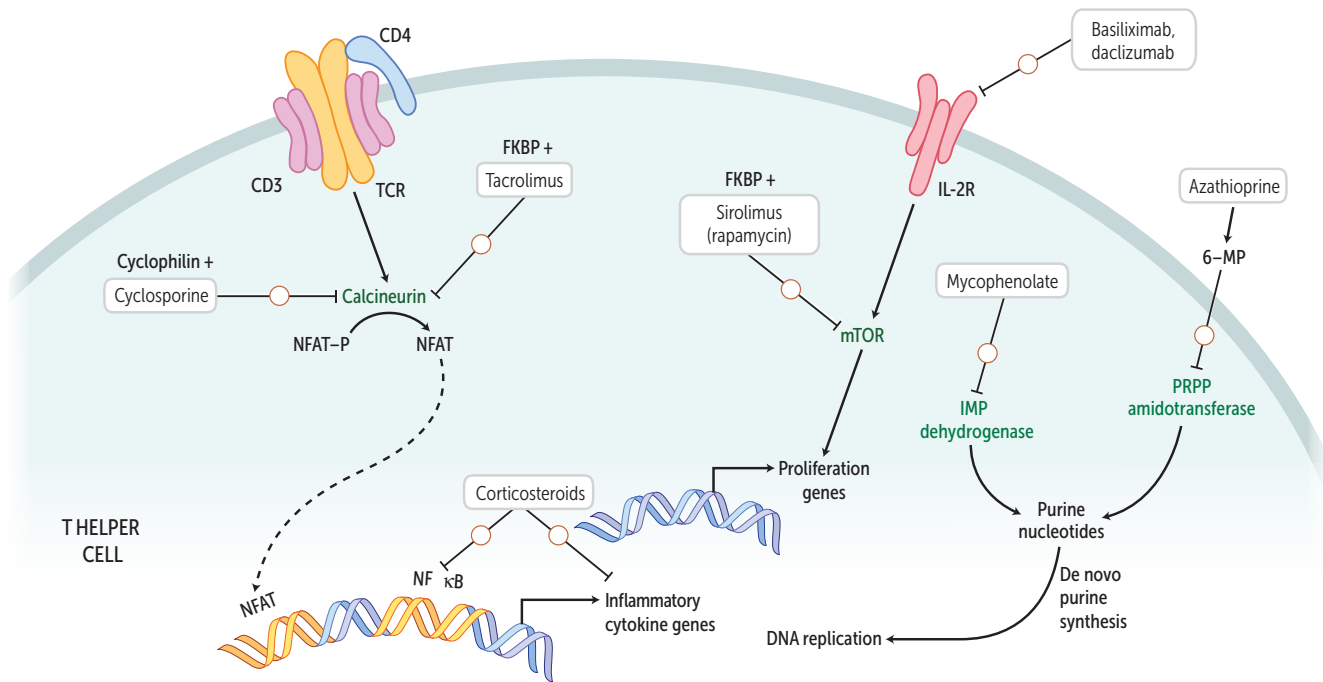
TYPE OF REJECTION	ONSET	PATHOGENESIS	FEATURES
Hyperacute	Within minutes	Pre-existing recipient antibodies react to donor antigen (type II hypersensitivity reaction), activate complement.	Widespread thrombosis of graft vessels → ischemia/necrosis. Graft must be removed.
Acute	Weeks to months	Cellular: CD8+ 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. 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. Organ-specific examples: <ul style="list-style-type: none"> ▪ Bronchiolitis obliterans (lung) ▪ Accelerated atherosclerosis (heart) ▪ Chronic graft nephropathy (kidney) ▪ Vanishing bile duct syndrome (liver)
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).

▶ IMMUNOLOGY—IMMUNOSUPPRESSANTS

Immunosuppressants Agents that block lymphocyte activation and proliferation. Reduce acute transplant rejection by suppressing cellular immunity. Frequently combined to achieve greater efficacy with ↓ toxicity. Chronic suppression ↑ risk of infection and malignancy.

DRUG	MECHANISM	USE	TOXICITY	NOTES
Cyclosporine	Calcineurin inhibitor; binds cyclophilin . Blocks T-cell activation by preventing IL-2 transcription .	Transplant rejection prophylaxis, 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 .	Transplant rejection prophylaxis.	Similar to cyclosporine, ↑ risk of diabetes and neurotoxicity; no gingival hyperplasia or hirsutism.	
Sirolimus (Rapamycin)	mTOR inhibitor; binds FKBP. Blocks T-cell activation and B-cell differentiation by preventing response to IL-2 .	Kidney transplant rejection prophylaxis.	“Pan Sirt openia” (pancytopenia), insulin resistance, hyperlipidemia; not nephrotoxic .	Kidney “ si -vives.” Synergistic with cyclosporine. Also used in drug-eluting stents.
Daclizumab, basiliximab	Monoclonal antibodies; block IL-2R.	Kidney transplant rejection prophylaxis.	Edema, hypertension, tremor.	
Azathioprine	Antimetabolite precursor of 6-mercaptopurine. Inhibits lymphocyte proliferation by blocking nucleotide synthesis.	Transplant rejection prophylaxis, rheumatoid arthritis, Crohn disease, glomerulonephritis, other autoimmune conditions.	Leukopenia, anemia, thrombocytopenia.	6-MP degraded by xanthine oxidase; toxicity ↑ by allopurinol. Pronounce “azathio purine .”
Mycophenolate mofetil	Reversibly inhibits IMP dehydrogenase, preventing purine synthesis of B and T cells.	Transplant rejection prophylaxis, lupus nephritis.	GI upset, pancytopenia, hypertension, hyperglycemia. Less nephrotoxic and neurotoxic.	Associated with invasive CMV infection.
Corticosteroids	Inhibit NF-κB. Suppress both B- and T-cell function by ↓ transcription of many cytokines. Induce apoptosis of T lymphocytes.	Transplant rejection prophylaxis, many autoimmune and inflammatory disorders.	Hyperglycemia, osteoporosis, central obesity, muscle breakdown, psychosis, acne, hypertension, cataracts, avascular necrosis (femoral head).	Can cause iatrogenic Cushing syndrome.

Immunosuppression targets



Recombinant cytokines and clinical uses

AGENT	CLINICAL USES
Aldesleukin (IL-2)	Renal cell carcinoma, metastatic melanoma
Epoetin alfa (erythropoietin)	Anemias (especially in renal failure)
Filgrastim (G-CSF)	Recovery of bone marrow
Sargramostim (GM-CSF)	Recovery of bone marrow
IFN- α	Chronic hepatitis B and C, Kaposi sarcoma, malignant melanoma
IFN- β	Multiple sclerosis
IFN- γ	Chronic granulomatous disease
Romiplostim, eltrombopag (thrombopoietin receptor agonists)	Thrombocytopenia
Oprelvekin (IL-11)	Thrombocytopenia

Therapeutic antibodies

AGENT	TARGET	CLINICAL USE	NOTES
Cancer therapy			
Alemtuzumab	CD52	CLL, MS	“ Aly mtuzumab”—chronic ly mphocytic leukemia
Bevacizumab	VEGF	Colorectal cancer, renal cell carcinoma	
Cetuximab	EGFR	Stage IV colorectal cancer, head and neck cancer	
Rituximab	CD20	B-cell non-Hodgkin lymphoma, CLL, rheumatoid arthritis, ITP	
Trastuzumab	HER2/neu	Breast cancer	HER2—“ tra s2zumab”
Autoimmune disease therapy			
Adalimumab, certolizumab, 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	
Natalizumab	α 4-integrin	Multiple sclerosis, Crohn disease	α 4-integrin: WBC adhesion Risk of PML in patients with JC virus
Other applications			
Abciximab	Platelet glycoproteins IIIb/IIIa	Antiplatelet agent for prevention of ischemic complications in patients undergoing percutaneous coronary intervention	IIIb times IIIa equals “ ab siximab”
Denosumab	RANKL	Osteoporosis; inhibits osteoclast maturation (mimics osteoprotegerin)	Den osumab affects oste oclasts
Digoxin immune Fab	Digoxin	Antidote for digoxin toxicity	
Omalizumab	IgE	Allergic asthma; prevents IgE binding to Fc ϵ RI	
Palivizumab	RSV F protein	RSV prophylaxis for high-risk infants	Pali VI zumab— VI rus
Ranibizumab, bevacizumab	VEGF	Neovascular age-related macular degeneration	

Pathology

“Digressions, objections, delight in mockery, carefree mistrust are signs of health; everything unconditional belongs in pathology.”

—Friedrich Nietzsche

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.

▶ Inflammation	216
▶ Neoplasia	226

► PATHOLOGY—INFLAMMATION

Apoptosis

ATP-dependent programmed cell death. Intrinsic or extrinsic pathway; both pathways → activation of cytosolic proteases called caspases that mediate cellular breakdown → cell shrinkage, chromatin condensation, membrane blebbing, and formation of apoptotic bodies, which are then phagocytosed.

Characterized by deeply eosinophilic cytoplasm and basophilic nucleus, pyknosis (nuclear shrinkage), and karyorrhexis (fragmentation caused by endonucleases cleaving at internucleosomal regions). DNA laddering (fragments in multiples of 180 bp) is a sensitive indicator of apoptosis.

Cell membrane typically remains intact without significant inflammation (unlike necrosis).

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 such as BAX and BAK (proapoptotic) and Bcl-2 (antiapoptotic).

Bcl-2 prevents cytochrome c release by binding to and inhibiting APAF-1. APAF-1 normally binds cytochrome c and induces activation of caspase 9, initiating caspase cascade. If Bcl-2 is overexpressed (eg, follicular lymphoma t[14;18]), then APAF-1 is overly inhibited, → ↓ caspase activation and tumorigenesis.

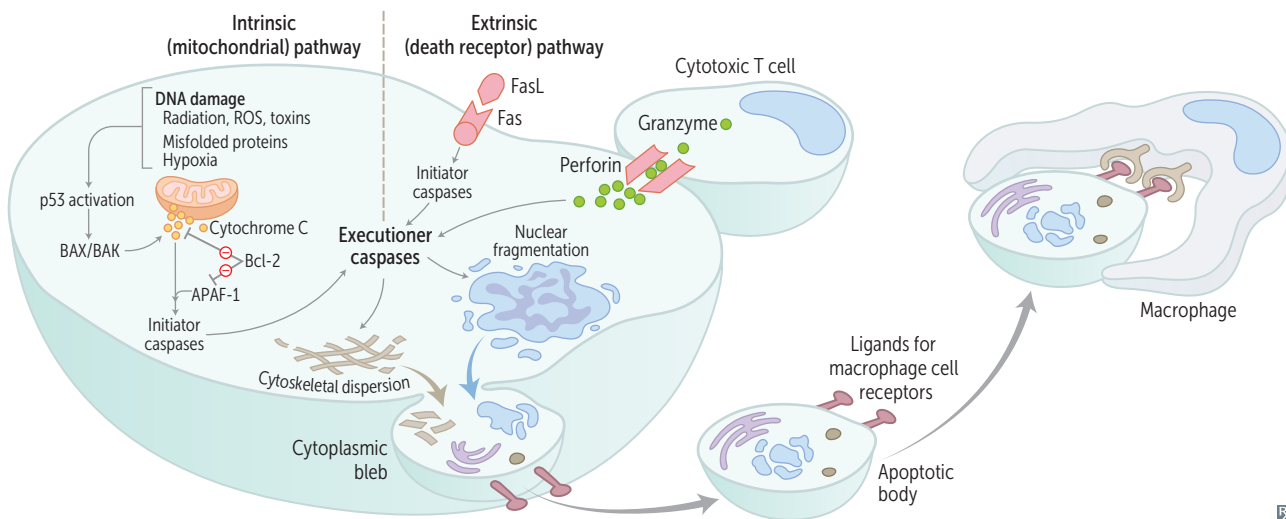
Extrinsic (death receptor) pathway

2 pathways:

- Ligand receptor interactions (FasL binding to Fas [CD95] or TNF- α binding to TNF)
- Immune cell (cytotoxic T-cell release of perforin and granzyme B)

Fas-FasL interaction is necessary in thymic medullary negative selection. Mutations in Fas ↑ numbers of circulating self-reacting lymphocytes due to failure of clonal deletion.

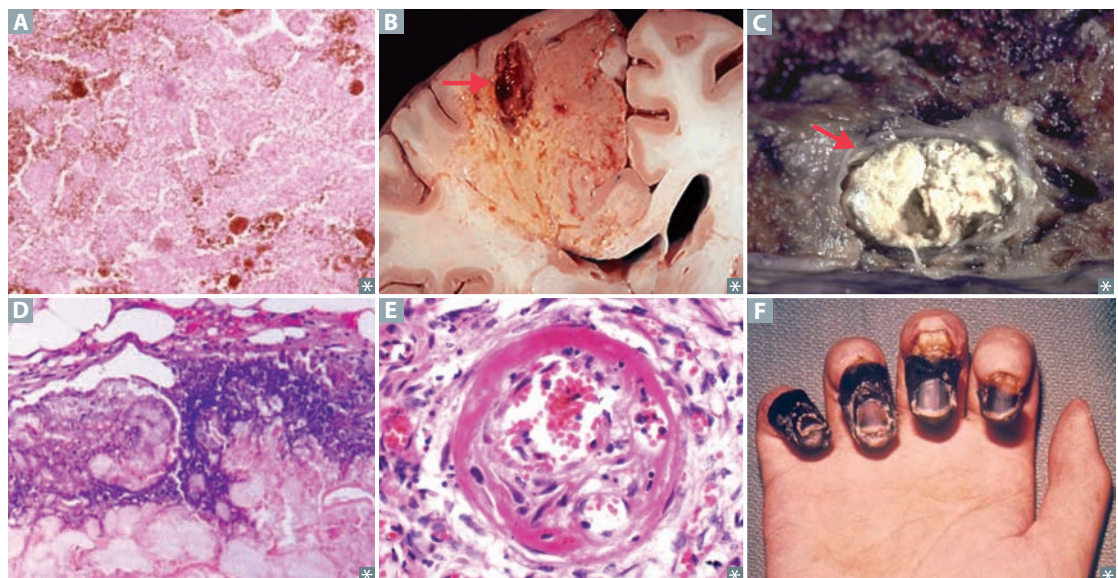
Defective Fas-FasL interactions cause autoimmune lymphoproliferative syndrome.



Necrosis

Enzymatic degradation and protein denaturation of cell due to exogenous injury → intracellular components leak. Inflammatory process (unlike apoptosis).

TYPE	SEEN IN	DUE TO	HISTOLOGY
Coagulative	Ischemia/infarcts in most tissues (except brain)	Ischemia or infarction; proteins denature, then enzymatic degradation	Cell outlines preserved; ↑ cytoplasmic binding of acidophilic dyes A
Liquefactive	Bacterial abscesses, brain infarcts (due to ↑ fat content)	Neutrophils release lysosomal enzymes that digest the tissue B ; enzymatic degradation first, then proteins denature	Early: cellular debris and macrophages Late: cystic spaces and cavitation (brain) Neutrophils and cell debris seen with bacterial infection
Caseous	TB, systemic fungi (eg, <i>Histoplasma capsulatum</i>), <i>Nocardia</i>	Macrophages wall off the infecting microorganism → granular debris C	Fragmented cells and debris surrounded by lymphocytes and macrophages
Fat	Enzymatic: acute pancreatitis (saponification of peripancreatic fat) Nonenzymatic: traumatic (eg, breast injury)	Damaged cells release lipase, which breaks down triglycerides in fat cells	Outlines of dead fat cells without peripheral nuclei; saponification of fat (combined with Ca ²⁺) appears dark blue on H&E stain D
Fibrinoid	Immune reactions in vessels (eg, polyarteritis nodosa, giant cell [temporal] arteritis)	Immune complexes combine with fibrin → vessel wall damage	Vessel walls are thick and pink E
Gangrenous	Distal extremity, after chronic ischemia	Dry: ischemia F Wet: superinfection	Coagulative Liquefactive superimposed on coagulative



Cell injuryREVERSIBLE WITH O₂

Cellular/mitochondrial swelling (↓ ATP
→ ↓ activity of Na⁺/K⁺ pumps)

Nuclear chromatin clumping

Membrane blebbing

↓ glycogen

Fatty change

Ribosomal/polysomal detachment (↓ protein
synthesis)

IRREVERSIBLE

Mitochondrial permeability/vacuolization;
phospholipid-containing amorphous densities
within mitochondria (swelling alone is
reversible)

Nuclear pyknosis (condensation), karyorrhexis
(fragmentation), karyolysis (fading)

Plasma membrane damage (degradation of
membrane phospholipid)

Lysosomal rupture

Ischemia

Inadequate blood supply to meet demand.

Regions most vulnerable to hypoxia/ischemia and subsequent infarction:

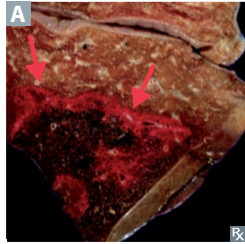
ORGAN	REGION
Brain	ACA/MCA/PCA boundary areas ^{a,b}
Heart	Subendocardium (LV)
Kidney	Straight segment of proximal tubule (medulla) Thick ascending limb (medulla)
Liver	Area around central vein (zone III)
Colon	Splenic flexure, ^a rectum ^a

^aWatershed 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.

^bNeurons most vulnerable to hypoxic-ischemic insults include Purkinje cells of the cerebellum and pyramidal cells of the hippocampus and neocortex.

Infarcts: red vs pale

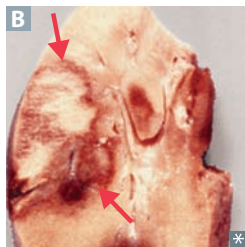
Red



Red (hemorrhagic) infarcts **A** occur in venous occlusion and tissues with multiple blood supplies, such as liver, lung, intestine, testes; reperfusion (eg, after angioplasty). Reperfusion injury is due to damage by free radicals.

Red = reperfusion.

Pale



Pale (anemic) infarcts **B** occur in solid organs with a single (end-arterial) blood supply, such as heart, kidney, and spleen.

Inflammation

Characterized by *rubor* (redness), *dolor* (pain), *calor* (heat), *tumor* (swelling), and *functio laesa* (loss of function).

Vascular component

↑ vascular permeability, vasodilation, endothelial injury.

Cellular component

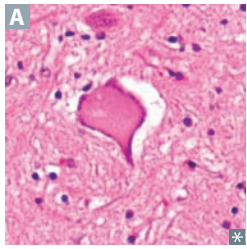
Neutrophils extravasate from circulation to injured tissue to participate in inflammation through phagocytosis, degranulation, and inflammatory mediator release.

Acute

Neutrophil, eosinophil, and antibody mediated. Acute inflammation is rapid onset (seconds to minutes) and of short duration (minutes to days). Outcomes include complete resolution, abscess formation, or progression to chronic inflammation.

Chronic

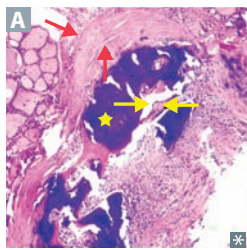
Mononuclear cell (monocytes/macrophages, lymphocytes, plasma cells) and fibroblast mediated. Characterized by persistent destruction and repair. Associated with blood vessel proliferation, fibrosis. Granuloma: nodular collections of epithelioid macrophages and giant cells. Outcomes include scarring and amyloidosis.

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

Concurrent with **Wallerian degeneration**—degeneration of axon distal to site of injury. Macrophages remove debris and myelin.

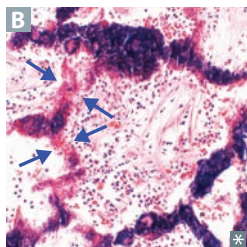
Types of calcification**Dystrophic calcification**

Ca²⁺ deposition in **abnormal tissues** 2° to injury or necrosis.

Tends to be localized (eg, calcific aortic stenosis). **A** shows dystrophic calcification (yellow star), small bony tissue (yellow arrows), and thick fibrotic wall (red arrows).

Seen in TB (lungs and pericardium), liquefactive necrosis of chronic abscesses, fat necrosis, infarcts, thrombi, schistosomiasis, Mönckeberg arteriosclerosis, congenital CMV + toxoplasmosis, psammoma bodies.

Is not directly associated with serum Ca²⁺ levels (patients are usually **normocalcemic**).

Metastatic calcification

Widespread (ie, diffuse, metastatic) deposition of Ca²⁺ in **normal tissue** 2° to hypercalcemia (eg, 1° hyperparathyroidism, sarcoidosis, hypervitaminosis D) or high calcium-phosphate product levels (eg, chronic renal failure with 2° hyperparathyroidism, long-term dialysis, calciphylaxis, warfarin).

B shows metastatic calcifications of alveolar walls in acute pneumonitis (blue arrows).

Ca²⁺ deposits predominantly in interstitial tissues of kidney, lung, and gastric mucosa (these tissues lose acid quickly; ↑ pH favors deposition).

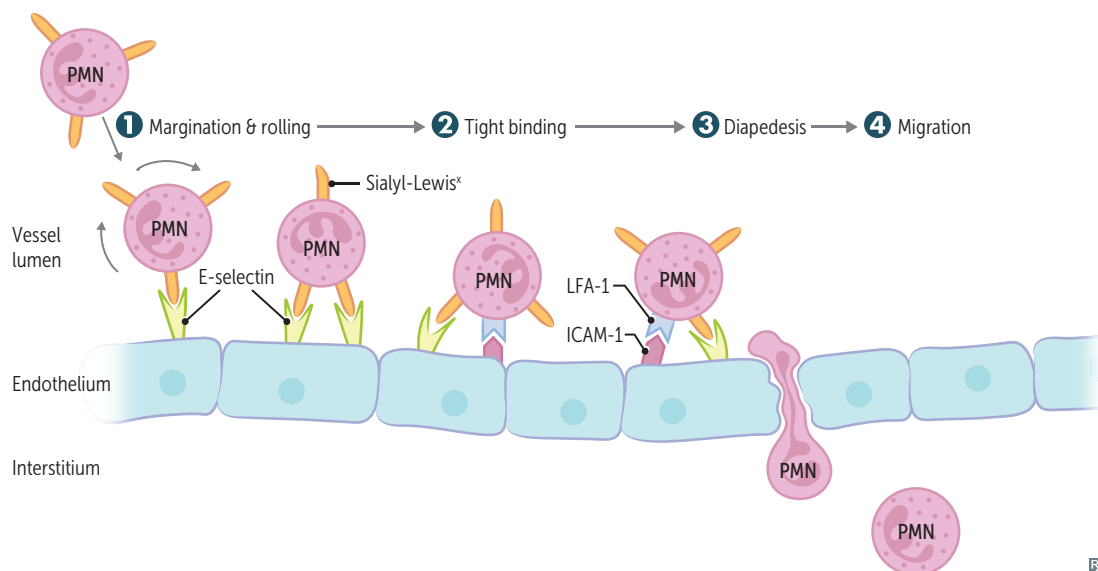
Patients are usually **not normocalcemic**.

Leukocyte extravasation

Extravasation predominantly occurs at postcapillary venules.

WBCs exit from blood vessels at sites of tissue injury and inflammation in 4 steps:

STEP	VASCULATURE/STROMA	LEUKOCYTE
1 Margination and rolling—defective in leukocyte adhesion deficiency type 2 (↓ Sialyl-Lewis ^X)	E-selectin P-selectin GlyCAM-1, CD34	Sialyl-Lewis ^X Sialyl-Lewis ^X L-selectin
2 Tight-binding—defective in leukocyte adhesion deficiency type 1 (↓ CD18 integrin subunit)	ICAM-1 (CD54) VCAM-1 (CD106)	CD11/18 integrins (LFA-1, Mac-1) VLA-4 integrin
3 Diapedesis—WBC travels between endothelial cells and exits blood vessel	PECAM-1 (CD31)	PECAM-1 (CD31)
4 Migration—WBC travels through interstitium to site of injury or infection guided by chemotactic signals	Chemotactic products released in response to bacteria: C5a, IL-8, LTB ₄ , kallikrein, platelet-activating factor	Various



Free radical injury

Free radicals damage cells via membrane lipid peroxidation, protein modification, and DNA breakage.

Initiated via radiation exposure (eg, cancer therapy), metabolism of drugs (phase I), redox reactions, nitric oxide, transition metals, WBC (eg, neutrophils, macrophages) oxidative burst.

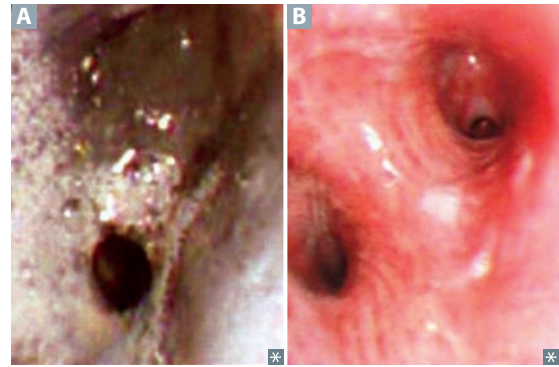
Free radicals can be eliminated by scavenging enzymes (eg, catalase, superoxide dismutase, glutathione peroxidase), spontaneous decay, antioxidants (eg, vitamins A, C, E), and certain metal carrier proteins (eg, transferrin, ceruloplasmin).

Examples:

- Oxygen toxicity: retinopathy of prematurity (abnormal vascularization), bronchopulmonary dysplasia
- Drug/chemical toxicity: carbon tetrachloride and acetaminophen overdose (hepatotoxicity)
- Metal storage diseases: hemochromatosis (iron) and Wilson disease (copper)

Inhalational injury and sequelae

Pulmonary complication associated with smoke and fire. Caused by heat, particulates (< 1 μm diameter), or irritants (eg, NH₃) → chemical tracheobronchitis, edema, pneumonia, ARDS. Many patients present 2° to burns, CO inhalation, or arsenic poisoning. Bronchoscopy shows severe edema, congestion of bronchus, and soot deposition (A, 18 hours after inhalation injury; B, resolution at 11 days after injury).



Scar formation

70–80% of tensile strength regained at 3 months; little additional tensile strength will be regained afterward.

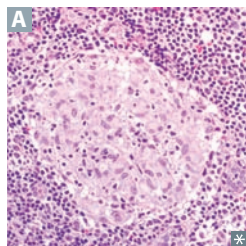
SCAR TYPE	Hypertrophic A	Keloid B
COLLAGEN SYNTHESIS	↑	↑↑↑
COLLAGEN ORGANIZATION	Parallel	Disorganized
EXTENT OF SCAR	Confined to borders of original wound	Extends beyond borders of original wound with “clawlike” projections
SCAR EVOLUTION OVER YEARS	Possible spontaneous regression	Possible progressive growth
RECURRENCE	Infrequent	Frequent
PREDISPOSITION	None	↑ incidence in ethnic groups with darker skin



Wound healing

Tissue mediators	MEDIATOR	ROLE
	PDGF	Secreted by activated platelets and macrophages Induces vascular remodeling and smooth muscle cell migration Stimulates fibroblast growth for collagen synthesis
	FGF	Stimulates angiogenesis
	EGF	Stimulates cell growth via tyrosine kinases (eg, EGFR/ <i>ErbB1</i>)
	TGF-β	Angiogenesis, fibrosis, cell cycle arrest
	Metalloproteinases	Tissue remodeling
	VEGF	Stimulates angiogenesis
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)
Remodeling (1 week–6+ months after wound)	Fibroblasts	Type III collagen replaced by type I collagen, ↑ tensile strength of tissue

Granulomatous diseases



Bacterial:

- *Mycobacteria* (tuberculosis, leprosy)
- *Bartonella henselae* (cat scratch disease)
- *Listeria monocytogenes* (granulomatosis infantiseptica)
- *Treponema pallidum* (3° syphilis)

Fungal: endemic mycoses (eg, histoplasmosis)

Parasitic: schistosomiasis

Chronic granulomatous disease

Autoinflammatory:

- Sarcoidosis **A**
- Crohn disease
- Primary biliary cirrhosis
- Subacute (de Quervain/granulomatous) thyroiditis
- Granulomatosis with polyangiitis (Wegener)
- Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)
- Giant cell (temporal) arteritis
- Takayasu arteritis

Foreign material: berylliosis, talcosis, hypersensitivity pneumonitis

Th₁ cells secrete IFN-γ, activating macrophages. TNF-α from macrophages induces and maintains granuloma formation. Anti-TNF drugs can, as a side effect, cause sequestering granulomas to break down, leading to disseminated disease. Always test for latent TB before starting anti-TNF therapy. Associated with hypercalcemia due to calcitriol (1,25-[OH]₂ vitamin D₃) production. Caseating necrosis more common with infectious causes (eg, TB). Diagnosing sarcoidosis requires noncaseating granulomas on biopsy.

Exudate vs transudate**Exudate (“Thick...”)**

Cellular (cloudy)

↑ protein, ↑ LDH (vs serum)

Specific gravity > 1.020

Due to:

- Lymphatic obstruction (chylous)
- Inflammation/infection
- Malignancy

Transudate (“and thin”)

Hypocellular (clear)

↓ protein, ↓ LDH (vs serum)

Specific gravity < 1.012

Due to:

- ↑ hydrostatic pressure (eg, HF, Na⁺ retention)
- ↓ oncotic pressure (eg, cirrhosis, nephrotic syndrome)

Erythrocyte sedimentation rate

Products of inflammation (eg, fibrinogen) coat RBCs and cause aggregation. The denser RBC aggregates fall at a faster rate within a pipette tube. Often co-tested with CRP levels.

↑ ESR

Most anemias

Infections

Inflammation (eg, giant cell [temporal] arteritis, polymyalgia rheumatica)

Cancer (eg, metastases, multiple myeloma)

Renal disease (end-stage or nephrotic syndrome)

Pregnancy

↓ ESR

Sickle cell anemia (altered shape)

Polycythemia (↑ RBCs “dilute” aggregation factors)

HF

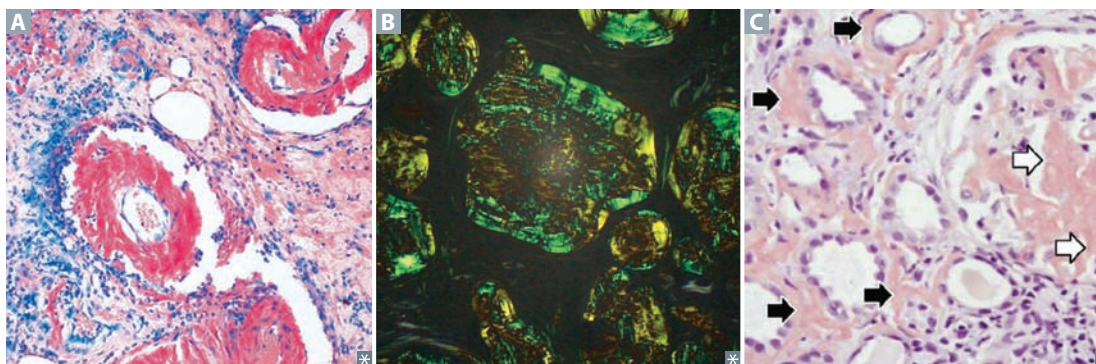
Microcytosis

Hypofibrinogenemia

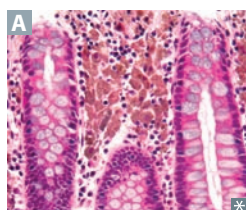
Amyloidosis

Abnormal aggregation of proteins (or their fragments) into β -pleated linear sheets → damage and apoptosis. Amyloid deposits visualized by Congo red stain **A**, polarized light (apple green birefringence) **B**, and H&E stain (**C** shows deposits in glomerular mesangial areas [white arrows], tubular basement membranes [black arrows]).

COMMON TYPES	DESCRIPTION
AL (primary)	Due to deposition of proteins from Ig L ight chains. Can occur as a plasma cell disorder or associated with multiple myeloma. Often affects multiple organ systems, including renal (nephrotic syndrome), cardiac (restrictive cardiomyopathy, arrhythmia), hematologic (easy bruising, splenomegaly), GI (hepatomegaly), and neurologic (neuropathy).
AA (secondary)	Seen with chronic inflammatory conditions such as rheumatoid arthritis, IBD, spondyloarthropathy, familial Mediterranean fever, protracted infection. Fibrils composed of serum A myloid A . Often multisystem like AL amyloidosis.
Dialysis-related	Fibrils composed of β_2 -microglobulin in patients with ESRD and/or on long-term dialysis. May present as carpal tunnel syndrome.
Heritable	Heterogeneous group of disorders, including familial amyloid polyneuropathies due to transthyretin gene mutation.
Age-related (senile) systemic	Due to deposition of normal (wild-type) transthyretin (TTR) predominantly in cardiac ventricles. Slower progression of cardiac dysfunction relative to AL amyloidosis.
Organ-specific	Amyloid deposition localized to a single organ. Most important form is amyloidosis in Alzheimer disease due to deposition of β -amyloid protein cleaved from amyloid precursor protein (APP). Islet amyloid polypeptide (IAPP) is commonly seen in diabetes mellitus type 2 and is caused by deposition of amylin in pancreatic islets. Isolated atrial amyloidosis due to atrial natriuretic peptide is common in normal aging.



Lipofuscin



A yellow-brown “wear and tear” pigment associated with normal aging. Formed by oxidation and polymerization of autophagocytosed organellar membranes. Autopsy of elderly person will reveal deposits in heart, colon **A**, liver, kidney, eye, and other organs.

▶ PATHOLOGY—NEOPLASIA

Reactive cellular changes

Atrophy	↓ in tissue mass due to ↓ in size and/or number of cells. Causes include disuse, denervation, loss of blood supply, loss of hormonal stimulation, poor nutrition.
Hypertrophy	↑ in size of cells.
Hyperplasia	↑ in number of cells. May be a risk factor for future malignancy (eg, endometrial hyperplasia) but not considered premalignant.
Metaplasia	Replacement of one cell type by another. Usually due to exposure to an irritant, such as gastric acid or cigarette smoke. Reversible if the irritant is removed but may undergo malignant transformation with persistent insult (eg, Barrett esophagus → esophageal adenocarcinoma).

Preneoplastic and neoplastic cellular changes

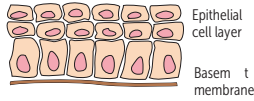
Neoplasia	Uncontrolled, clonal proliferation of cells. Can be benign or malignant.
Dysplasia	Disordered, non-neoplastic cell growth. Used only with epithelial cells. Mild dysplasia is usually reversible; severe dysplasia usually progresses to carcinoma in situ.
Differentiation	The degree to which a malignant tumor resembles its tissue of origin. Well-differentiated tumors closely resemble their tissue of origin; poorly differentiated look almost nothing like their tissue of origin.
Anaplasia	Complete lack of differentiation of cells in a malignant neoplasm.

Neoplastic progression

Hallmarks of cancer: evasion of apoptosis, growth signal self-sufficiency, anti-growth signal insensitivity, sustained angiogenesis, limitless replicative potential, tissue invasion, and metastasis.

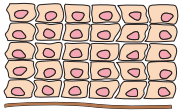
Normal cells

Normal cells with basal → apical differentiation. See cervical example **A**, which shows normal cells and spectrum of dysplasia, as discussed below.



Dysplasia

Abnormal proliferation of cells with loss of size, shape, and orientation. Compare vs hyperplasia (cells ↑ in number).



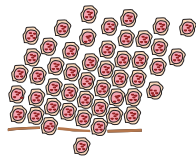
Carcinoma in situ/ preinvasive

Neoplastic cells have not invaded the intact basement membrane.
 ↑ nuclear/cytoplasmic (N/C) ratio and clumped chromatin.
 Neoplastic cells encompass entire thickness.



Invasive carcinoma

Cells have invaded basement membrane using collagenases and hydrolases (metalloproteinases).
 Cell-cell contacts lost by inactivation of E-cadherin.

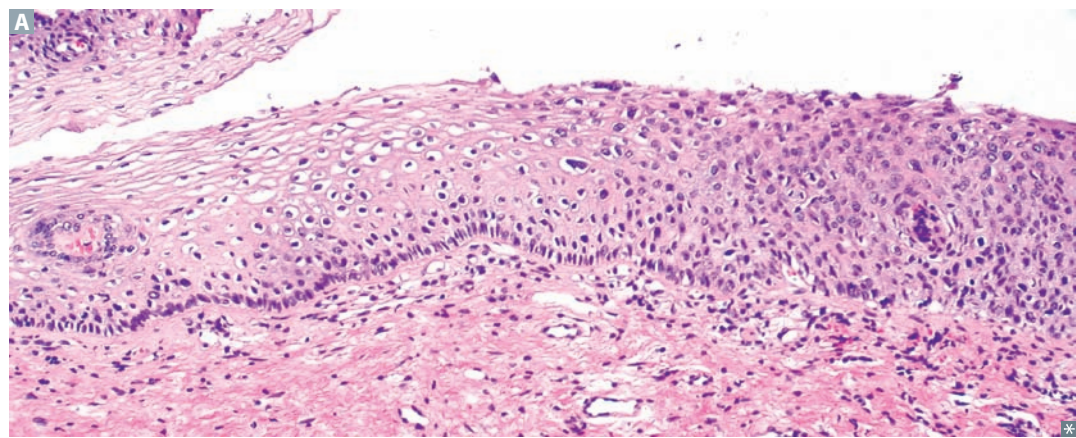
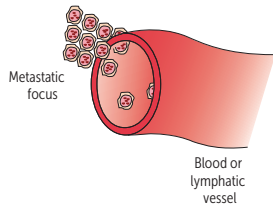


Metastasis

Spread to distant organ, eg, metastatic cells in liver parenchyma.

“Seed and soil” theory of metastasis:

- Seed = tumor embolus.
- Soil = target organ is often the first-encountered capillary bed (eg, liver, lungs, bone, brain, etc).



Normal

Mild dysplasia

Moderate dysplasia

Severe dysplasia/
carcinoma in situ

Tumor grade vs stage

Grade	Degree of cellular differentiation and mitotic activity on histology. Range from low grade (well differentiated) to high grade (poorly differentiated, undifferentiated or anaplastic).	Stage almost always has more prognostic value than 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 pathology (p) findings. Example: cT3N1M0	TNM staging system (S tage = S pread): T = T umor size N = N ode involvement M = M etastases Each TNM factor has independent prognostic value; M factor often most important.

Tumor nomenclature

Carcinoma implies epithelial origin, whereas **sarcoma** denotes mesenchymal origin. Both terms imply malignancy.

Terms for non-neoplastic malformations include hamartoma (disorganized overgrowth of tissues in their native location, eg, Peutz-Jeghers polyps) and choristoma (normal tissue in a foreign location, eg, gastric tissue located in distal ileum in Meckel diverticulum).

Benign tumor is usually well differentiated, well demarcated, low mitotic activity, no metastasis, no necrosis.

Malignant tumor may show poor differentiation, erratic growth, local invasion, metastasis, and ↓ apoptosis. Upregulation of telomerase prevents chromosome shortening and cell death.

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

Cancer epidemiology

Skin cancer (basal > squamous >> melanoma) is the most common cancer (not included in list).

	MALE	FEMALE	NOTES
Incidence	1. Prostate 2. Lung 3. Colon/rectum	1. Breast 2. Lung 3. Colon/rectum	Lung cancer incidence has dropped in men, but has not changed significantly in women.
Mortality	1. Lung 2. Prostate 3. Colon/rectum	1. Lung 2. Breast 3. Colon/rectum	Cancer is the 2nd leading cause of death in the United States (heart disease is 1st).

Paraneoplastic syndromes

MANIFESTATION	DESCRIPTION/MECHANISM	MOST COMMONLY ASSOCIATED CANCER(S)
Cutaneous		
Acanthosis nigricans	Hyperpigmented velvety plaques in axilla and neck	Gastric adenocarcinoma and other visceral malignancies (but more commonly associated with obesity and insulin resistance)
Sign of Leser-Trélat	Sudden onset of multiple seborrheic keratoses	GI adenocarcinomas and other visceral malignancies
Endocrine		
Hypercalcemia	PTHrP ↑ 1,25-(OH) ₂ vitamin D ₃ (calcitriol)	Squamous cell carcinomas of lung, head, and neck; renal, bladder, breast, and ovarian carcinomas Lymphoma
Cushing syndrome	↑ ACTH	Small cell lung cancer
Hyponatremia (SIADH)	↑ ADH	Small cell lung cancer
Hematologic		
Polycythemia	↑ Erythropoietin	Renal cell carcinoma, hepatocellular carcinoma, hemangioblastoma, pheochromocytoma, leiomyoma
Pure red cell aplasia	Anemia with low reticulocytes	Thymoma
Good syndrome	Hypogammaglobulinemia	Thymoma
Trousseau syndrome	Migratory superficial thrombophlebitis	Adenocarcinomas, especially pancreatic
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 Hu, Yo, and Tr antigens in Purkinje cells	Small cell lung cancer, gynecologic and breast cancers, and Hodgkin lymphoma
Paraneoplastic encephalomyelitis	Antibodies against Hu antigens in neurons	Small cell lung cancer
Lambert-Eaton myasthenic syndrome	Antibodies against presynaptic (P/Q-type) Ca ²⁺ channels at NMJ	Small cell lung cancer
Myasthenia gravis	Antibodies against postsynaptic AChR at NMJ	Thymoma

Oncogenes

Gain of function → ↑ cancer risk. Need damage to only 1 allele.

GENE	GENE PRODUCT	ASSOCIATED NEOPLASM
<i>ALK</i>	Receptor tyrosine kinase	Lung adenocarcinoma
<i>BCR-ABL</i>	Tyrosine kinase	CML, ALL
<i>BCL-2</i>	Antiapoptotic molecule (inhibits apoptosis)	Follicular and diffuse large B cell lymphomas
<i>BRAF</i>	Serine/threonine kinase	Melanoma, non-Hodgkin lymphoma
<i>c-KIT</i>	Cytokine receptor	Gastrointestinal stromal tumor (GIST)
<i>c-MYC</i>	Transcription factor	Burkitt lymphoma
<i>HER2/neu (c-erbB2)</i>	Tyrosine kinase	Breast and gastric carcinomas
<i>JAK2</i>	Tyrosine kinase	Chronic myeloproliferative disorders
<i>KRAS</i>	GTPase	Colon cancer, lung cancer, pancreatic cancer
<i>MYCL1</i>	Transcription factor	Lung tumor
<i>MYCN</i>	Transcription factor	Neuroblastoma
<i>RET</i>	Tyrosine kinase	MEN 2A and 2B, medullary thyroid cancer

Tumor suppressor genes

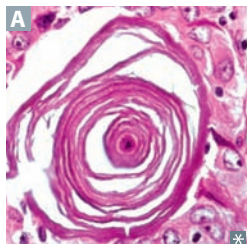
Loss of function → ↑ cancer risk; both alleles must be lost for expression of disease.

GENE	ASSOCIATED CONDITION	GENE PRODUCT
<i>APC</i>	Colorectal cancer (associated with FAP)	
<i>BRCA1/BRCA2</i>	Breast and ovarian cancer	DNA repair protein
<i>CDKN2A</i>	Melanoma, pancreatic cancer	p16, blocks G ₁ → S phase
<i>DCC</i>	Colon cancer	DCC—Deleted in Colon Cancer
<i>DPC4/SMAD4</i>	Pancreatic cancer	DPC—Deleted in Pancreatic Cancer
<i>MEN1</i>	MEN 1	Menin
<i>NF1</i>	NeuroFibromatosis type 1	Ras GTPase activating protein (neurofibromin)
<i>NF2</i>	NeuroFibromatosis type 2	Merlin (schwannomin) protein
<i>PTEN</i>	Breast cancer, prostate cancer, endometrial cancer	
<i>Rb</i>	Retinoblastoma, osteosarcoma	Inhibits E2F; blocks G ₁ → S phase
<i>TP53</i>	Most human cancers, Li-Fraumeni syndrome	p53, activates p21, blocks G ₁ → S phase
<i>TSC1</i>	Tuberous sclerosis	Hamartin protein
<i>TSC2</i>	Tuberous sclerosis	Tuberin protein
<i>VHL</i>	von Hippel-Lindau disease, renal cell carcinoma	Inhibits hypoxia inducible factor 1 α
<i>WT1/WT2</i>	Wilms Tumor (nephroblastoma)	

Oncogenic microbes	Microbe	Associated cancer
	EBV	Burkitt lymphoma, Hodgkin lymphoma, nasopharyngeal carcinoma, 1° CNS lymphoma (in immunocompromised patients)
	HBV, HCV	Hepatocellular carcinoma, lymphoma
	HHV-8	Kaposi sarcoma
	HPV	Cervical and penile/anal carcinoma (types 16, 18), head and neck cancer
	<i>H pylori</i>	Gastric adenocarcinoma and MALT lymphoma
	HTLV-1	Adult T-cell leukemia/lymphoma
	Liver fluke (<i>Clonorchis sinensis</i>)	Cholangiocarcinoma
	<i>Schistosoma haematobium</i>	Bladder cancer (squamous cell)

Carcinogens

TOXIN	ORGAN	IMPACT
Aflatoxins (<i>Aspergillus</i>)	Liver	Hepatocellular carcinoma
Alkylating agents	Blood	Leukemia/lymphoma
Aromatic amines (eg, benzidine, 2-naphthylamine)	Bladder	Transitional cell carcinoma
Arsenic	Liver Lung Skin	Angiosarcoma Lung cancer Squamous cell carcinoma
Asbestos	Lung	Bronchogenic carcinoma > mesothelioma
Carbon tetrachloride	Liver	Centrilobular necrosis, fatty change
Cigarette smoke	Bladder Cervix Esophagus Kidney Larynx Lung Pancreas	Transitional cell carcinoma Cervical carcinoma Squamous cell carcinoma/adenocarcinoma Renal cell carcinoma Squamous cell carcinoma Squamous cell and small cell carcinoma Pancreatic adenocarcinoma
Ethanol	Esophagus Liver	Squamous cell carcinoma Hepatocellular carcinoma
Ionizing radiation	Thyroid	Papillary thyroid carcinoma
Nitrosamines (smoked foods)	Stomach	Gastric cancer
Radon	Lung	Lung cancer (2nd leading cause after cigarette smoke)
Vinyl chloride	Liver	Angiosarcoma

Psammoma bodies

Laminated, concentric spherules with dystrophic calcification **A**, **PSaMM**oma bodies are seen in:

- **P**apillary carcinoma of thyroid
- **S**erous papillary cystadenocarcinoma of ovary
- **M**eningioma
- **M**alignant mesothelioma

Serum tumor markers

Tumor markers should not be used as the 1° tool for cancer diagnosis or screening. They may be used to monitor tumor recurrence and response to therapy, but definitive diagnosis is usually made via biopsy.

Alkaline phosphatase

Metastases to bone or liver, Paget disease of bone, seminoma (placental ALP).

α-fetoprotein

Hepatocellular carcinoma, hepatoblastoma, yolk sac (endodermal sinus) tumor, mixed germ cell tumor.

Normally made by fetus. Transiently elevated in pregnancy. High levels associated with neural tube and abdominal wall defects, low levels associated with Down syndrome.

β-hCG

Hydantidiform moles and **C**horiocarcinomas (**G**estational 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.

CEA

Carcino**E**mbrionic **A**ntigen. Very nonspecific but produced by ~ 70% of colorectal and pancreatic cancers; also produced by gastric, breast, and medullary thyroid carcinomas.

PSA

Prostate-specific antigen. Prostate cancer.

Can also be elevated in BPH and prostatitis. Questionable risk/benefit for screening.

P-glycoprotein

Also known as multidrug resistance protein 1 (MDR1). Classically seen in adrenal cell carcinoma but also expressed by other cancer cells (eg, colon, liver). Used to pump out toxins, including chemotherapeutic agents (one mechanism of ↓ responsiveness or resistance to chemotherapy over time).

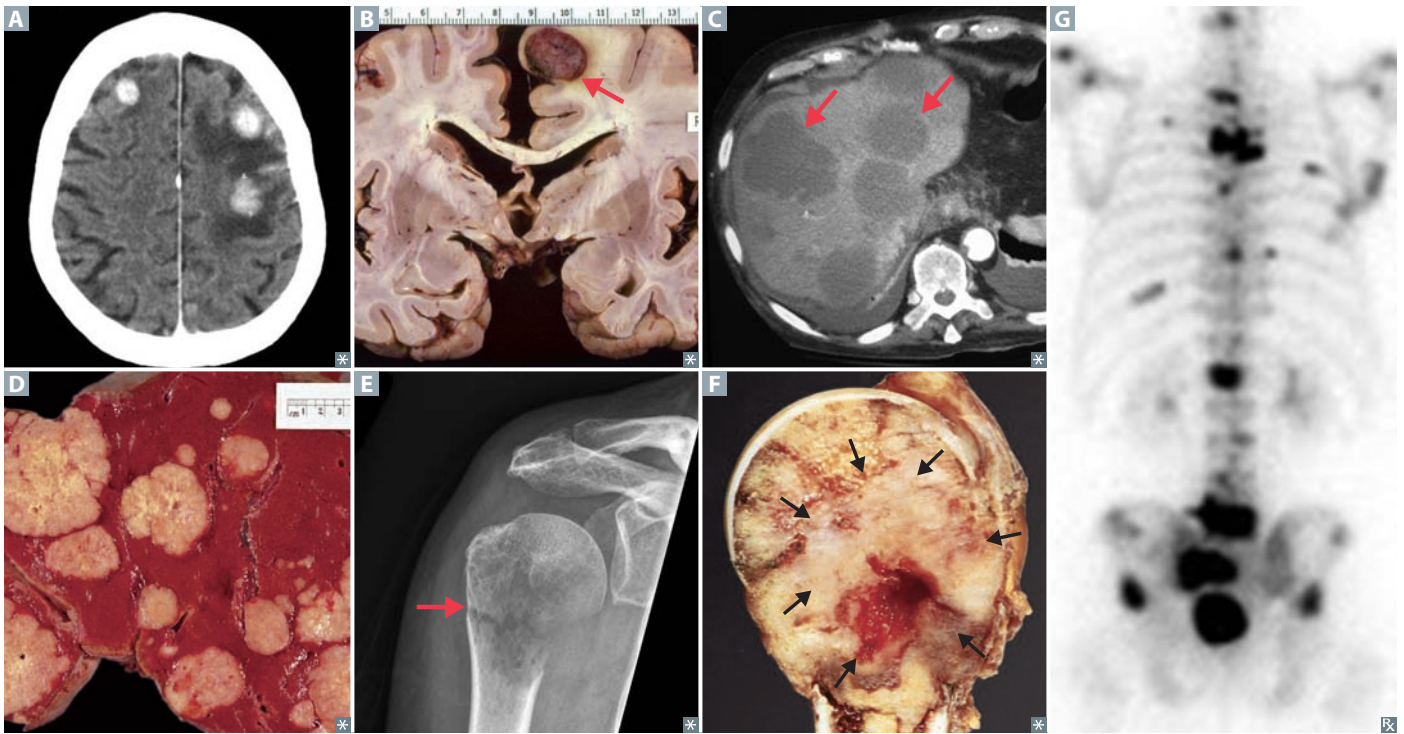
Cachexia

Weight loss, muscle atrophy, and fatigue that occur in chronic disease (eg, cancer, AIDS, heart failure, COPD). Mediated by TNF, IFN-γ, IL-1, and IL-6.

Common metastases

Most sarcomas spread hematogenously; most carcinomas spread via lymphatics (except hepatocellular carcinoma, renal cell carcinoma, follicular thyroid carcinoma, and choriocarcinoma).

SITE OF METASTASIS	1° TUMOR	NOTES
Brain	Lung > breast > prostate > melanoma > GI.	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.	Liver C D and lung are the most common sites of metastasis after the regional lymph nodes.
Bone	Prostate, breast > lung, thyroid, kidney.	Bone metastasis E F >>> 1° bone tumors (eg, multiple myeloma, lytic). Common mets to bone: breast (mixed), lung (mixed), thyroid (lytic), kidney (lytic), prostate (blastic). Predilection for axial skeleton G .



Pharmacology

“Take me, I am the drug; take me, I am hallucinogenic.”

—Salvador Dali

“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

“Once you get locked into a serious drug collection, the tendency is to push it as far as you can.”

—Hunter S. Thompson

Preparation for questions on pharmacology is straightforward. Memorizing 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. Specific drug dosages or trade names are generally not testable. 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 on NSAIDs. Much of the material is clinically relevant. We occasionally mention drugs that are no longer available in the US, but help illustrate high-yield pharmacologic or disease mechanisms. They are highlighted as being of historical significance and should not appear on the USMLE. However, recently approved drugs are fair game for the exam.

▶ Pharmacokinetics & Pharmacodynamics	236
▶ Autonomic Drugs	241
▶ Toxicities and Side Effects	251
▶ Miscellaneous	255

▶ PHARMACOLOGY—PHARMACOKINETICS & PHARMACODYNAMICS

Enzyme kinetics

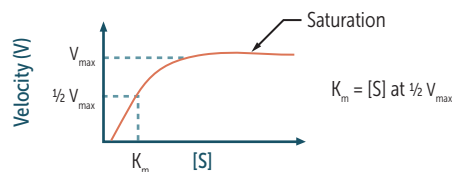
Michaelis-Menten kinetics

K_m is inversely related to the affinity of the enzyme for its substrate.

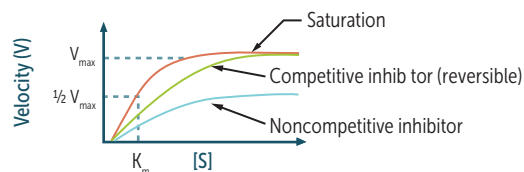
V_{max} is directly proportional to the enzyme concentration.

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

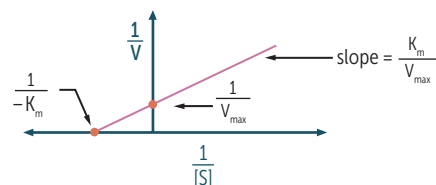


Lineweaver-Burk plot

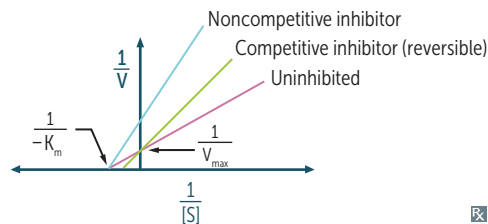
↑ y-intercept, ↓ V_{max} .

The further to the right the x-intercept (ie, closer to zero), the greater the K_m and the lower the affinity.

Reversible competitive inhibitors cross each other competitively, whereas noncompetitive inhibitors do not.



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_{max}	Unchanged	↓	↓
Effect on K_m	↑	Unchanged	Unchanged
Pharmacodynamics	↓ potency	↓ efficacy	↓ efficacy

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.

Volume of distribution (V_d) 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 (↓ protein binding, ↑ 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 _d	COMPARTMENT	DRUG TYPES
Low	Blood	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.

$$CL = \frac{\text{rate of elimination of drug}}{\text{plasma drug concentration}} = V_d \times K_e \text{ (elimination constant)}$$

Half-life (t_{1/2}) The time required to change the amount of drug in the body by ½ 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.

$$t_{1/2} = \frac{0.693 \times V_d}{CL} \text{ in first-order elimination}$$

# of half-lives	1	2	3	4
% remaining	50%	25%	12.5%	6.25%

Dosage calculations

$$\text{Loading dose} = \frac{C_p \times V_d}{F}$$

$$\text{Maintenance dose} = \frac{C_p \times CL \times \tau}{F}$$

C_p = target plasma concentration at steady state
 τ = 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.

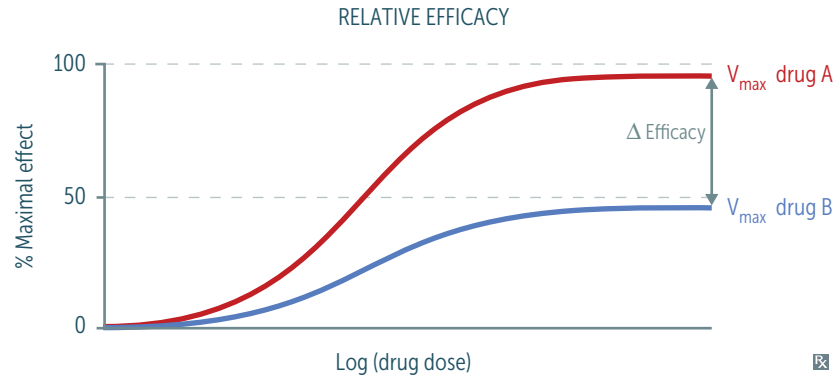
Types of drug interactions

TERM	DEFINITION	EXAMPLE
Additive	Effect of substance A and B together is equal to the sum of their individual effects	Aspirin and acetaminophen
Permissive	Presence of substance A is required for the full effects of substance B	Cortisol on catecholamine responsiveness
Synergistic	Effect of substance A and B together is greater than the sum of their individual effects	Clopidogrel with aspirin
Tachyphylactic	Acute decrease in response to a drug after initial/repeated administration	MDMA and LSD

Efficacy vs potency

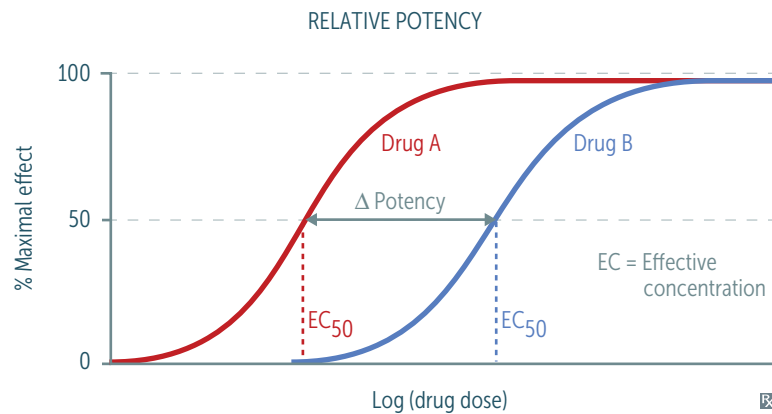
Efficacy

Maximal effect a drug can produce. Represented by the y-value (V_{max}). \uparrow y-value = $\uparrow V_{max}$ = \uparrow efficacy. Unrelated to potency (ie, efficacious drugs can have high or low potency). Partial agonists have less efficacy than full agonists.

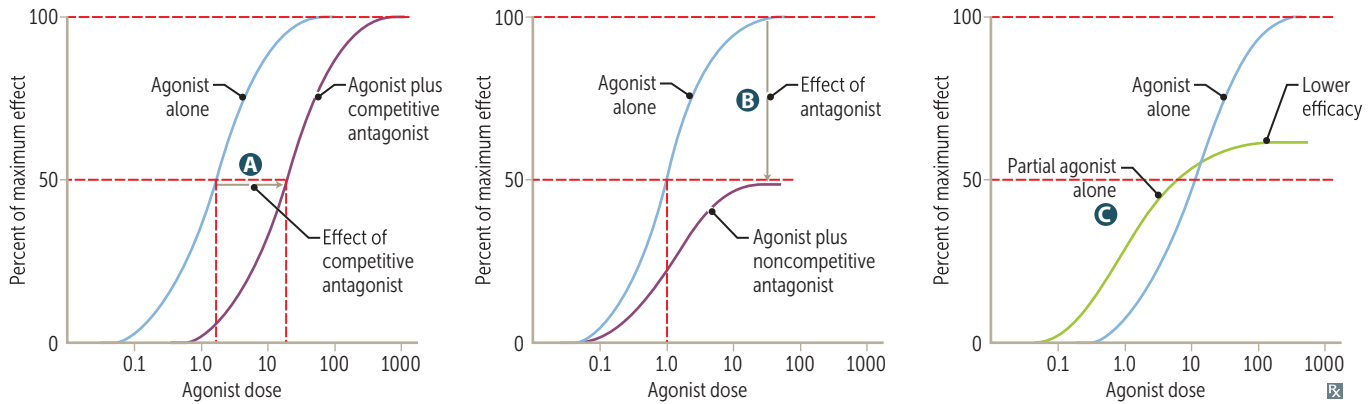


Potency

Amount of drug needed for a given effect. Represented by the x-value (EC_{50}). Left shifting = $\downarrow EC_{50}$ = \uparrow potency = \downarrow drug needed. Unrelated to efficacy (ie, potent drugs can have high or low efficacy).



Receptor binding



AGONIST WITH	EFFECT	EXAMPLE
A Competitive antagonist	Shifts curve right (↓ potency), no change in efficacy. Can be overcome by ↑ the concentration of agonist substrate.	Diazepam (agonist) + flumazenil (competitive antagonist) on GABA receptor.
B Noncompetitive antagonist	Shifts curve down (↓ efficacy). Cannot be overcome by ↑ agonist substrate concentration.	Norepinephrine (agonist) + phenoxybenzamine (noncompetitive antagonist) on α-receptors.
C Partial agonist (alone)	Acts at same site as full agonist, but with lower maximal effect (↓ efficacy). Potency is an independent variable.	Morphine (full agonist) vs buprenorphine (partial agonist) at opioid μ-receptors.

Therapeutic index

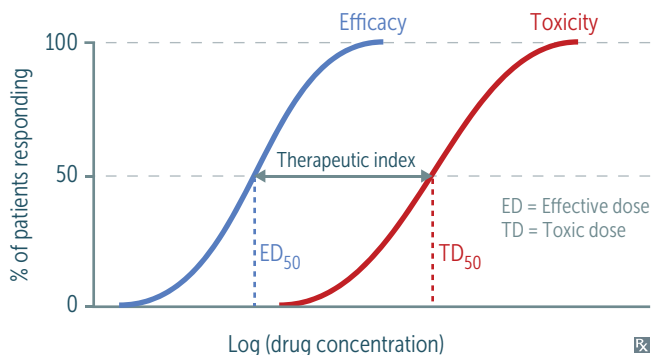
Measurement of drug safety.

$$\frac{TD_{50}}{ED_{50}} = \frac{\text{median toxic dose}}{\text{median effective dose}}$$

Therapeutic window—dosage range that can safely and effectively treat disease.

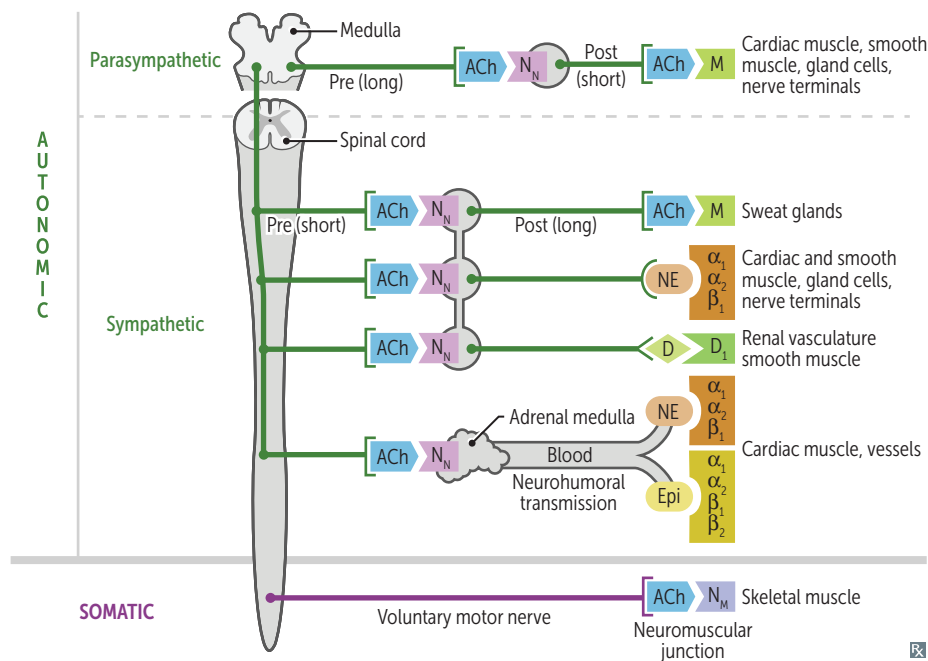
TITE: Therapeutic Index = TD_{50} / ED_{50} .

Safer drugs have higher TI values. Drugs with lower TI values frequently require monitoring (eg, digoxin, lithium, theophylline, warfarin). LD₅₀ (lethal median dose) often replaces TD₅₀ in animal studies.



▶ PHARMACOLOGY—AUTONOMIC DRUGS

Central and peripheral nervous system



Note that the adrenal medulla and sweat glands are part of the sympathetic nervous system but are innervated by cholinergic fibers.
 Botulinum toxin prevents release of acetylcholine at cholinergic terminals.

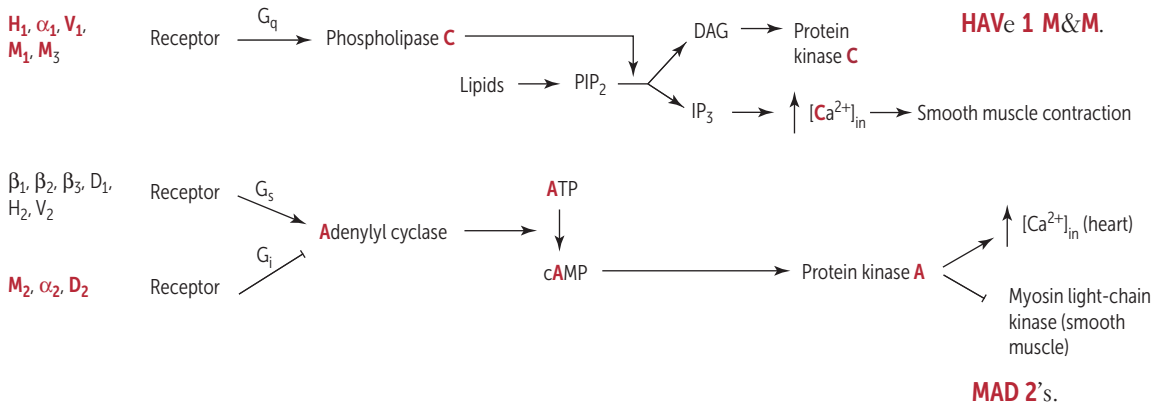
ACh receptors

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).

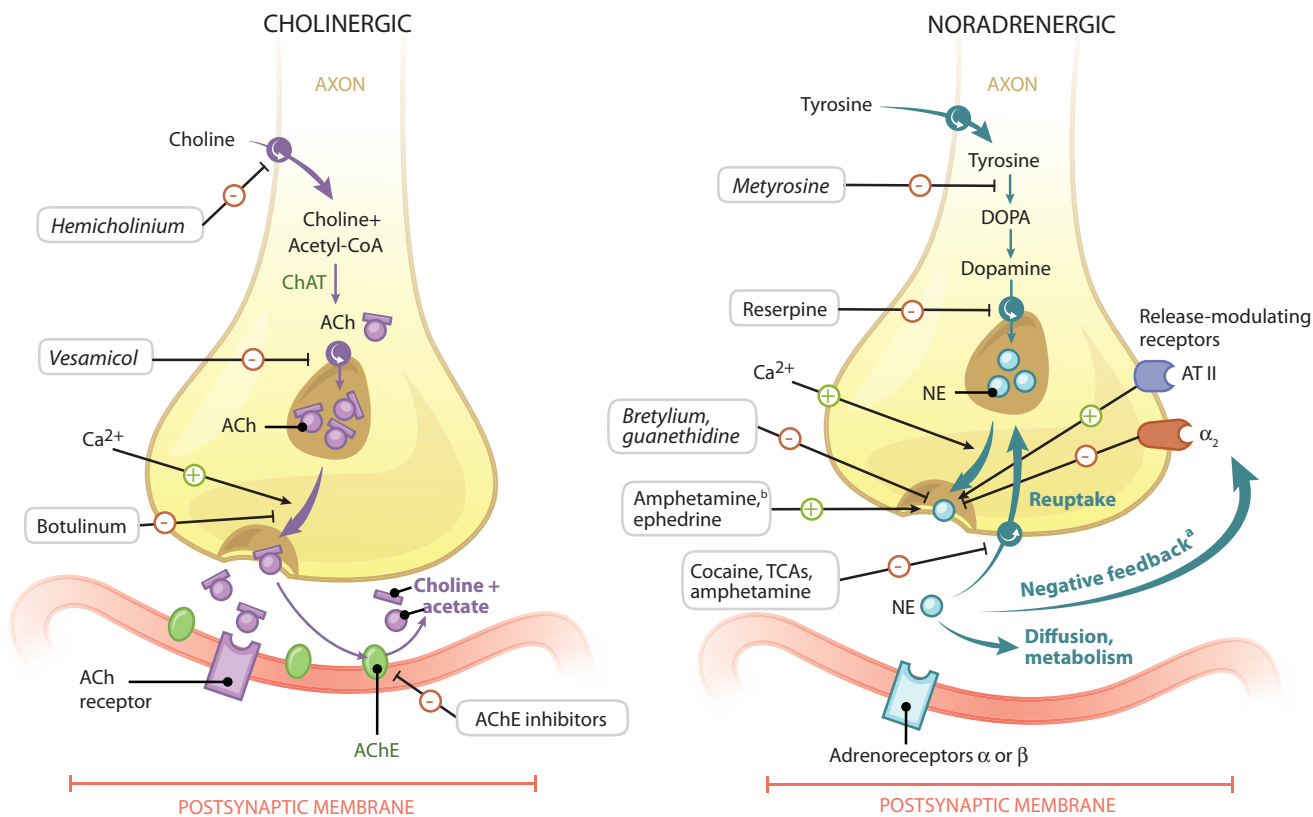
G-protein–linked 2nd messengers

RECEPTOR	G-PROTEIN CLASS	MAJOR FUNCTIONS
Sympathetic		
α_1	q	↑ vascular smooth muscle contraction, ↑ pupillary dilator muscle contraction (mydriasis), ↑ intestinal and bladder sphincter muscle contraction
α_2	i	↓ sympathetic (adrenergic) outflow, ↓ insulin release, ↓ lipolysis, ↑ platelet aggregation, ↓ aqueous humor production
β_1	s	↑ heart rate, ↑ contractility, ↑ renin release, ↑ lipolysis
β_2	s	Vasodilation, bronchodilation, ↑ lipolysis, ↑ insulin release, ↓ uterine tone (tocolysis), ciliary muscle relaxation, ↑ aqueous humor production
β_3	s	↑ lipolysis, ↑ thermogenesis in skeletal muscle
Parasympathetic		
M_1	q	CNS, enteric nervous system
M_2	i	↓ heart rate and contractility of atria
M_3	q	↑ exocrine gland secretions (eg, lacrimal, sweat, salivary, gastric acid), ↑ gut peristalsis, ↑ bladder contraction, bronchoconstriction, ↑ pupillary sphincter muscle contraction (miosis), ciliary muscle contraction (accommodation)
Dopamine		
D_1	s	Relaxes renal vascular smooth muscle
D_2	i	Modulates transmitter release, especially in brain
Histamine		
H_1	q	↑ nasal and bronchial mucus production, ↑ vascular permeability, contraction of bronchioles, pruritus, pain
H_2	s	↑ gastric acid secretion
Vasopressin		
V_1	q	↑ vascular smooth muscle contraction
V_2	s	↑ H ₂ O permeability and reabsorption in collecting tubules of kidney (V_2 is found in the 2 kidneys)

“After **q**isses (kisses), you get a **q**iq (kick) out of **s**iq (sick) **s**qs (super kinky sex).”



Autonomic drugs



Circles with rotating arrows represent transporters. Drugs in *italics* are of historical significance.

^aRelease of norepinephrine from a sympathetic nerve ending is modulated by norepinephrine itself, acting on presynaptic α₂-autoreceptors.

^bAmphetamines 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.

Tyramine

Normally degraded by monoamine oxidase (MAO). Levels ↑ in patients taking MAO inhibitors who ingest tyramine-rich foods (eg, cheese, wine). Excess tyramine enters presynaptic vesicles and displaces other neurotransmitters (eg, NE) → ↑ active presynaptic neurotransmitters → ↑ diffusion of neurotransmitters into synaptic cleft → ↑ sympathetic stimulation. Classically results in a hypertensive crisis.

Cholinomimetic agents

DRUG	ACTION	APPLICATIONS
Direct agonists		
Bethanechol	Activates b owel and b ladder smooth muscle; resistant to AChE. “ B ethany, call (b ethanechol) me to activate your b owels and b ladder.”	Postoperative ileus, neurogenic ileus, urinary retention
Carbachol	C arbon copy of a cetyl ch oline.	Constricts pupil and relieves intraocular pressure in open-angle glaucoma
Methacholine	Stimulates m uscarinic receptors in airway when inhaled.	Challenge test for diagnosis of asthma
Pilocarpine	Contracts ciliary muscle of eye (open-angle glaucoma), pupillary sphincter (closed-angle glaucoma); resistant to AChE. “You cry, drool, and sweat on your ‘ p ilow.’”	Potent stimulator of sweat, tears, and saliva Open-angle and closed-angle glaucoma, xerostomia (Sjögren syndrome)
Indirect agonists (anticholinesterases)		
Donepezil, galantamine, rivastigmine	↑ ACh.	Alzheimer disease.
Edrophonium	↑ ACh.	Historically, diagnosis of myasthenia gravis (extremely short acting). Myasthenia now diagnosed by anti-AChR Ab (anti-acetylcholine receptor antibody) test.
Neostigmine	↑ ACh. Neo CNS = No CNS penetration (quaternary amine).	Postoperative and neurogenic ileus and urinary retention, myasthenia gravis, reversal of neuromuscular junction blockade (postoperative).
Physostigmine	↑ ACh. Phys ostigmine “ phy xes” atropine overdose.	Anticholinergic toxicity; crosses blood-brain barrier → CNS (tertiary amine).
Pyridostigmine	↑ ACh; ↑ muscle strength. Pyrid ostigmine gets rid of m asthenia g ra ^v is.	Myasthenia gravis (long acting); does not penetrate CNS (quaternary amine).

Note: With all cholinomimetic agents, watch for exacerbation of COPD, asthma, and peptic ulcers when giving to susceptible patients.

Cholinesterase inhibitor poisoning

Often due to organophosphates, such as parathion, that **irreversibly** inhibit AChE. Causes **D**iarrhea, **U**rination, **M**iosis, **B**ronchospasm, **B**radycardia, **E**xcitation of skeletal muscle and CNS, **L**acrimation, **S**weating, and **S**alivation. May lead to respiratory failure if untreated.

DUMBBELSS.

Organophosphates are often components of insecticides; poisoning usually seen in farmers. Antidote—atropine (competitive inhibitor) + pralidoxime (regenerates AChE if given early).

Muscarinic antagonists

DRUGS	ORGAN SYSTEMS	APPLICATIONS
Atropine, homatropine, tropicamide	Eye	Produce mydriasis and cycloplegia.
Benztropine	CNS	P arkinson 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.

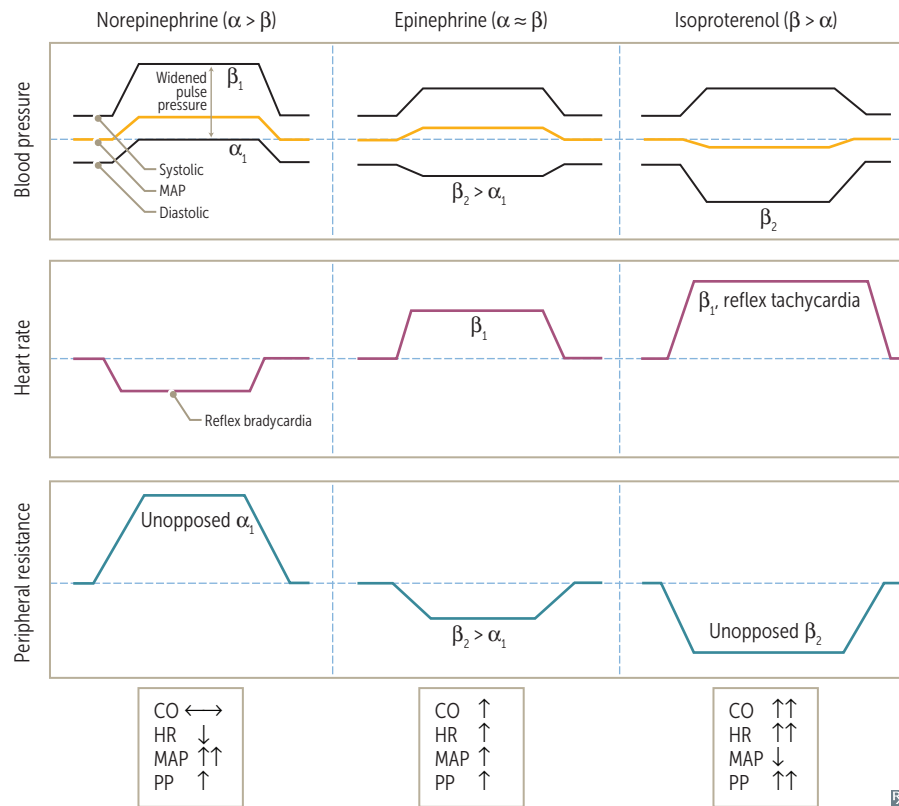
ORGAN SYSTEM	ACTION	NOTES
Eye	↑ pupil dilation, cycloplegia	Blocks DUMBBE LSS in cholinesterase inhibitor poisoning. Does not block excitation of skeletal muscle and CNS (mediated by nicotinic receptors).
Airway	↓ secretions	
Stomach	↓ acid secretion	
Gut	↓ motility	
Bladder	↓ urgency in cystitis	
ADVERSE EFFECTS	↑ body temperature (due to ↓ sweating); rapid pulse; dry mouth; dry, flushed skin; cycloplegia ; constipation; disorientation Can cause acute angle-closure glaucoma in elderly (due to mydriasis), urinary retention in men with prostatic hyperplasia, and hyperthermia in infants	Side effects: H ot as a hare D ry as a bone R ed as a beet B lind as a bat M ad as a hatter Jimson weed (<i>Datura</i>) → gardener’s pupil (mydriasis due to plant alkaloids)

Sympathomimetics

DRUG	ACTION	APPLICATIONS
Direct sympathomimetics		
Albuterol, salmeterol	$\beta_2 > \beta_1$	Albuterol for acute asthma or COPD. Salmeterol for long-term asthma or COPD control.
Dobutamine	$\beta_1 > \beta_2, \alpha$	Heart failure (HF) (inotropic > chronotropic), cardiac stress testing.
Dopamine	$D_1 = D_2 > \beta > \alpha$	Unstable bradycardia, HF, shock; inotropic and chronotropic effects at lower doses due to β effects; vasoconstriction at high doses due to α effects.
Epinephrine	$\beta > \alpha$	Anaphylaxis, asthma, open-angle glaucoma; α effects predominate at high doses. Significantly stronger effect at β_2 -receptor than norepinephrine.
Fenoldopam	D_1	Postoperative hypertension, hypertensive crisis. Vasodilator (coronary, peripheral, renal, and splanchnic). Promotes natriuresis. Can cause hypotension and tachycardia.
Isoproterenol	$\beta_1 = \beta_2$	Electrophysiologic evaluation of tachyarrhythmias. Can worsen ischemia.
Midodrine	α_1	Autonomic insufficiency and postural hypotension. May exacerbate supine hypertension.
Norepinephrine	$\alpha_1 > \alpha_2 > \beta_1$	Hypotension, septic shock.
Phenylephrine	$\alpha_1 > \alpha_2$	Hypotension (vasoconstrictor), ocular procedures (mydriatic), rhinitis (decongestant).
Indirect sympathomimetics		
Amphetamine	Indirect general agonist, reuptake inhibitor, also releases stored catecholamines	Narcolepsy, obesity, ADHD.
Cocaine	Indirect general agonist, reuptake inhibitor	Causes vasoconstriction and local anesthesia. Never give β -blockers if cocaine intoxication is suspected (can lead to unopposed α_1 activation and extreme hypertension).
Ephedrine	Indirect general agonist, releases stored catecholamines	Nasal decongestion, urinary incontinence, hypotension.

Norepinephrine vs isoproterenol

Norepinephrine ↑ systolic and diastolic pressures as a result of α_1 -mediated vasoconstriction → ↑ mean arterial pressure → reflex bradycardia. However, isoproterenol (no longer commonly used) has little α effect but causes β_2 -mediated vasodilation, resulting in ↓ mean arterial pressure and ↑ heart rate through β_1 and reflex activity.

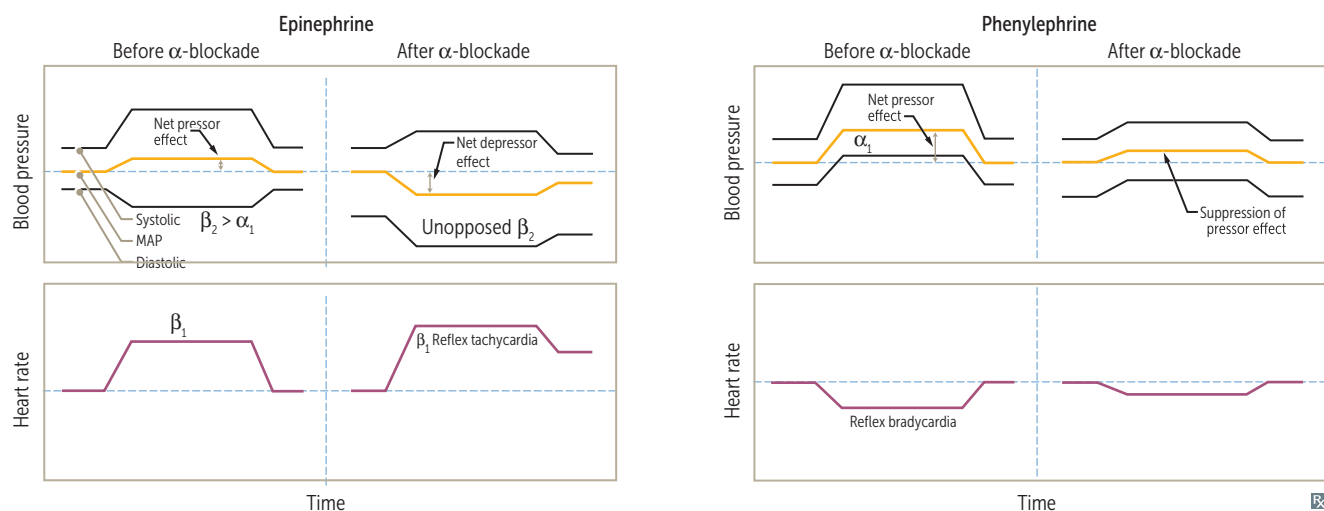


Sympatholytics (α_2 -agonists)

DRUG	APPLICATIONS	ADVERSE EFFECTS
Clonidine, guanfacine	Hypertensive urgency (limited situations), ADHD, Tourette syndrome	CNS depression, bradycardia, hypotension, respiratory depression, miosis
α-methyl dopa	Hypertension in pregnancy	Direct Coombs ⊕ hemolysis, SLE-like syndrome

α -blockers

DRUG	APPLICATIONS	ADVERSE EFFECTS
Nonselective		
Phenoxybenzamine (irreversible)	Pheochromocytoma (used preoperatively) to prevent catecholamine (hypertensive) crisis	Orthostatic hypotension, reflex tachycardia
Phentolamine (reversible)	Give to patients on MAO inhibitors who eat tyramine-containing foods	
α_1 selective (-osin ending)		
Prazosin, terazosin, doxazosin, tamsulosin	Urinary symptoms of BPH; PTSD (prazosin); hypertension (except tamsulosin)	1st-dose orthostatic hypotension, dizziness, headache
α_2 selective		
Mirtazapine	Depression	Sedation, \uparrow serum cholesterol, \uparrow appetite

 α -blockade of epinephrine vs phenylephrine

Shown above are the effects of an α -blocker (eg, phentolamine) on blood pressure responses to epinephrine and phenylephrine. The epinephrine response exhibits reversal of the mean blood pressure change, from a net increase (the α response) to a net decrease (the β_2 response). The response to phenylephrine is suppressed but not reversed because phenylephrine is a “pure” α -agonist without β action.

β-blockers

Acebutolol, atenolol, betaxolol, carvedilol, esmolol, labetalol, metoprolol, nadolol, nebivolol, pindolol, propranolol, timolol.

APPLICATION	ACTIONS	NOTES
Angina pectoris	↓ heart rate and contractility, resulting in ↓ O ₂ consumption	
MI	↓ mortality	
SVT (metoprolol, esmolol)	↓ AV conduction velocity (class II antiarrhythmic)	
Hypertension	↓ cardiac output, ↓ renin secretion (due to β ₁ -receptor blockade on JGA cells)	
HF	↓ mortality (bisoprolol, carvedilol, metoprolol)	
Glaucoma (timolol)	↓ secretion of aqueous humor	
Variceal bleeding (nadolol, propranolol)	↓ hepatic venous pressure gradient and portal hypertension	
ADVERSE EFFECTS	Erectile dysfunction, cardiovascular adverse effects (bradycardia, AV block, HF), CNS adverse effects (seizures, sedation, sleep alterations), dyslipidemia (metoprolol), and asthma/COPD exacerbations	Use with caution in cocaine users due to risk of unopposed α-adrenergic receptor agonist activity Despite theoretical concern of masking hypoglycemia in diabetics, benefits likely outweigh risks; not contraindicated
SELECTIVITY	β ₁ -selective antagonists (β ₁ > β ₂)— a cebutolol (partial agonist), a tenolol, b etaxolol, e smolol, m etoprolol	Selective antagonists mostly go from A to M (β ₁ with 1 st half of alphabet)
	Nonselective antagonists (β ₁ = β ₂)— n adolol, p indolol (partial agonist), p ropranolol, t imolol	N onselective antagonists mostly go from N to Z (β ₂ with 2 nd half of alphabet)
	Nonselective α- and β-antagonists—carvedilol, labetalol	Nonselective α- and β-antagonists have modified suffixes (instead of “-olol”)
	Nebivolol combines cardiac-selective β ₁ -adrenergic blockade with stimulation of β ₃ -receptors, which activate nitric oxide synthase in the vasculature	

Ingested seafood toxins

TOXIN	SOURCE	ACTION	SYMPTOMS	TREATMENT
Tetrodotoxin	Pufferfish.	Highly potent toxin; binds fast voltage-gated Na ⁺ channels in cardiac/nerve tissue, preventing depolarization.	Nausea, diarrhea, paresthesias, weakness, dizziness, loss of reflexes.	Primarily supportive.
Ciguatoxin	Reef fish such as barracuda, snapper, and moray eel.	Opens Na ⁺ channels, causing depolarization.	Symptoms mimic cholinergic poisoning.	Primarily supportive.
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.

▶ PHARMACOLOGY—TOXICITIES AND SIDE EFFECTS

Specific toxicity treatments

TOXIN	TREATMENT
Acetaminophen	N-acetylcysteine (replenishes glutathione)
AChE inhibitors, organophosphates	Atropine > pralidoxime
Amphetamines (basic)	NH ₄ Cl (acidify urine)
Antimuscarinic, anticholinergic agents	Physostigmine, control hyperthermia
Arsenic	Dimercaprol, succimer
Benzodiazepines	Flumazenil
β-blockers	Saline, atropine, glucagon
Carbon monoxide	100% O ₂ , hyperbaric O ₂
Copper	Penicillamine, trientine
Cyanide	Nitrite + thiosulfate, hydroxocobalamin
Digitalis (digoxin)	Anti-dig Fab fragments
Gold	Penicillamine, dimercaprol (BAL), succimer
Heparin	Protamine sulfate
Iron	Deferoxamine, deferasirox, deferiprone
Lead	EDTA, dimercaprol, succimer, penicillamine
Mercury	Dimercaprol, succimer
Methanol, ethylene glycol (antifreeze)	Fomepizole > ethanol, dialysis
Methemoglobin	Meth ylene blue, vitamin C
Opioids	Naloxone
Salicylates	NaHCO ₃ (alkalinize urine), dialysis
TCAs	NaHCO ₃
Warfarin	Vitamin K (delayed effect), fresh frozen plasma (immediate)

Drug reactions—cardiovascular

DRUG REACTION	CAUSAL AGENTS
Coronary vasospasm	Cocaine, sumatriptan, ergot alkaloids
Cutaneous flushing	Vancomycin, Adenosine, Niacin, Ca ²⁺ channel blockers, Echinocandins (VANCE)
Dilated cardiomyopathy	Anthracyclines (eg, doxorubicin, daunorubicin); prevent with dexrazoxane
Torsades de pointes	AntiArrhythmics (class IA, III), antiBiotics (eg, macrolides), anti“C”ychotics (eg, haloperidol), antiDeypressants (eg, TCAs), antiEmetics (eg, ondansetron) (ABCDE).

Drug reactions—endocrine/reproductive

DRUG REACTION	CAUSAL AGENTS	NOTES
Adrenocortical insufficiency	HPA suppression 2° to glucocorticoid withdrawal	
Hot flashes	Tamoxifen, clomiphene	
Hyperglycemia	Tacrolimus, Protease inhibitors, Niacin, HCTZ, Corticosteroids	Taking Pills Necessitates Having blood Checked
Hypothyroidism	Lithium, amiodarone, sulfonamides	

Drug reactions—GI

DRUG REACTION	CAUSAL AGENTS	NOTES
Acute cholestatic hepatitis, jaundice	Erythromycin	
Diarrhea	Acamprosate, acarbose, cholinesterase inhibitors, colchicine, erythromycin, ezetimibe, metformin, misoprostol, orlistat, pramlintide, quinidine, SSRIs	
Focal to massive hepatic necrosis	Halothane, <i>Amanita phalloides</i> (death cap mushroom), Valproic acid, Acetaminophen	Liver “ HAVAc ”
Hepatitis	Rifampin, isoniazid, pyrazinamide, statins, fibrates	
Pancreatitis	Didanosine, Corticosteroids, Alcohol, Valproic acid, Azathioprine, Diuretics (furosemide, HCTZ)	Drugs Causing A Violent Abdominal Distress
Pill-induced esophagitis	Tetracyclines, bisphosphonates, potassium chloride	Caustic effect minimized with upright posture and adequate water ingestion.
Pseudomembranous colitis	Clindamycin, ampicillin, cephalosporins	Antibiotics predispose to superinfection by resistant <i>C difficile</i>

Drug reactions—hematologic

DRUG REACTION	CAUSAL AGENTS	NOTES
Agranulocytosis	Clozapine, Carbamazepine, Propylthiouracil, Methimazole, Colchicine, Ganciclovir	Can Cause Pretty Major Collapse of Granulocytes
Aplastic anemia	Carbamazepine, Methimazole, NSAIDs, Benzene, Chloramphenicol, Propylthiouracil	Can't Make New Blood Cells Properly
Direct Coombs-positive hemolytic anemia	Methyldopa, penicillin	
Gray baby syndrome	Chloramphenicol	
Hemolysis in G6PD deficiency	Isoniazid, Sulfonamides, Dapsone, Primaquine, Aspirin, Ibuprofen, Nitrofurantoin	Hemolysis IS D PAIN
Megaloblastic anemia	Phenytoin, Methotrexate, Sulfa drugs	Having a blast with PMS
Thrombocytopenia	Heparin	
Thrombotic complications	OCPs, hormone replacement therapy	

Drug reactions—musculoskeletal/skin/connective tissue

DRUG REACTION	CAUSAL AGENTS	NOTES
Fat redistribution	Protease inhibitors, Glucocorticoids	Fat PiG
Gingival hyperplasia	Phenytoin, Ca ²⁺ channel blockers, cyclosporine	
Hyperuricemia (gout)	Pyrazinamide, Thiazides, Furosemide, Niacin, Cyclosporine	Painful Tophi and Feet Need Care
Myopathy	Fibrates, niacin, colchicine, hydroxychloroquine, interferon- α , penicillamine, statins, glucocorticoids	
Osteoporosis	Corticosteroids, heparin	
Photosensitivity	Sulfonamides, Amiodarone, Tetracyclines, 5-FU	SAT For Photo
Rash (Stevens-Johnson syndrome)	Anti-epileptic drugs (especially lamotrigine), allopurinol, sulfa drugs, penicillin	Steven Johnson has epileptic allergy to sulfa drugs and penicillin
SLE-like syndrome	Sulfa drugs, Hydralazine, Isoniazid, Procainamide, Phenytoin, Etanercept	Having lupus is “ SHIPP-E ”
Teeth discoloration	Tetracyclines	
Tendonitis, tendon rupture, and cartilage damage	Fluoroquinolones	

Drug reactions—neurologic

DRUG REACTION	CAUSAL AGENTS	NOTES
Cinchonism	Quinidine, quinine	
Parkinson-like syndrome	Antipsychotics, Reserpine, Metoclopramide	Cogwheel rigidity of ARM
Seizures	Isoniazid (vitamin B ₆ deficiency), Bupropion, Imipenem/cilastatin, Tramadol, Enflurane	With seizures, I BITE my tongue
Tardive dyskinesia	Antipsychotics, metoclopramide	

Drug reactions—renal/genitourinary

DRUG REACTION	CAUSAL AGENTS	NOTES
Diabetes insipidus	Lithium, demeclocycline	
Fanconi syndrome	Tenofovir, ifosfamide	
Hemorrhagic cystitis	Cyclophosphamide, ifosfamide	Prevent by coadministering with mesna
Interstitial nephritis	Methicillin, NSAIDs, furosemide	
SIADH	Carbamazepine, Cyclophosphamide, SSRIs	Can't Concentrate Serum Sodium

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
Antimuscarinic	Atropine, TCAs, H ₁ -blockers, antipsychotics
Disulfiram-like reaction	Metronidazole, certain cephalosporins, griseofulvin, procarbazine, 1st-generation sulfonyleureas
Nephrotoxicity/ototoxicity	Aminoglycosides, vancomycin, loop diuretics, cisplatin. Cisplatin toxicity may respond to amifostine.

Cytochrome P-450 interactions (selected)

Inducers (+)	Substrates	Inhibitors (-)
Chronic alcohol use	Anti-epileptics	Acute Alcohol Abuse
St. John's wort	Theophylline	Ritonavir
Phenytoin	Warfarin	Amiodarone
Phenobarbital	OCPs	Cimetidine/ciprofloxacin
Nevirapine		Ketoconazole
Rifampin		Sulfonamides
Griseofulvin		Isoniazid (INH)
Carbamazepine		Grapefruit juice
		Quinidine
		Macrolides (except azithromycin)
Chronic alcoholics Steal Phen-Phen and Never Refuse Greasy Carbs	Always Think When Outdoors	AAA RACKS IN GQ Magazine

Sulfa drugs

Sulfonamide antibiotics, Sulfasalazine, Probenecid, Furosemide, Acetazolamide, Celecoxib, Thiazides, Sulfonyleureas. Patients with sulfa allergies may develop fever, urinary tract infection, Stevens-Johnson syndrome, hemolytic anemia, thrombocytopenia, agranulocytosis, and urticaria (hives). Symptoms range from mild to life threatening.	Scary Sulfa Pharm FACTS
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▶ PHARMACOLOGY—MISCELLANEOUS

Drug names

ENDING	CATEGORY	EXAMPLE
Antimicrobial		
-azole	Ergosterol synthesis inhibitor	Ketoconazole
-bendazole	Antiparasitic/antihelminthic	Mebendazole
-cillin	Peptidoglycan synthesis inhibitor	Ampicillin
-cycline	Protein synthesis inhibitor	Tetracycline
-ivir	Neuraminidase inhibitor	Oseltamivir
-navir	Protease inhibitor	Ritonavir
-ovir	DNA polymerase inhibitor	Acyclovir
-thromycin	Macrolide antibiotic	Azithromycin
CNS		
-ane	Inhalational general anesthetic	Halothane
-azine	Typical antipsychotic	Thioridazine
-barbital	Barbiturate	Phenobarbital
-caine	Local anesthetic	Lidocaine
-etine	SSRI	Fluoxetine
-ipramine, -triptyline	TCA	Imipramine, amitriptyline
-triptan	5-HT _{1B/1D} agonists	Sumatriptan
-zepam, -zolam	Benzodiazepine	Diazepam, alprazolam
Autonomic		
-chol	Cholinergic agonist	Bethanechol, carbachol
-curium, -curonium	Nondepolarizing paralytic	Atracurium, vecuronium
-olol	β-blocker	Propranolol
-stigmine	AChE inhibitor	Neostigmine
-terol	β ₂ -agonist	Albuterol
-zosin	α ₁ -antagonist	Prazosin
Cardiovascular		
-afil	PDE-5 inhibitor	Sildenafil
-dipine	Dihydropyridine Ca ²⁺ channel blocker	Amlodipine
-pril	ACE inhibitor	Captopril
-sartan	Angiotensin-II receptor blocker	Losartan
-statin	HMG-CoA reductase inhibitor	Atorvastatin
-xaban	Direct factor Xa inhibitors	Apixaban, edoxaban, rivaroxaban
Other		
-dronate	Bisphosphonate	Alendronate
-glitazone	PPAR-γ activator	Rosiglitazone
-prazole	Proton pump inhibitor	Omeprazole
-prost	Prostaglandin analog	Latanoprost
-tidine	H ₂ -antagonist	Cimetidine
-tropin	Pituitary hormone	Somatotropin
-ximab	Chimeric monoclonal Ab	Basiliximab
-zumab	Humanized monoclonal Ab	Daclizumab

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

“Learn that you are a machine, your heart an engine, your lungs a fanning machine and a sieve, your brain with its two lobes an electric battery.”
—Andrew T. Still

▶ Approaching the Organ Systems	258
▶ Cardiovascular	261
▶ Endocrine	305
▶ Gastrointestinal	337
▶ Hematology and Oncology	377
▶ Musculoskeletal and Connective Tissue	415
▶ Neurology	449
▶ Psychiatry	507
▶ Renal	529
▶ Reproductive	561
▶ Respiratory	605

▶ 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

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. Memorizing 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.

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

▶ Embryology	262
▶ Anatomy	265
▶ Physiology	266
▶ Pathology	282
▶ Pharmacology	298

▶ CARDIOVASCULAR—EMBRYOLOGY

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
Endocardial cushion	Atrial septum, membranous interventricular septum; AV and semilunar valves
Primitive atrium	Trabeculated part of left and right atria
Primitive ventricle	Trabeculated part of left and right ventricles
Primitive pulmonary vein	Smooth part of left atrium
Left horn of sinus venosus	Coronary sinus
Right horn of sinus venosus	Smooth part of right atrium (sinus venarum)
Right common cardinal vein and right anterior cardinal vein	Superior vena cava (SVC)

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 gestation.

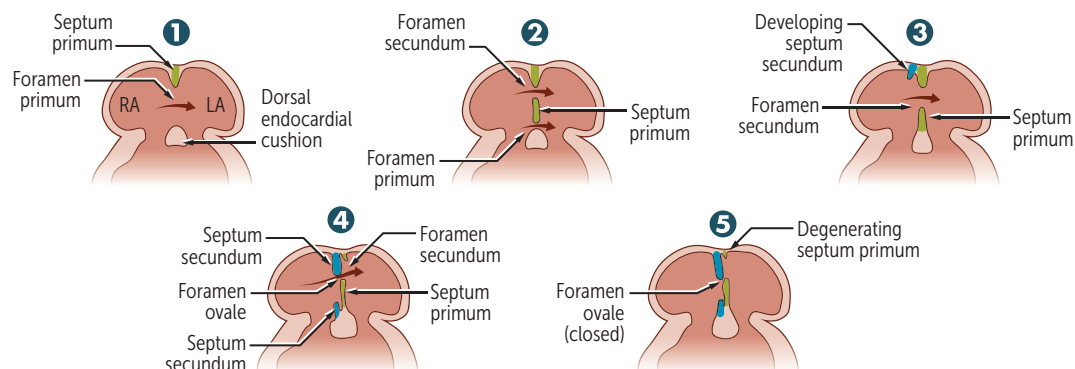
Defect in left-right dynein (involved in L/R asymmetry) can lead to dextrocardia, as seen in Kartagener syndrome (primary ciliary dyskinesia).

Septation of the chambers**Atria**

- Septum primum grows toward endocardial cushions, narrowing foramen primum.
- Foramen secundum forms in septum primum (foramen primum disappears).
- Septum secundum develops as foramen secundum maintains right-to-left shunt.
- Septum secundum expands and covers most of the foramen secundum. The residual foramen is the foramen ovale.
- Remaining portion of septum primum forms valve of foramen ovale.

- (Not shown) Septum secundum and septum primum fuse to form the atrial septum.
- (Not shown) Foramen ovale usually closes soon after birth because of ↑ LA pressure.

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 that enter systemic arterial circulation), similar to those resulting from an ASD.

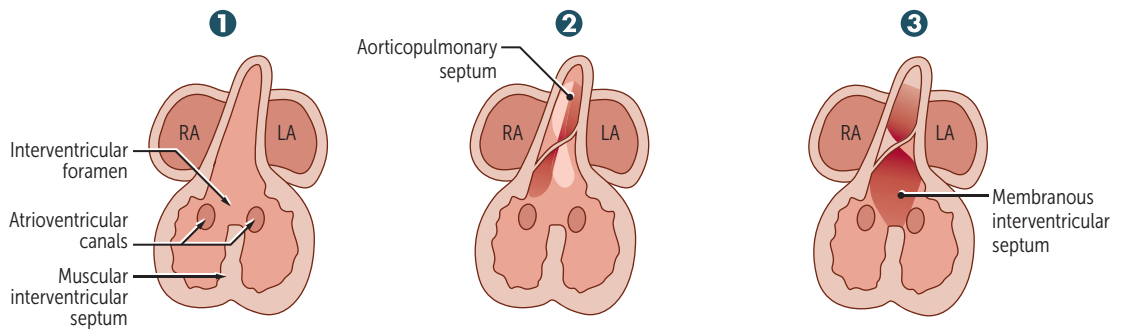


Heart morphogenesis (continued)

Ventricles

- 1 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 (VSD)—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:

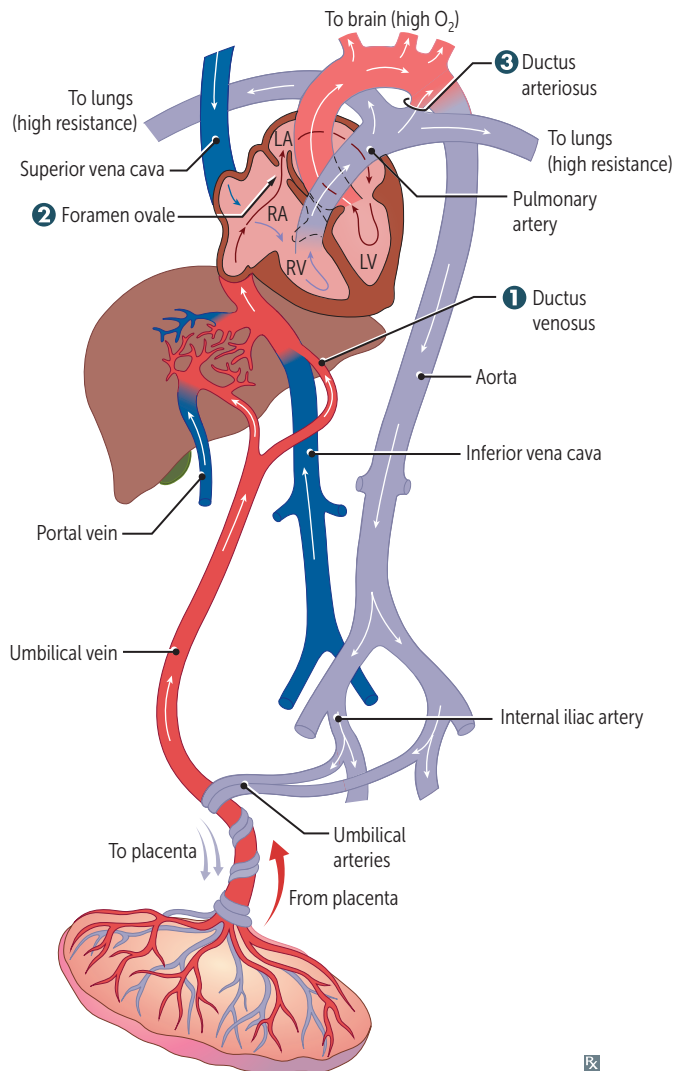
- Transposition of great vessels.
- Tetralogy of Fallot.
- Persistent truncus arteriosus.

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).

Fetal circulation



Blood in umbilical vein has a P_{O_2} of ≈ 30 mm Hg and is $\approx 80\%$ saturated with O_2 . Umbilical arteries have low O_2 saturation.

3 important shunts:

- 1 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** and pumped into the aorta to supply the head and body.
- 3 Deoxygenated blood from the SVC passes through the RA \rightarrow RV \rightarrow main pulmonary artery \rightarrow patent ductus arteriosus \rightarrow descending aorta; shunt is due to high fetal pulmonary artery resistance (due partly to low O_2 tension).

At birth, infant takes a breath; \downarrow resistance in pulmonary vasculature \rightarrow \uparrow left atrial pressure vs right atrial pressure; foramen ovale closes (now called fossa ovalis); \uparrow in O_2 (from respiration) and \downarrow in prostaglandins (from placental separation) \rightarrow closure of ductus arteriosus.

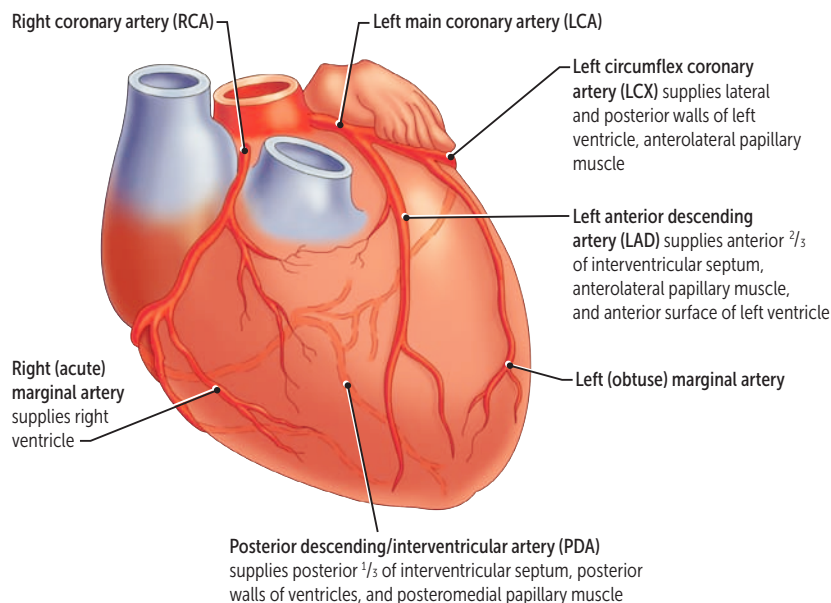
Indomethacin helps close PDA \rightarrow ligamentum arteriosum (remnant of ductus arteriosus). Prostaglandins E_1 and E_2 keep PDA open.

Fetal-postnatal derivatives

Allantois \rightarrow urachus	Median umbilical ligament	Urachus is part of allantoic duct between bladder and umbilicus.
Ductus arteriosus	Ligamentum arteriosum	
Ductus venosus	Ligamentum venosum	
Foramen ovale	Fossa ovalis	
Notochord	Nucleus pulposus	
Umbilical arteries	Median umbilical ligaments	
Umbilical vein	Ligamentum teres hepatis	Contained in falciform ligament.

▶ CARDIOVASCULAR—ANATOMY

Coronary artery anatomy



SA and AV nodes are usually supplied by RCA. Infarct may cause nodal dysfunction (bradycardia or heart block).

Right-dominant circulation (85%) = PDA arises from RCA.

Left-dominant circulation (8%) = PDA arises from LCX.

Codominant circulation (7%) = PDA arises from both LCX and RCA.

Coronary artery occlusion most commonly occurs in the LAD.

Coronary blood flow peaks in early diastole.

The most posterior part of the heart is the left atrium; enlargement can cause dysphagia (due to compression of the esophagus) or hoarseness (due to compression of the left recurrent laryngeal nerve, a branch of the vagus).

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.

▶ CARDIOVASCULAR—PHYSIOLOGY

Cardiac output

CO = stroke volume (SV) × heart rate (HR)

Fick principle:

$$\text{CO} = \frac{\text{rate of O}_2 \text{ consumption}}{\text{arterial O}_2 \text{ content} - \text{venous O}_2 \text{ content}}$$

Mean arterial pressure (MAP) = CO × total peripheral resistance (TPR)

MAP = $\frac{2}{3}$ diastolic pressure + $\frac{1}{3}$ systolic pressure

Pulse pressure = systolic pressure – diastolic pressure

Pulse pressure is proportional to SV, inversely proportional to arterial compliance.

SV = end-diastolic volume (EDV) – end-systolic volume (ESV)

During the early stages of exercise, CO is maintained by ↑ HR and ↑ SV. During the late stages of exercise, CO is maintained by ↑ HR only (SV plateaus).

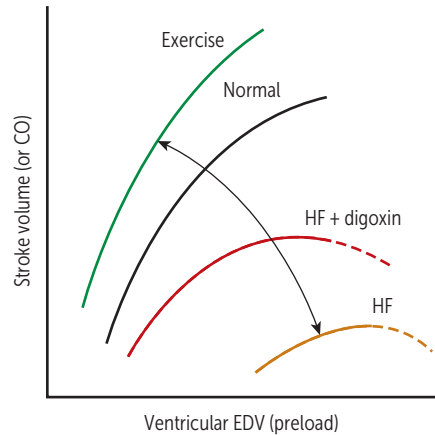
Diastole is preferentially shortened with ↑ HR; less filling time → ↓ CO (eg, ventricular tachycardia).

↑ pulse pressure in hyperthyroidism, aortic regurgitation, aortic stiffening (isolated systolic hypertension in elderly), obstructive sleep apnea (↑ sympathetic tone), exercise (transient).

↓ pulse pressure in aortic stenosis, cardiogenic shock, cardiac tamponade, advanced heart failure (HF).

Cardiac output variables

Stroke volume	<p>Stroke Volume affected by Contractility, Afterload, and Preload.</p> <p>↑ SV with:</p> <ul style="list-style-type: none"> ▪ ↑ Contractility (eg, anxiety, exercise) ▪ ↑ Preload (eg, early pregnancy) ▪ ↓ Afterload 	<p>SV CAP.</p> <p>A failing heart has ↓ SV (systolic and/or diastolic dysfunction)</p>
Contractility	<p>Contractility (and SV) ↑ with:</p> <ul style="list-style-type: none"> ▪ Catecholamines (inhibition of phospholamban → ↑ Ca²⁺ entry into sarcoplasmic reticulum → ↑ Ca²⁺-induced Ca²⁺ release) ▪ ↑ intracellular Ca²⁺ ▪ ↓ extracellular Na⁺ (↓ activity of Na⁺/Ca²⁺ exchanger) ▪ Digitalis (blocks Na⁺/K⁺ pump → ↑ intracellular Na⁺ → ↓ Na⁺/Ca²⁺ exchanger activity → ↑ intracellular Ca²⁺) 	<p>Contractility (and SV) ↓ with:</p> <ul style="list-style-type: none"> ▪ β₁-blockade (↓ cAMP) ▪ HF with systolic dysfunction ▪ Acidosis ▪ Hypoxia/hypercapnia (↓ Po₂/↑ Pco₂) ▪ Non-dihydropyridine Ca²⁺ channel blockers
Myocardial oxygen demand	<p>↑ MyoCARDial O₂ demand is ↑ by:</p> <ul style="list-style-type: none"> ▪ ↑ Contractility ▪ ↑ Afterload (proportional to arterial pressure) ▪ ↑ heart Rate ▪ ↑ Diameter of ventricle (↑ wall tension) 	<p>Wall tension follows Laplace's law:</p> $\text{Wall tension} = \frac{\text{pressure} \times \text{radius}}{2 \times \text{wall thickness}}$
Preload	<p>Preload approximated by ventricular EDV; depends on venous tone and circulating blood volume.</p>	<p>Venodilators (eg, nitroglycerin) ↓ prEload.</p>
Afterload	<p>Afterload approximated by MAP.</p> <p>↑ afterload → ↑ pressure → ↑ wall tension per Laplace's law.</p> <p>LV compensates for ↑ afterload by thickening (hypertrophy) in order to ↓ wall tension.</p>	<p>Vasodilators (eg, hydrAlAzine) ↓ Afterload (Arterial).</p> <p>ACE inhibitors and ARBs ↓ both preload and afterload.</p> <p>Chronic hypertension (↑ MAP) → LV hypertrophy.</p>
Ejection fraction	$EF = \frac{SV}{EDV} = \frac{EDV - ESV}{EDV}$ <p>Left ventricular EF is an index of ventricular contractility; normal EF is ≥ 55%.</p>	<p>EF ↓ in systolic HF.</p> <p>EF normal in diastolic HF.</p>

Starling curve

Force of contraction is proportional to end-diastolic length of cardiac muscle fiber (preload).

↑ contractility with catecholamines, positive inotropes (eg, digoxin).

↓ contractility with loss of myocardium (eg, MI), β-blockers (acutely), non-dihydropyridine Ca²⁺ channel blockers, dilated cardiomyopathy.

Resistance, pressure, flow

$$\Delta P = Q \times R$$

Similar to Ohm's law: $\Delta V = IR$

Volumetric flow rate (Q) = flow velocity (v) × cross-sectional area (A)

Resistance

$$= \frac{\text{driving pressure } (\Delta P)}{\text{flow } (Q)} = \frac{8\eta \text{ (viscosity)} \times \text{length}}{\pi r^4}$$

Total resistance of vessels in series:

$$R_T = R_1 + R_2 + R_3 \dots$$

Total resistance of vessels in parallel:

$$\frac{1}{R_T} = \frac{1}{R_1} + \frac{1}{R_2} + \frac{1}{R_3} \dots$$

Viscosity depends mostly on hematocrit

Viscosity ↑ in hyperproteinemic states (eg, multiple myeloma), polycythemia

Viscosity ↓ in anemia

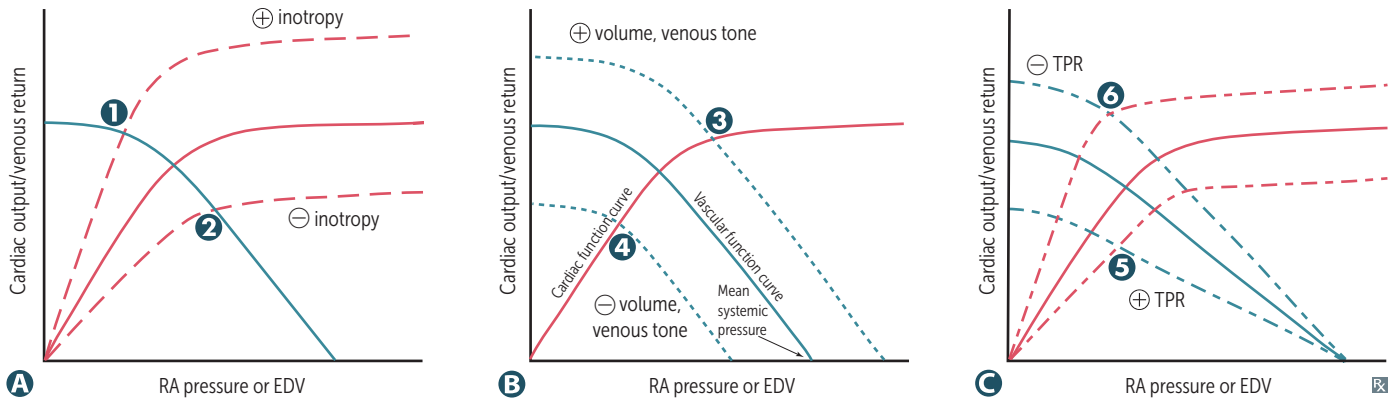
Capillaries have highest total cross-sectional area and lowest flow velocity.

Removal of organs in parallel arrangement (eg, nephrectomy) → ↓ TPR and ↑ CO.

Pressure gradient drives flow from high pressure to low pressure.

Arterioles account for most of TPR. Veins provide most of blood storage capacity.

Cardiac and vascular function curves

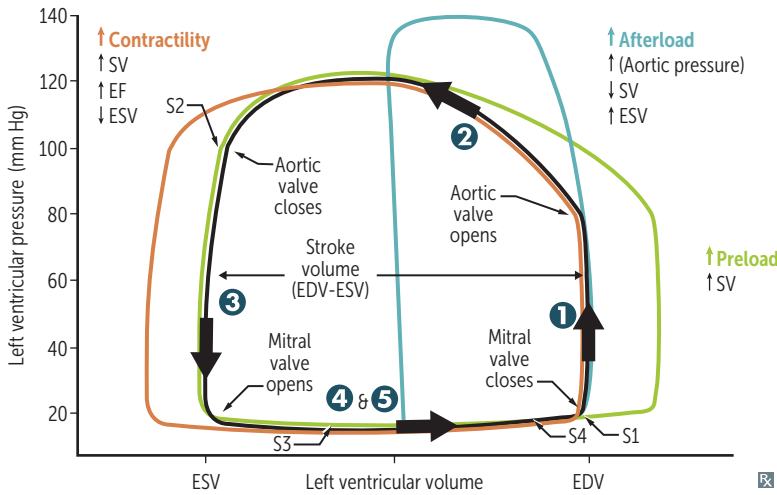


Intersection of curves = operating point of heart (ie, venous return and CO are equal).

CURVE	EFFECT	EXAMPLES
A Inotropy	Changes in contractility → altered CO for a given RA pressure (preload).	1 Catecholamines, digoxin ⊕ 2 Uncompensated HF, narcotic overdose ⊖
B Venous return	Changes in circulating volume or venous tone → altered RA pressure for a given CO. Mean systemic pressure (x-intercept) changes with volume/venous tone.	3 Fluid infusion, sympathetic activity ⊕ 4 Acute hemorrhage, spinal anesthesia ⊖
C Total peripheral resistance	At a given mean systemic pressure (x-intercept) and RA pressure, changes in TPR → altered CO.	5 Vasopressors ⊕ 6 Exercise, AV shunt ⊖

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).

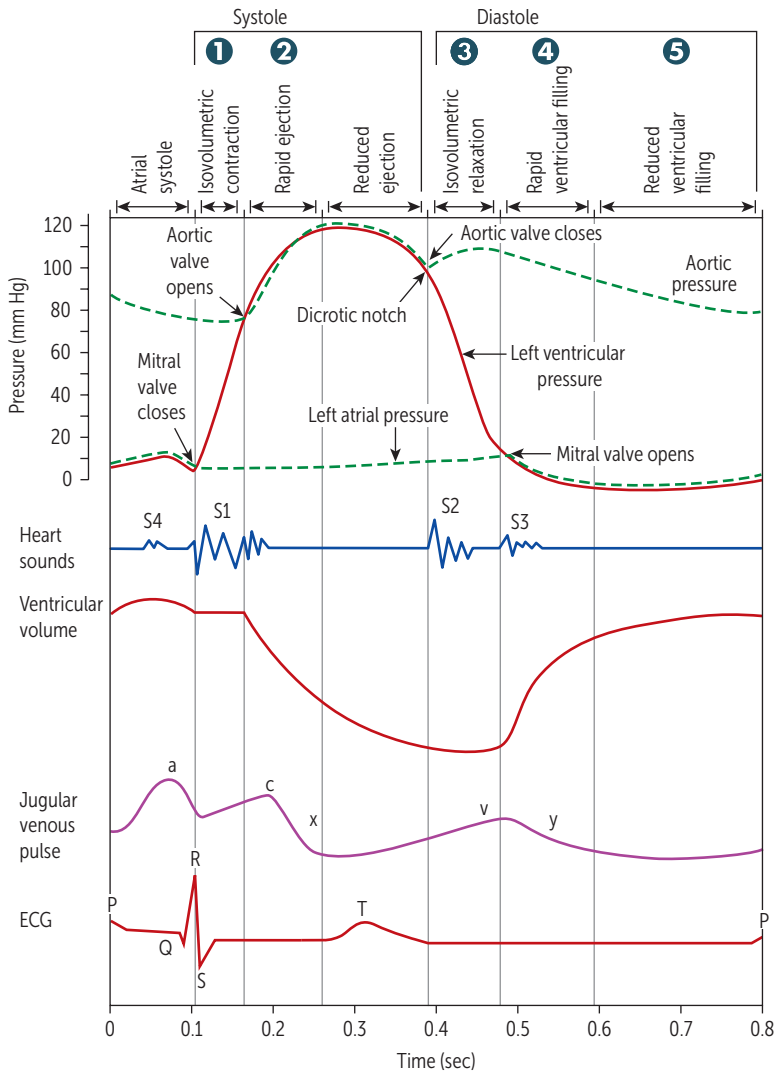
Pressure-volume loops and cardiac cycle



The black loop represents normal cardiac physiology.

Phases—left ventricle:

- 1 Isovolumetric contraction—period between mitral valve closing and aortic valve opening; period of highest O₂ consumption
- 2 Systolic ejection—period between aortic valve opening and closing
- 3 Isovolumetric relaxation—period between aortic valve closing and mitral valve opening
- 4 Rapid filling—period just after mitral valve opening
- 5 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. Associated with ↑ filling pressures (eg, mitral regurgitation, HF) and more common in dilated ventricles (but can be normal in children and young adults).
- 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. Consider abnormal, regardless of patient age.

Jugular venous pulse (JVP):

- a** wave—atrial contraction. Absent in atrial fibrillation (AF).
- c** wave—RV contraction (closed tricuspid valve bulging into atrium).
- x** descent—atrial relaxation and downward displacement of closed tricuspid valve during ventricular contraction. Absent in tricuspid insufficiency and right HF.
- 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.

Splitting

Normal 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.

Expiration | | |
 S1 A2 P2
 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.

Expiration | | |
 S1 A2 P2
 Inspiration | | |

Fixed splitting

Heard in ASD. ASD → left-to-right shunt → ↑ RA and RV volumes → ↑ flow through pulmonic valve such that, regardless of breath, pulmonic closure is greatly delayed.

Expiration | | |
 S1 A2 P2
 Inspiration | | |

Paradoxical splitting

Heard in conditions that delay aortic valve closure (eg, aortic stenosis, left bundle branch block). Normal order of valve closure is reversed so that P2 sound occurs before delayed A2 sound. Therefore on inspiration, P2 closes later and moves closer to A2, thereby “paradoxically” eliminating the split (usually heard in expiration).

Expiration | | |
 S1 P2 A2
 Inspiration | | |

Auscultation of the heart

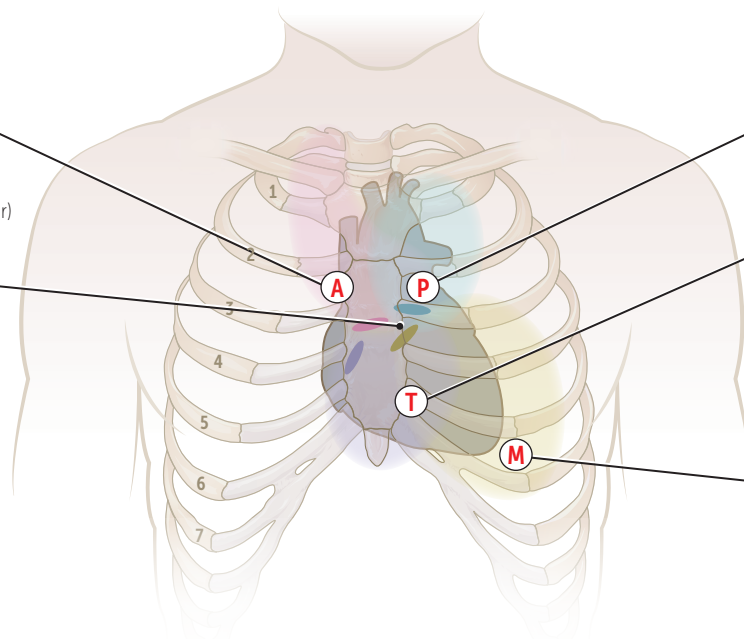
Where to listen: **APT M****Aortic area:**

Systolic murmur
Aortic stenosis
Flow murmur
(eg, physiologic murmur)
Aortic valve sclerosis

Left sternal border:

Diastolic murmur
Aortic regurgitation
Pulmonic regurgitation
Systolic murmur
Hypertrophic
cardiomyopathy

— Aortic
— Pulmonic
— Tricuspid
— Mitral

**Pulmonic area:**

Systolic ejection murmur
Pulmonic stenosis
Flow murmur

Tricuspid area:

Holosystolic murmur
Tricuspid regurgitation
Ventricular septal defect
Diastolic murmur
Tricuspid stenosis
Atrial septal defect (↑ flow
across tricuspid valve)

Mitral area:

Holosystolic murmur
Mitral regurgitation
Diastolic murmur
Mitral stenosis

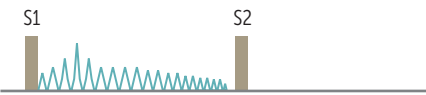
Bx

BEDSIDE MANEUVER	EFFECT
Inspiration (↑ venous return to right atrium)	↑ intensity of right heart sounds
Hand grip (↑ afterload)	↑ intensity of MR, AR, VSD murmurs ↓ hypertrophic cardiomyopathy murmurs MVP: later onset of click/murmur
Valsalva (phase II), standing up (↓ preload)	↓ intensity of most murmurs (including AS) ↑ intensity of hypertrophic cardiomyopathy murmur MVP: earlier onset of click/murmur
Rapid squatting (↑ venous return, ↑ preload, ↑ afterload)	↓ intensity of hypertrophic cardiomyopathy murmur ↑ intensity of AS murmur MVP: later onset of click/murmur
Systolic heart sounds include aortic/pulmonic stenosis, mitral/tricuspid regurgitation, VSD, MVP. Diastolic heart sounds include aortic/pulmonic regurgitation, mitral/tricuspid stenosis.	

Heart murmurs

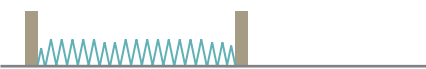
Systolic

Aortic stenosis



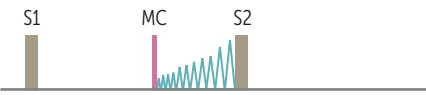
Crescendo-decrescendo systolic ejection murmur (ejection click may be present). LV >> aortic pressure during systole. Loudest at heart base; radiates to carotids. “Pulsus parvus et tardus”—pulses are weak with a delayed peak. Can lead to **S**yncope, **A**ngina, and **D**yspnea on exertion (**SAD**). Most commonly due to age-related calcification in older patients (> 60 years old) or in younger patients with early-onset calcification of bicuspid aortic valve.

Mitral/tricuspid regurgitation



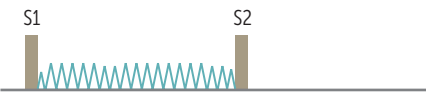
Holosystolic, high-pitched “blowing murmur.” Mitral—loudest at apex and radiates toward axilla. MR is often due to ischemic heart disease (post-MI), MVP, LV dilatation. Tricuspid—loudest at tricuspid area and radiates to right sternal border. TR commonly caused by RV dilatation. Rheumatic fever and infective endocarditis can cause either MR or TR.

Mitral valve prolapse



Late systolic crescendo murmur with midsystolic click (MC; due to sudden tensing of chordae tendineae). Most frequent valvular lesion. Best heard over apex. Loudest just before S2. Usually benign. Can predispose to infective endocarditis. Can be caused by myxomatous degeneration (1° or 2° to connective tissue disease such as Marfan or Ehlers-Danlos syndrome), rheumatic fever, chordae rupture.

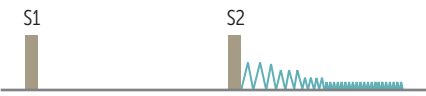
Ventricular septal defect



Holosystolic, harsh-sounding murmur. Loudest at tricuspid area.

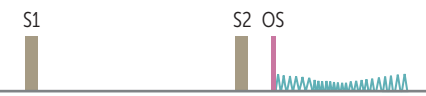
Diastolic

Aortic regurgitation



High-pitched “blowing” early diastolic decrescendo murmur. Long diastolic murmur, hyperdynamic pulse, and head bobbing when severe and chronic. Wide pulse pressure. Often due to aortic root dilation, bicuspid aortic valve, endocarditis, rheumatic fever. Progresses to left HF.

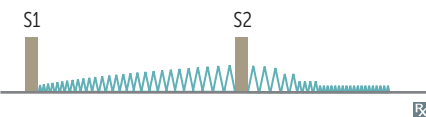
Mitral stenosis



Follows opening snap (OS; due to abrupt halt in leaflet motion in diastole, after rapid opening due to fusion at leaflet tips). Delayed rumbling late diastolic murmur (↓ interval between S2 and OS correlates with ↑ severity). LA >> LV pressure during diastole. Often occurs 2° to rheumatic fever. Chronic MS can result in LA dilatation.

Continuous

Patent ductus arteriosus



Continuous machine-like murmur. Loudest at S2. Often due to congenital rubella or prematurity. Best heard at left infraclavicular area.

Myocardial action potential

Also occurs in bundle of His and Purkinje fibers.

Phase 0 = rapid upstroke and depolarization—voltage-gated Na^+ channels open.

Phase 1 = initial repolarization—inactivation of voltage-gated Na^+ channels. Voltage-gated K^+ channels begin to open.

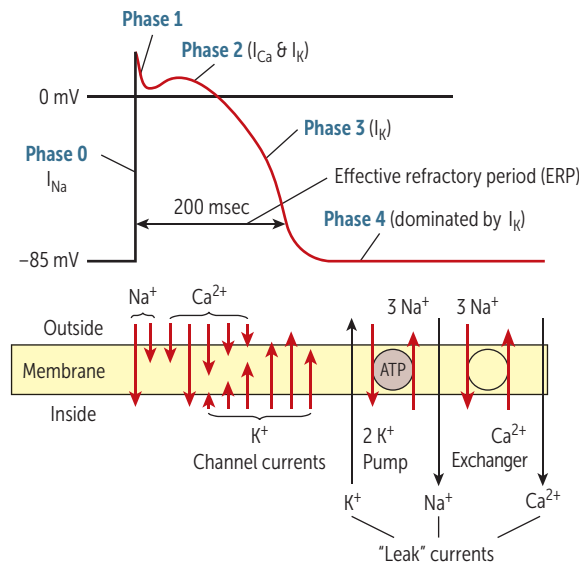
Phase 2 = plateau— Ca^{2+} influx through voltage-gated Ca^{2+} channels balances K^+ efflux. Ca^{2+} influx triggers Ca^{2+} release from sarcoplasmic reticulum and myocyte contraction.

Phase 3 = rapid repolarization—massive K^+ efflux due to opening of voltage-gated slow K^+ channels and closure of voltage-gated Ca^{2+} channels.

Phase 4 = resting potential—high K^+ permeability through K^+ channels.

In contrast to skeletal muscle:

- Cardiac muscle action potential has a plateau, which is due to Ca^{2+} influx and K^+ efflux.
- Cardiac muscle contraction requires Ca^{2+} influx from ECF to induce Ca^{2+} release from sarcoplasmic reticulum (Ca^{2+} -induced Ca^{2+} release).
- Cardiac myocytes are electrically coupled to each other by gap junctions.



Pacemaker action potential

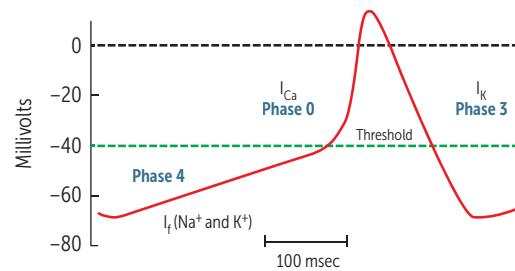
Occurs in the SA and AV nodes. Key differences from the ventricular action potential include:

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 = inactivation of the Ca^{2+} channels and \uparrow activation of K^+ channels $\rightarrow \uparrow \text{K}^+$ 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.



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 “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—Purkinje > atria
 > ventricles > AV node.

P wave—atrial depolarization. Atrial
 repolarization is masked by QRS complex.

PR interval—time from start of atrial
 depolarization to start of ventricular
 depolarization (normally < 200 msec).

QRS complex—ventricular depolarization
 (normally < 120 msec).

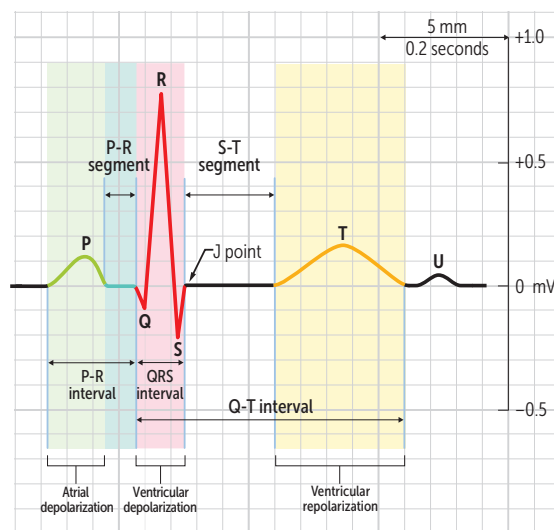
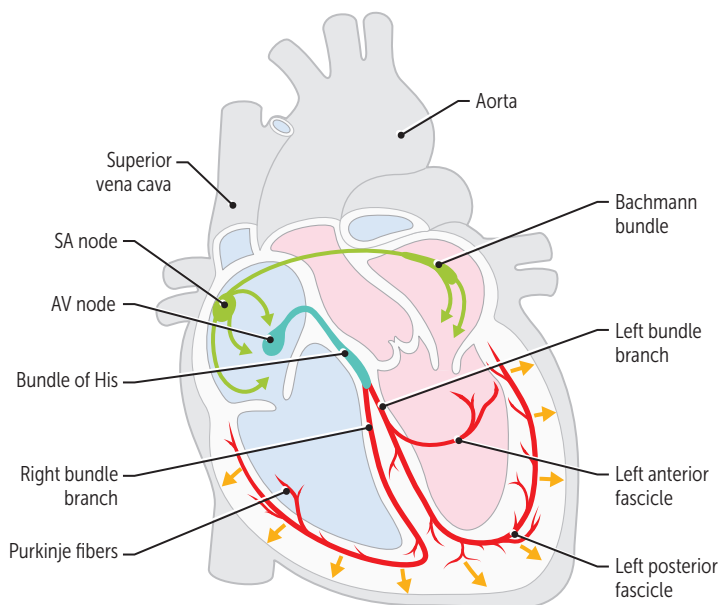
QT interval—ventricular depolarization,
 mechanical contraction of the ventricles,
 ventricular repolarization.

T wave—ventricular repolarization. T-wave
 inversion may indicate recent MI.

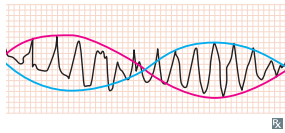
J point—junction between end of QRS complex
 and start of ST segment.

ST segment—isoelectric, ventricles depolarized.

U wave—prominent in hypokalemia,
 bradycardia.



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, ↓ K⁺, ↓ Mg²⁺, 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; ↑ risk of sudden cardiac death (SCD) due to torsades de pointes. Includes:

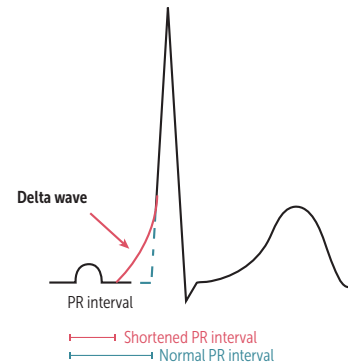
- Romano-Ward syndrome—autosomal dominant, pure cardiac phenotype (no deafness).
- Jervell and Lange-Nielsen syndrome—autosomal recessive, sensorineural deafness.

Brugada syndrome

Autosomal dominant disorder most common in Asian males. ECG pattern of pseudo-right bundle branch block and ST elevations in V₁-V₃. ↑ risk of ventricular tachyarrhythmias and SCD. Prevent SCD with implantable cardioverter-defibrillator (ICD).

Wolff-Parkinson-White syndrome

Most common type of ventricular pre-excitation 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.



ECG tracings

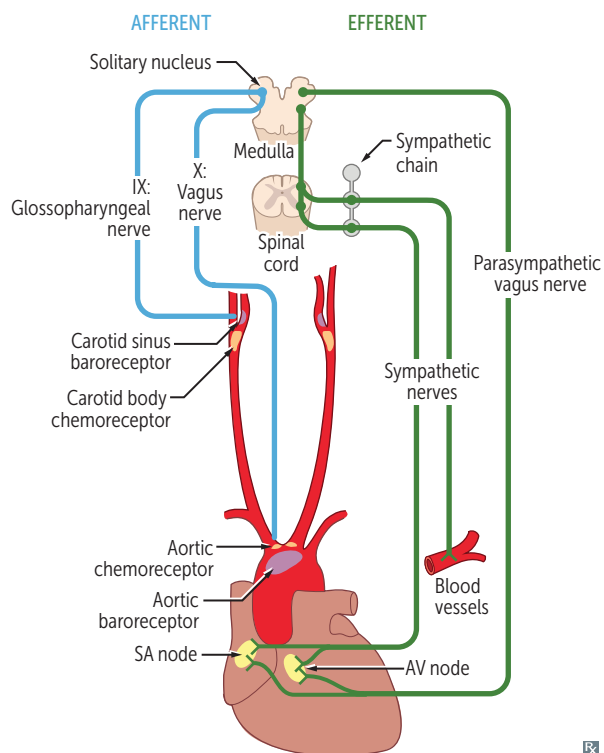
RHYTHM	DESCRIPTION	EXAMPLE
Atrial fibrillation	<p>Chaotic and erratic baseline with no discrete P waves in between irregularly spaced QRS complexes. Irregularly irregular heartbeat. Most common risk factors include hypertension and coronary artery disease (CAD). Can lead to thromboembolic events, particularly stroke.</p> <p>Treatment includes anticoagulation, rate control, rhythm control, and/or cardioversion.</p>	
Atrial flutter	<p>A rapid succession of identical, back-to-back atrial depolarization waves. The identical appearance accounts for the “sawtooth” appearance of the flutter waves.</p> <p>Treat like atrial fibrillation. Definitive treatment is catheter ablation.</p>	
Ventricular fibrillation	<p>A completely erratic rhythm with no identifiable waves. Fatal arrhythmia without immediate CPR and defibrillation.</p>	
AV block		
1st degree	<p>The PR interval is prolonged (> 200 msec). Benign and asymptomatic. No treatment required.</p>	
2nd degree		
Mobitz type I (Wenckebach)	<p>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).</p>	
Mobitz type II	<p>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.</p>	
3rd degree (complete)	<p>The atria and ventricles beat independently of each other. P waves and QRS complexes not rhythmically associated. Atrial rate > ventricular rate. Usually treated with pacemaker. Can be caused by Lyme disease.</p>	

Atrial natriuretic peptide

Released from **atrial myocytes** in response to \uparrow blood volume and atrial pressure. Acts via cGMP. Causes vasodilation and \downarrow Na^+ 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 \uparrow 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 \downarrow and \uparrow in BP).
- Carotid sinus (dilated region at carotid bifurcation) transmits via glossopharyngeal nerve to solitary nucleus of medulla (responds to \downarrow and \uparrow in BP).

Baroreceptors:

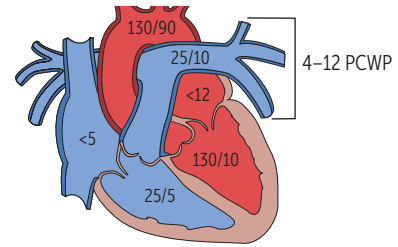
- Hypotension— \downarrow arterial pressure \rightarrow \downarrow stretch \rightarrow \downarrow afferent baroreceptor firing \rightarrow \uparrow efferent sympathetic firing and \downarrow efferent parasympathetic stimulation \rightarrow vasoconstriction, \uparrow HR, \uparrow contractility, \uparrow BP. Important in the response to severe hemorrhage.
- Carotid massage— \uparrow pressure on carotid sinus \rightarrow \uparrow stretch \rightarrow \uparrow afferent baroreceptor firing \rightarrow \uparrow AV node refractory period \rightarrow \downarrow HR.
- Contributes to Cushing reaction (triad of hypertension, bradycardia, and respiratory depression)— \uparrow intracranial pressure constricts arterioles \rightarrow cerebral ischemia \rightarrow \uparrow pCO_2 and \downarrow pH \rightarrow central reflex sympathetic \uparrow in perfusion pressure (hypertension) \rightarrow \uparrow stretch \rightarrow peripheral reflex baroreceptor-induced bradycardia.

Chemoreceptors:

- Peripheral—carotid and aortic bodies are stimulated by \downarrow PO_2 (< 60 mm Hg), \uparrow PCO_2 , and \downarrow pH of blood.
- Central—are stimulated by changes in pH and PCO_2 of brain interstitial fluid, which in turn are influenced by arterial CO_2 . Do not directly respond to PO_2 .

Normal cardiac pressures

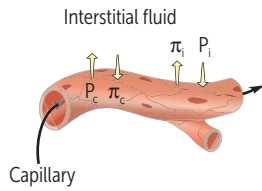
Pulmonary capillary wedge pressure (PCWP; in mm Hg) is a good approximation of left atrial pressure. In mitral stenosis, PCWP > LV end diastolic pressure. PCWP is measured with pulmonary artery catheter (Swan-Ganz catheter).

**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, CO ₂ , ↓ O ₂	Note: the pulmonary vasculature is unique in that hypoxia causes vasoconstriction so that only well-ventilated areas are perfused. In other organs, hypoxia causes vasodilation.
Brain	Local metabolites (vasodilatory): CO ₂ (pH)	
Kidneys	Myogenic and tubuloglomerular feedback	
Lungs	Hypoxia causes vasoconstriction	
Skeletal muscle	Local metabolites during exercise: lactate, adenosine, K ⁺ , H ⁺ , CO ₂ At rest: sympathetic tone	
Skin	Sympathetic stimulation most important mechanism: temperature control	CO ₂ , H ⁺ , Adenosine, Lactate, K ⁺ (CHALK)

Capillary fluid exchange



Starling forces determine fluid movement through capillary membranes:

- P_c = capillary pressure—pushes fluid out of capillary
- P_i = interstitial fluid pressure—pushes fluid into capillary
- π_c = plasma colloid osmotic (oncotic) pressure—pulls fluid into capillary
- π_i = interstitial fluid colloid osmotic pressure—pulls fluid out of capillary

$$J_v = \text{net fluid flow} = K_f [(P_c - P_i) - \zeta(\pi_c - \pi_i)]$$

K_f = permeability of capillary to fluid

ζ = permeability of capillary to protein

Edema—excess fluid outflow into interstitium commonly caused by:

- \uparrow capillary pressure ($\uparrow P_c$; eg, HF)
- \downarrow plasma proteins ($\downarrow \pi_c$; eg, nephrotic syndrome, liver failure, protein malnutrition)
- \uparrow capillary permeability ($\uparrow K_f$; eg, toxins, infections, burns)
- \uparrow interstitial fluid colloid osmotic pressure ($\uparrow \pi_i$; eg, lymphatic blockage)

▶ 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 Ts:

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

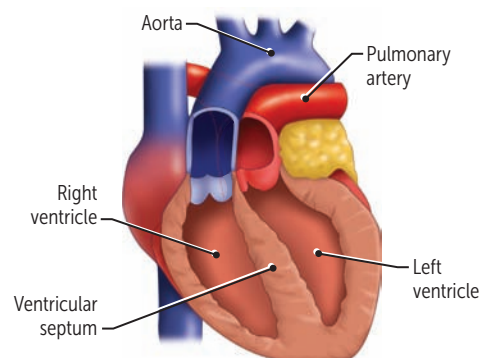
Truncus arteriosus fails to divide into pulmonary trunk and aorta due to lack of aorticopulmonary septum formation; most patients have accompanying VSD.

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.

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 anterosuperior displacement of the infundibular septum. Most common cause of early childhood cyanosis.

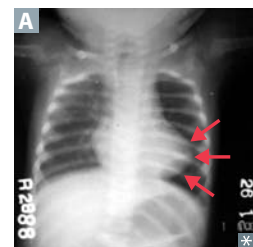
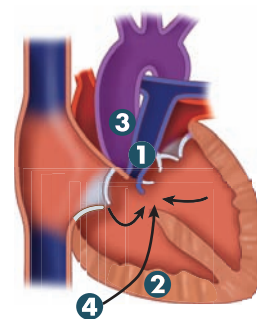
- 1 Pulmonary infundibular stenosis (most important determinant for prognosis)
- 2 Right ventricular hypertrophy (RVH)—boot-shaped heart on CXR **A**
- 3 Overriding aorta
- 4 VSD

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.

Treatment: early surgical correction.



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

Characterized by displacement of tricuspid valve leaflets downward into RV, artificially “atrializing” the ventricle. Associated with tricuspid regurgitation and right HF. Can be caused by lithium exposure in utero.

Congenital heart diseases (continued)

LEFT-TO-RIGHT SHUNTS

Late cyanosis (2° to Eisenmenger syndrome)—
“blue kids.”
Frequency: VSD > ASD > PDA.

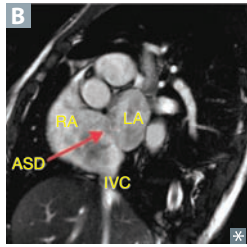
Right-to-Left shunts: ea**RL**y cyanosis.
Left-to-Right shunts: “**LateR**” cyanosis.

Ventricular septal defect

Most common congenital cardiac defect.
Asymptomatic at birth, may manifest weeks later or remain asymptomatic throughout life. Most self resolve; larger lesions may lead to LV overload and HF.

O₂ saturation ↑ in RV and pulmonary artery.

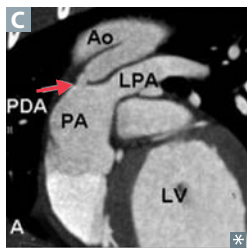
Atrial septal defect



Defect in interatrial septum **B**; loud S1; wide, fixed split S2. Ostium secundum defects most common and usually occur as isolated findings; ostium primum defects rarer yet 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.

O₂ saturation ↑ in RA, RV, and pulmonary artery.

Patent ductus arteriosus



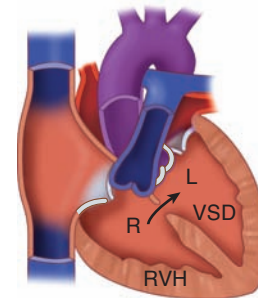
In fetal period, shunt is right to left (normal). In neonatal period, ↓ pulmonary vascular resistance → shunt becomes left to right → progressive RVH and/or LVH and HF. Associated with a continuous, “machine-like” murmur. Patency is maintained by PGE synthesis and low O₂ tension. Uncorrected PDA **C** can eventually result in late cyanosis in the lower extremities (differential cyanosis).

“**Endomethacin**” (indomethacin) **ends** patency of PDA; PGE keeps ductus **G**oing (may be necessary to sustain life in conditions such as transposition of the great vessels). 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 **D**, and polycythemia. Age of onset varies.



OTHER ANOMALIES

Coarctation of the aorta

Aortic narrowing 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.

Congenital cardiac defect associations

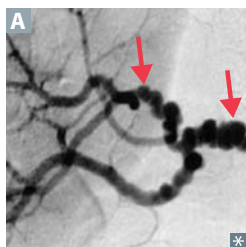
DISORDER	DEFECT
Alcohol exposure in utero (fetal alcohol syndrome)	VSD, PDA, ASD, tetralogy of Fallot
Congenital rubella	PDA, pulmonary artery stenosis, septal defects
Down syndrome	AV septal defect (endocardial cushion defect), VSD, ASD
Infant of diabetic mother	Transposition of great vessels
Marfan 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

Defined as persistent systolic BP ≥ 140 mm Hg and/or diastolic BP ≥ 90 mm Hg

RISK FACTORS

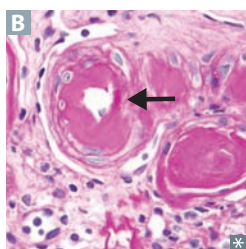
↑ age, obesity, diabetes, physical inactivity, excess salt intake, excess alcohol intake, family history; African American > Caucasian > Asian.

FEATURES

90% of hypertension is 1° (essential) and related to ↑ CO or ↑ TPR; remaining 10% mostly 2° to renal/renovascular disease (eg, fibromuscular dysplasia [“string of beads” appearance **A**], usually found in younger women) and 1° hyperaldosteronism.

Hypertensive urgency—severe ($\geq 180/\geq 120$ 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).

PREDISPOSES TO

CAD, LVH, HF, AF; aortic dissection, aortic aneurysm; stroke; chronic kidney disease (hypertensive nephropathy) **B**; retinopathy.

Hyperlipidemia signs

Xanthomas	Plaques or nodules composed of lipid-laden histiocytes in skin A , especially the eyelids (xanthelasma B).
Tendinous xanthoma	Lipid deposit in tendon C , especially Achilles.
Corneal arcus	Lipid deposit in cornea. Common in elderly (arcus senilis D), but appears earlier in life in hypercholesterolemia.



Arteriosclerosis

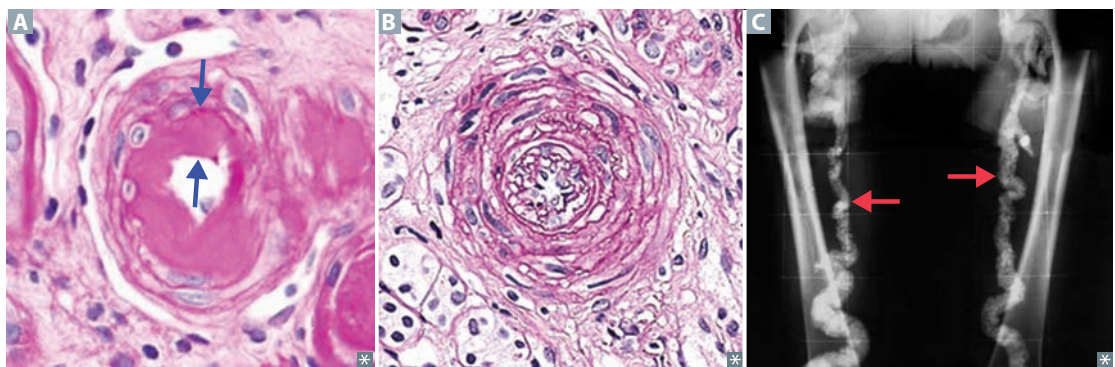
Hardening of arteries, with arterial wall thickening and loss of elasticity.

Arteriolosclerosis

Common. Affects small arteries and arterioles. Two types: hyaline (thickening of vessel walls in essential hypertension or diabetes mellitus **A**) and hyperplastic (“onion skinning” in severe hypertension **B** with proliferation of smooth muscle cells).

Mönckeberg sclerosis (medial calcific sclerosis)

Uncommon. Affects medium-sized arteries. Calcification of internal elastic lamina and media of arteries → vascular stiffening without obstruction. “Pipestem” appearance on x-ray **C**. Does not obstruct blood flow; intima not involved.



Atherosclerosis

Very common. Disease of elastic arteries and large- and medium-sized muscular arteries; a form of arteriosclerosis caused by buildup of cholesterol plaques.

LOCATION

Abdominal aorta > coronary artery > popliteal artery > carotid artery **A**.

**RISK FACTORS**

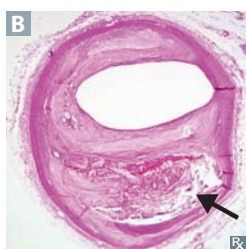
Modifiable: smoking, hypertension, hyperlipidemia (↑ LDL), diabetes.
Nonmodifiable: age, sex (↑ in men and postmenopausal women), family history.

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 **B**.

**COMPLICATIONS**

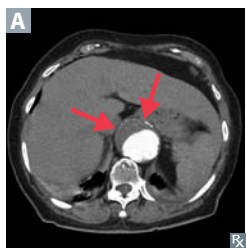
Aneurysms, ischemia, infarcts, peripheral vascular disease, thrombus, emboli.

Aortic aneurysm

Localized pathologic dilatation of the aorta. May cause abdominal and/or back pain, which is a sign of leaking, dissection, or imminent rupture.

Abdominal aortic aneurysm

Associated with atherosclerosis. Risk factors include history of tobacco use, ↑ age, male sex, family history. May present as palpable pulsatile abdominal mass **A**.

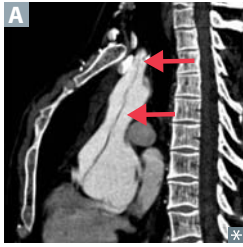
**Thoracic aortic aneurysm**

Associated with cystic medial degeneration. Risk factors include hypertension, bicuspid aortic valve, connective tissue disease (eg, Marfan syndrome). Also historically associated with 3° syphilis (obliterative endarteritis of the vasa vasorum).

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).

Aortic dissection



Longitudinal intimal tear forming a false lumen **A**. Associated with hypertension, bicuspid aortic valve, inherited connective tissue disorders (eg, Marfan syndrome). Can present with tearing chest pain, of sudden onset, radiating to the back +/- markedly unequal BP in arms. CXR shows mediastinal widening. Can result in organ ischemia, aortic rupture, death. Two types:

- **Stanford type A** (proximal): involves Ascending aorta. May extend to aortic arch or descending aorta. May result in acute aortic regurgitation or cardiac tamponade. Treatment: surgery.
- **Stanford type B** (distal): involves descending aorta and/or aortic arch. No ascending aorta involvement. Treat medically with β -blockers, then vasodilators.

Ischemic heart disease manifestations

Angina

Chest pain due to ischemic myocardium 2° to coronary artery narrowing or spasm; no myocyte necrosis.

- **Stable**—usually 2° to atherosclerosis; exertional chest pain in classic distribution (usually with ST depression on ECG), resolving with rest or nitroglycerin.
- **Variant (Prinzmetal)**—occurs at rest 2° to coronary artery spasm; transient ST elevation on ECG. Known triggers include tobacco, cocaine, and triptans, but trigger is often unknown. Treat with Ca^{2+} 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.

Coronary steal syndrome

Distal to coronary stenosis, vessels are maximally dilated at baseline. Administration of vasodilators (eg, dipyridamole, regadenoson) dilates normal vessels and shunts blood toward well-perfused areas → ↓ flow and ischemia in poststenotic region. Principle behind pharmacologic stress tests.

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 implantable cardioverter-defibrillator (ICD).

Chronic ischemic heart disease

Progressive onset of HF over many years due to chronic ischemic myocardial damage.

Myocardial infarction

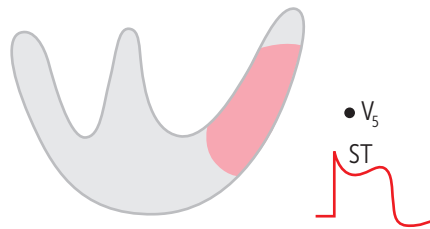
Most often acute thrombosis due to rupture of coronary artery atherosclerotic plaque. ↑ cardiac biomarkers (CK-MB, troponins) are diagnostic.

ST-segment elevation MI (STEMI)

Transmural infarcts
Full thickness of myocardial wall involved
ST elevation on ECG, Q waves

Non-ST-segment elevation MI (NSTEMI)

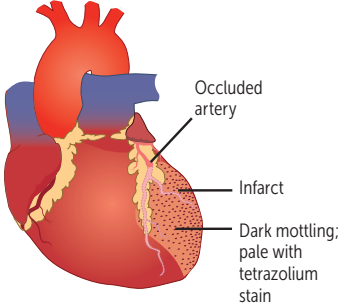
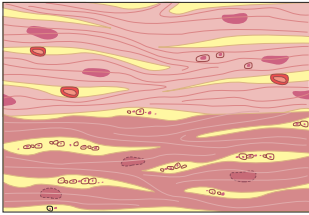
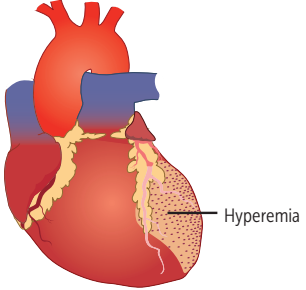
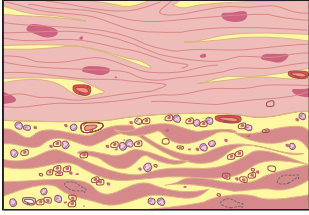
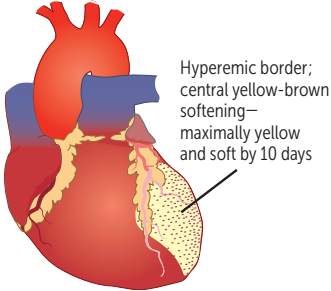
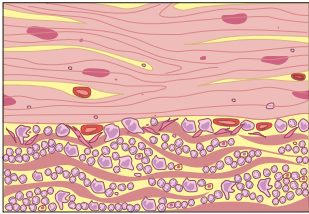
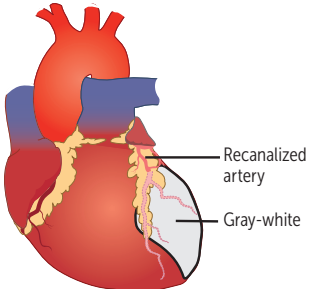
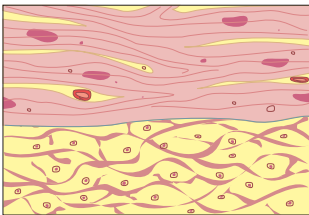
Subendocardial infarcts
Subendocardium (inner 1/3) especially vulnerable to ischemia
ST depression on ECG



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	None  <p>Occluded artery Infarct Dark mottling; pale with tetrazolium stain</p>	Early coagulative necrosis, release of necrotic cell contents into blood; edema, hemorrhage, wavy fibers. Neutrophils appear. Reperfusion injury, associated with generation of free radicals, leads to hypercontraction of myofibrils through ↑ free calcium influx. 	Ventricular arrhythmia, HF, cardiogenic shock.
1–3 days	 <p>Hyperemia</p>	Extensive coagulative necrosis. Tissue surrounding infarct shows acute inflammation with neutrophils. 	Postinfarction fibrinous pericarditis.
3–14 days	 <p>Hyperemic border; central yellow-brown softening—maximally yellow and soft by 10 days</p>	Macrophages, then granulation tissue at margins. 	Free wall rupture → tamponade; papillary muscle rupture → mitral regurgitation; interventricular septal rupture due to macrophage-mediated structural degradation. LV pseudoaneurysm (risk of rupture).
2 weeks to several months	 <p>Recanalized artery Gray-white</p>	Contracted scar complete. 	Dressler syndrome, HF, arrhythmias, true ventricular aneurysm (risk of mural thrombus).

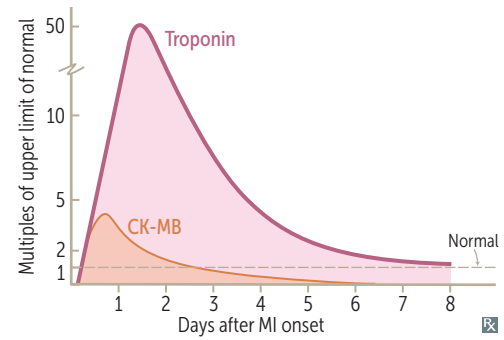
Diagnosis of myocardial infarction

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.

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).

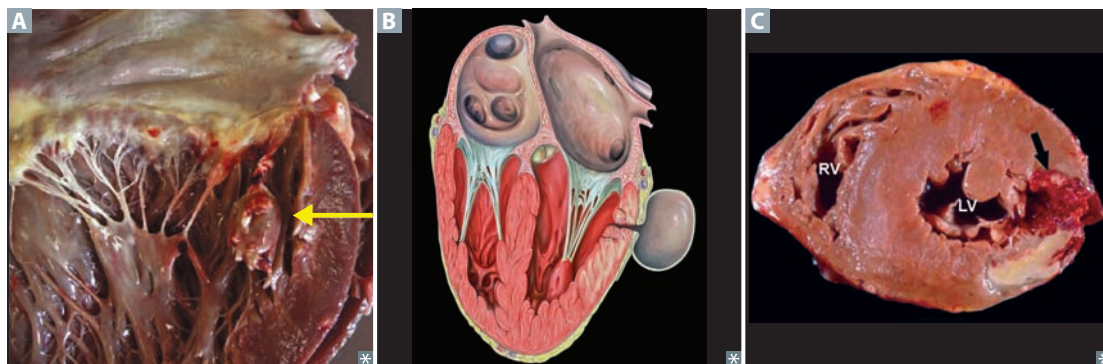


ECG localization of STEMI

INFARCT LOCATION	LEADS WITH ST ELEVATIONS OR Q WAVES
Anteroseptal (LAD)	V ₁ –V ₂
Anteroapical (distal LAD)	V ₃ –V ₄
Anterolateral (LAD or LCX)	V ₅ –V ₆
Lateral (LCX)	I, aVL
Inferior (RCA)	II, III, aVF
Posterior (PDA)	V ₇ –V ₉ , ST depression in V ₁ –V ₃ with tall R waves

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	Occurs 1–3 days after MI. Friction rub.
Papillary muscle rupture	Occurs 2–7 days after MI. Posteromedial papillary muscle rupture A ↑ risk due to single blood supply from posterior descending artery. Can result in severe mitral regurgitation.
Interventricular septal rupture	Occurs 3–5 days after MI. Macrophage-mediated degradation → VSD.
Ventricular pseudoaneurysm formation	Occurs 3–14 days after MI. Contained free wall rupture B ; ↓ CO, risk of arrhythmia, embolus from mural thrombus.
Ventricular free wall rupture	Occurs 5–14 days after MI. Free wall rupture C → cardiac tamponade.
True ventricular aneurysm	Occurs 2 weeks to several months after MI. Outward bulge with contraction (“dyskinesia”), associated with fibrosis.
Dressler syndrome	Occurs several weeks after MI. 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.

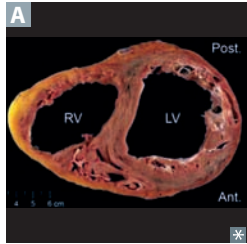
**Acute coronary syndrome treatments**

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).

Cardiomyopathies

Dilated cardiomyopathy



Most common cardiomyopathy (90% of cases). Often idiopathic or familial. Other etiologies include chronic **A**lcohol abuse, wet **B**eriberi, **C**oxsackie B viral myocarditis, chronic **C**ocaine use, **C**hagas disease, **D**oxorubicin toxicity, hemochromatosis, sarcoidosis, peripartum cardiomyopathy.

Findings: HF, S3, systolic regurgitant murmur, dilated heart on echocardiogram, balloon appearance of heart on CXR.

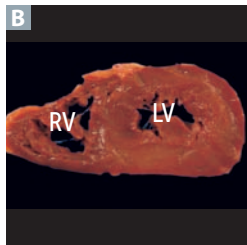
Treatment: Na⁺ restriction, ACE inhibitors, β-blockers, diuretics, digoxin, ICD, heart transplant.

Systolic dysfunction ensues.

Eccentric hypertrophy **A** (sarcomeres added in series).

ABCCCD.

Hypertrophic cardiomyopathy



60–70% of cases are familial, autosomal dominant (commonly a β-myosin heavy-chain mutation). Can be associated with Friedreich ataxia. Causes syncope during exercise and may lead to sudden death 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 β-blocker or non-dihydropyridine Ca²⁺ channel blockers (eg, verapamil). ICD if patient is high risk.

Diastolic dysfunction ensues.

Marked ventricular hypertrophy **B**, often septal predominance. Myofibrillar disarray and fibrosis.

Obstructive hypertrophic cardiomyopathy (subset)—asymmetric septal hypertrophy and systolic anterior motion of mitral valve → outflow obstruction → dyspnea, possible syncope.

Restrictive/infiltrative cardiomyopathy

Major causes include sarcoidosis, amyloidosis, postradiation fibrosis, endocardial fibroelastosis (thick fibroelastic tissue in endocardium of young children), **Löffler syndrome** (endomyocardial fibrosis with a prominent eosinophilic infiltrate), and hemochromatosis (although dilated cardiomyopathy is more common).

Diastolic dysfunction ensues. Can have low-voltage ECG despite thick myocardium (especially amyloid).

Heart failure



Clinical syndrome of cardiac pump dysfunction → congestion and low perfusion. Symptoms include dyspnea, orthopnea, fatigue; signs include 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 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. Thiazide or loop 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: ↑ venous return from redistribution of blood (immediate gravity effect) exacerbates pulmonary vascular congestion.

Paroxysmal nocturnal dyspnea Breathless awakening from sleep: ↑ venous return from redistribution of blood, reabsorption of peripheral edema, etc.

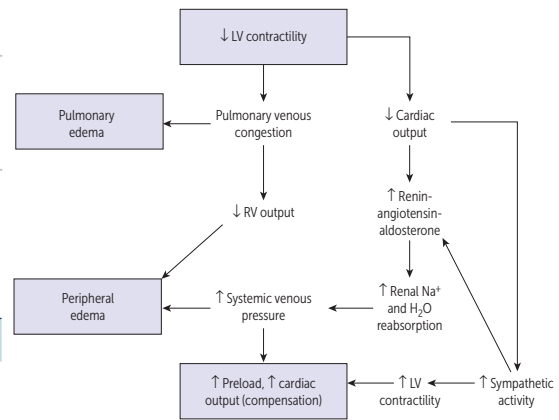
Pulmonary edema ↑ pulmonary venous pressure → pulmonary venous distention and transudation of fluid. Presence of hemosiderin-laden macrophages (“HF” cells) in lungs.

Right heart failure

Hepatomegaly (nutmeg liver) ↑ central venous pressure → ↑ resistance to portal flow. Rarely, leads to “cardiac cirrhosis.”

Jugular venous distention ↑ venous pressure.

Peripheral edema ↑ venous pressure → fluid transudation.



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)	CO	SVR (AFTERLOAD)	TREATMENT
Hypovolemic	Hemorrhage, dehydration, burns	Cold, clammy	↓↓	↓	↑	IV fluids
Cardiogenic	Acute MI, HF, valvular dysfunction, arrhythmia	Cold, clammy	↑	↓↓	↑	Inotropes, diuresis
Obstructive	Cardiac tamponade, pulmonary embolism					Relieve obstruction
Distributive	Sepsis, anaphylaxis CNS injury	Warm Dry	↓ ↓	↑ ↓	↓↓ ↓↓	IV fluids, pressors

Bacterial endocarditis

Fever (most common symptom), new murmur, Roth spots (round white spots on retina surrounded by hemorrhage), Osler nodes (tender raised lesions on finger or toe pads), Janeway lesions (small, painless, erythematous lesions on palm or sole) **A**, glomerulonephritis, septic arterial or pulmonary emboli, splinter hemorrhages **B** on nail bed. Multiple blood cultures necessary for diagnosis.

- **Acute**—*S aureus* (high virulence). Large vegetations on previously normal valves **C**. Rapid onset.
- **Subacute**—viridans streptococci (low virulence). Smaller vegetations on congenitally abnormal or diseased valves. Sequela of dental procedures. Gradual onset.

S bovis (*gallolyticus*) is present in colon cancer, *S epidermidis* on prosthetic valves.

Endocarditis may also be nonbacterial (marantic/thrombotic) 2° to malignancy, hypercoagulable state, or lupus.

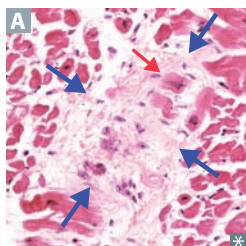
Mitral valve is most frequently involved.

Tricuspid valve endocarditis is associated with IV **d**rug abuse (don't "**tri**" **d**rugs). Associated with *S aureus*, *Pseudomonas*, and *Candida*. Culture ⊖—most likely *Coxiella burnetii*, *Bartonella* spp., HACEK (*Haemophilus*, *Aggregatibacter* (formerly *Actinobacillus*), *Cardiobacterium*, *Eikenella*, *Kingella*)

♥ Bacteria **FROM JANE** ♥:

- F**ever
- R**oth spots
- O**sler nodes
- M**urmur
- J**aneway lesions
- A**nemia
- N**ail-bed hemorrhage
- E**mboli



Rheumatic fever

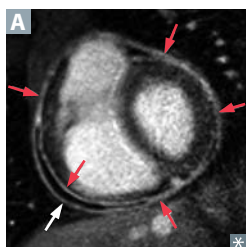
A consequence of pharyngeal infection with group A β -hemolytic streptococci. Late sequelae include rheumatic heart disease, which affects heart valves—mitral > aortic >> tricuspid (high-pressure valves affected most). Early lesion is mitral valve regurgitation; late lesion is mitral stenosis. Associated 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**]), \uparrow anti-streptolysin O (ASO) titers.

Immune mediated (type II hypersensitivity); not a direct effect of bacteria. Antibodies to M protein cross-react with self antigens (molecular mimicry).

Treatment/prophylaxis: penicillin.

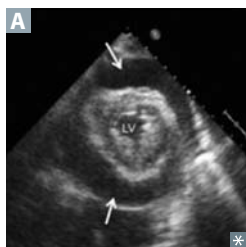
JONES (major criteria):

- J**oint (migratory polyarthritits)
- ♥** (carditis)
- N**odules in skin (subcutaneous)
- E**rythema marginatum
- S**ydenham chorea

Acute pericarditis

Inflammation of the pericardium [**A**, arrows]. Commonly presents with sharp pain, aggravated by inspiration, and relieved by sitting up and leaning forward. Often complicated by pericardial effusion [white arrow 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), neoplasia, autoimmune (eg, SLE, rheumatoid arthritis), uremia, cardiovascular (acute STEMI or Dressler syndrome), radiation therapy.

Cardiac tamponade

Compression of the heart by fluid (eg, blood, effusions [arrows in **A**] in pericardial space) \rightarrow \downarrow CO. Equilibration of diastolic pressures in all 4 chambers.

Findings: Beck triad (hypotension, distended neck veins, distant heart sounds), \uparrow HR, pulsus paradoxus. ECG shows low-voltage QRS and electrical alternans (due to “swinging” movement of heart in large effusion).

Pulsus paradoxus— \downarrow in amplitude of systolic BP by > 10 mm Hg during inspiration. Seen in cardiac tamponade, asthma, obstructive sleep apnea, pericarditis, croup.

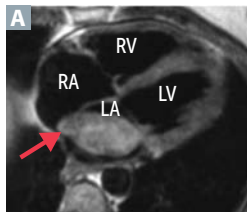
Syphilitic heart disease

3^o syphilis disrupts the vasa vasorum of the aorta with consequent atrophy of vessel wall and dilatation of aorta and valve ring. May see calcification of aortic root and ascending aortic arch. Leads to “tree bark” appearance of aorta.

Can result in aneurysm of ascending aorta or aortic arch, aortic insufficiency.

Cardiac tumors

Most common heart tumor is a metastasis.

Myxomas

Most common 1° cardiac tumor in adults **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). May hear early diastolic “tumor plop” sound.

Rhabdomyomas

Most frequent 1° cardiac tumor in children (associated with tuberous sclerosis).

Kussmaul sign

↑ in JVP on inspiration instead of a normal ↓.

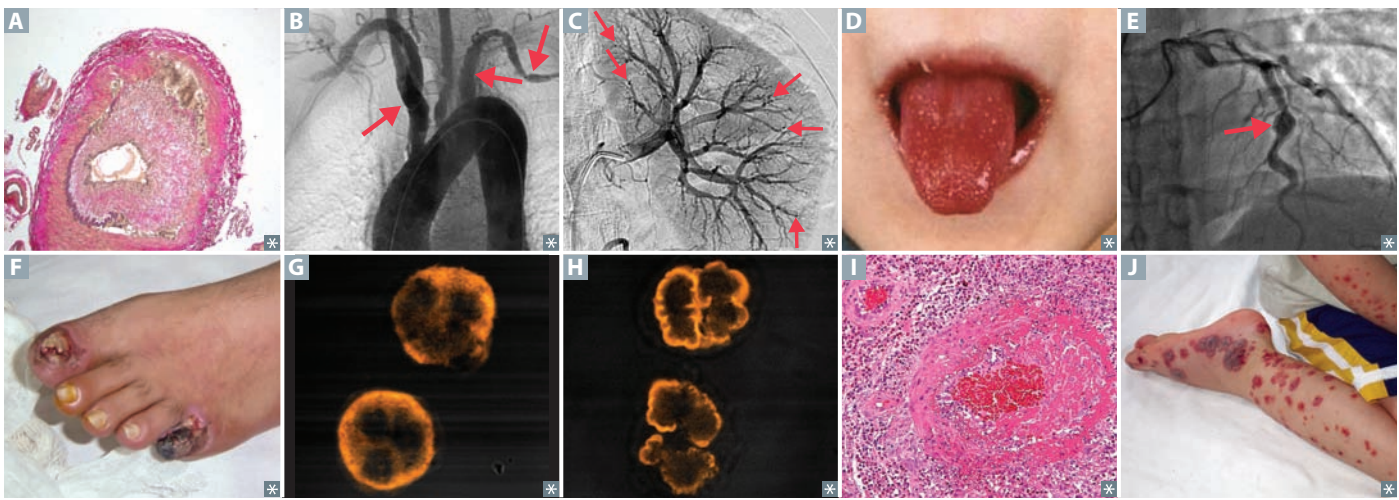
Inspiration → negative intrathoracic pressure not transmitted to heart → impaired filling of right ventricle → blood backs up into venae cavae → JVD. May be seen with constrictive pericarditis, restrictive cardiomyopathies, right atrial or ventricular tumors.

Vasculitides

	EPIDEMIOLOGY/PRESENTATION	PATHOLOGY/LABS
Large-vessel vasculitis		
Giant cell (temporal) arteritis	Usually elderly females. Unilateral headache (temporal artery), 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 B and proximal great vessels. ↑ ESR. Treat with corticosteroids.
Medium-vessel vasculitis		
Polyarteritis nodosa	Young adults. 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. Immune complex mediated. Transmural inflammation of the arterial wall with fibrinoid necrosis. Different stages of inflammation may coexist in different vessels. Innumerable renal microaneurysms C and spasms on arteriogram. Treat with corticosteroids, cyclophosphamide.
Kawasaki disease (mucocutaneous lymph node syndrome)	Asian children < 4 years old. C onjunctival injection, R ash (polymorphous → desquamating), A denopathy (cervical), S trawberry tongue (oral mucositis) D , H and-foot changes (edema, erythema), f ever.	CRASH and burn . May develop coronary artery aneurysms E ; thrombosis or rupture can cause death. Treat with IV immunoglobulin and aspirin.
Buerger disease (thromboangiitis obliterans)	Heavy smokers, males < 40 years old. Intermittent claudication may lead to gangrene F , autoamputation of digits, superficial nodular phlebitis. Raynaud phenomenon is often present.	Segmental thrombosing vasculitis. Treat with smoking cessation.
Small-vessel vasculitis		
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.	Triad: ▪ Focal necrotizing vasculitis ▪ Necrotizing granulomas in the lung and upper airway ▪ Necrotizing glomerulonephritis PR3-ANCA/c-ANCA G (anti-proteinase 3). CXR: large nodular densities. Treat with cyclophosphamide, 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 H (anti-myeloperoxidase). Treat with cyclophosphamide, corticosteroids.

Vasculitides (continued)

	EPIDEMIOLOGY/PRESENTATION	PATHOLOGY/LABS
Small-vessel vasculitis (continued)		
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 I . MPO-ANCA/p-ANCA, ↑ IgE level.
Henoch-Schönlein purpura	Most common childhood systemic vasculitis. Often follows URI. Classic triad: <ul style="list-style-type: none"> ▪ Skin: palpable purpura on buttocks/legs J ▪ Arthralgias ▪ GI: abdominal pain 	Vasculitis 2° to IgA immune complex deposition. Associated with IgA nephropathy (Berger disease).



▶ CARDIOVASCULAR—PHARMACOLOGY

Hypertension treatment

Primary (essential) hypertension	Thiazide diuretics, ACE inhibitors, angiotensin II receptor blockers (ARBs), dihydropyridine Ca ²⁺ 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.
Hypertension with diabetes mellitus	ACE inhibitors/ARBs, Ca ²⁺ channel blockers, thiazide diuretics, β -blockers.	ACE inhibitors/ARBs are protective against diabetic nephropathy.
Hypertension in pregnancy	Hydralazine, labetalol, methyldopa, nifedipine.	

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 Prinzmetal), Raynaud phenomenon.

Nimodipine: subarachnoid hemorrhage (prevents cerebral vasospasm).

Clevidipine: hypertensive urgency or emergency.

Non-dihydropyridines: hypertension, angina, atrial fibrillation/flutter.

ADVERSE EFFECTS

Non-dihydropyridine: cardiac depression, AV block, hyperprolactinemia, constipation.

Dihydropyridine: peripheral edema, flushing, dizziness, gingival hyperplasia.

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.

Lupus-like syndrome.

Hypertensive emergency

Drugs include clevidipine, fenoldopam, labetalol, nicardipine, nitroprusside.

Nitroprusside

Short acting; ↑ 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.

Antianginal therapy

Goal is reduction of myocardial O₂ consumption (MVO₂) by ↓ 1 or more of the determinants of MVO₂: end-diastolic volume, BP, HR, contractility.

COMPONENT	NITRATES	β-BLOCKERS	NITRATES + β-BLOCKERS
End-diastolic volume	↓	No effect or ↑	No effect or ↓
Blood pressure	↓	↓	↓
Contractility	No effect	↓	Little/no effect
Heart rate	↑ (reflex response)	↓	No effect or ↓
Ejection time	↓	↑	Little/no effect
MVO ₂	↓	↓	↓↓

Verapamil is similar to β-blockers in effect.

Pindolol and acebutolol—partial β-agonists contraindicated in angina.

Ranolazine

MECHANISM

Inhibits the late phase of sodium current thereby reducing diastolic wall tension and oxygen consumption. Does not affect heart rate or contractility.

CLINICAL USE

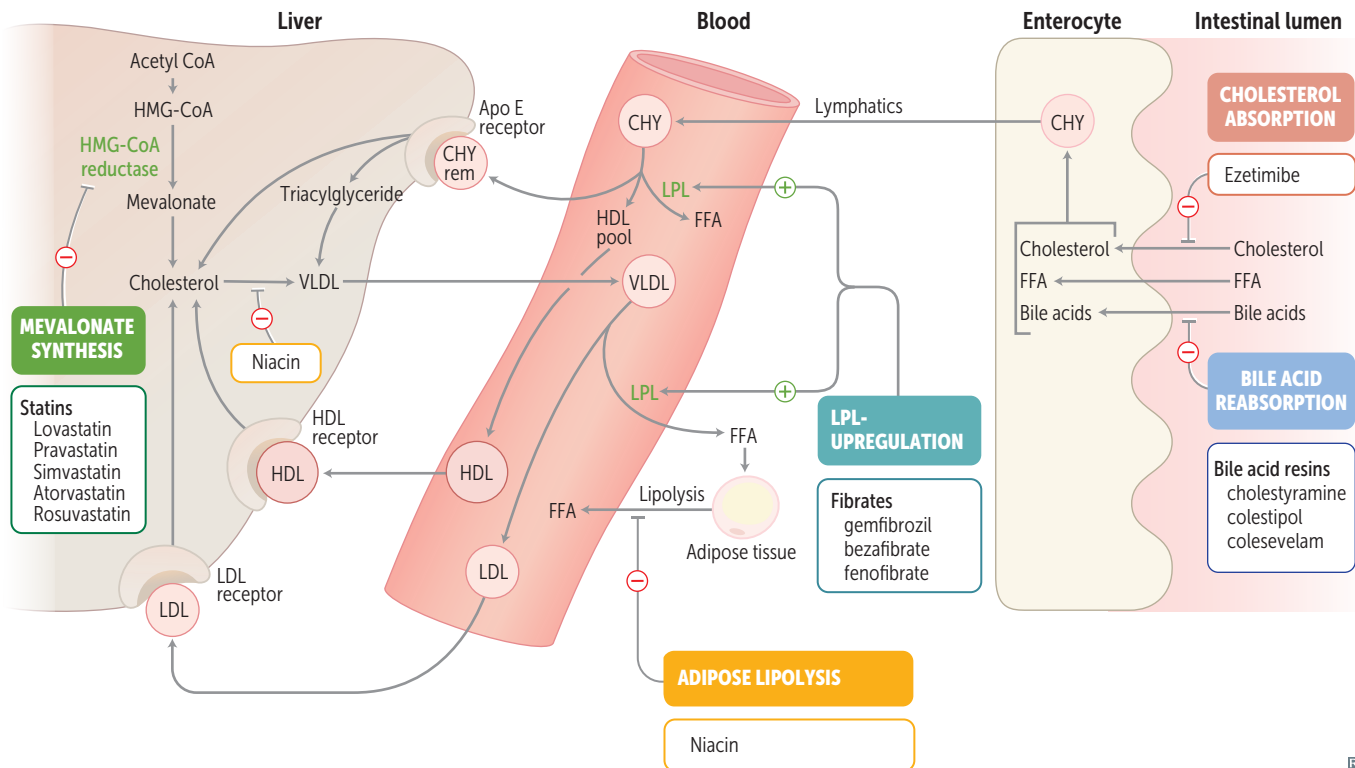
Angina refractory to other medical therapies.

ADVERSE EFFECTS

Constipation, dizziness, headache, nausea, QT prolongation.

Lipid-lowering agents

DRUG	LDL	HDL	TRIGLYCERIDES	MECHANISMS OF ACTION	ADVERSE EFFECTS/PROBLEMS
HMG-CoA reductase inhibitors (eg, lovastatin, pravastatin)	↓↓↓	↑	↓	Inhibit conversion of HMG-CoA to mevalonate, a cholesterol precursor; ↓ mortality in CAD patients	Hepatotoxicity (↑ LFTs), myopathy (esp. when used with fibrates or niacin)
Bile acid resins Cholestyramine, colestipol, colesevelam	↓↓	Slightly ↑	Slightly ↑	Prevent intestinal reabsorption of bile acids; liver must use cholesterol to make more	GI upset, ↓ absorption of other drugs and fat-soluble vitamins
Ezetimibe	↓↓	—	—	Prevent cholesterol absorption at small intestine brush border	Rare ↑ LFTs, diarrhea
Fibrates Gemfibrozil, bezafibrate, fenofibrate	↓	↑	↓↓↓	Upregulate LPL → ↑ TG clearance Activates PPAR-α to induce HDL synthesis	Myopathy (↑ risk with statins), cholesterol gallstones
Niacin (vitamin B₃)	↓↓	↑↑	↓	Inhibits lipolysis (hormone-sensitive lipase) in adipose tissue; reduces hepatic VLDL synthesis	Red, flushed face, which is ↓ by NSAIDs or long-term use Hyperglycemia Hyperuricemia

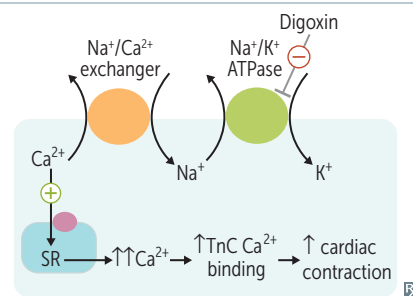


Cardiac glycosides

Digoxin.

MECHANISM

Direct inhibition of Na^+/K^+ ATPase
 → indirect inhibition of $\text{Na}^+/\text{Ca}^{2+}$ exchanger.
 $\uparrow [\text{Ca}^{2+}]_i \rightarrow$ positive inotropy. Stimulates vagus nerve $\rightarrow \downarrow$ HR.



CLINICAL USE

HF (\uparrow contractility); atrial fibrillation (\downarrow conduction at AV node and depression of SA node).

ADVERSE EFFECTS

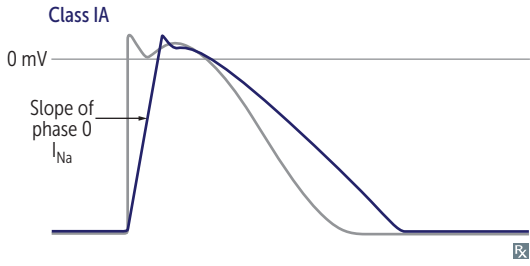
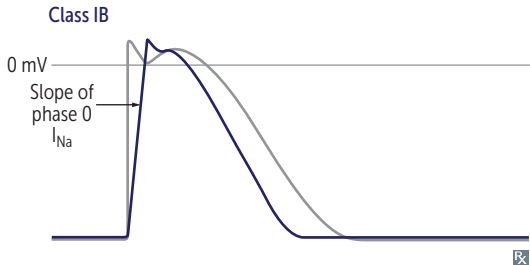
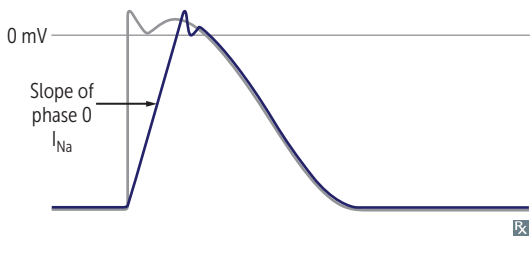
Cholinergic—nausea, vomiting, diarrhea, blurry yellow vision (think van Gogh), arrhythmias, AV block.
 Can lead to hyperkalemia, which indicates poor prognosis.
 Factors predisposing to toxicity: renal failure (\downarrow excretion), hypokalemia (permissive for digoxin binding at K^+ -binding site on Na^+/K^+ ATPase), drugs that displace digoxin from tissue-binding sites, and \downarrow clearance (eg, verapamil, amiodarone, quinidine).

ANTIDOTE

Slowly normalize K^+ , cardiac pacer, anti-digoxin Fab fragments, Mg^{2+} .

**Antiarrhythmics—
sodium channel
blockers (class I)**

Slow or block (↓) conduction (especially in depolarized cells). ↓ slope of phase 0 depolarization. Are state dependent (selectively depress tissue that is frequently depolarized [eg, tachycardia]).

Class IA	Quinidine, Procainamide, Disopyramide. “The Q ueen P roclaims D iso’s p yramide.”	
MECHANISM	↑ AP duration, ↑ effective refractory period (ERP) in ventricular action potential, ↑ QT interval.	
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), heart failure (disopyramide), thrombocytopenia, torsades de pointes due to ↑ QT interval.	
Class IB	Lidocaine, Mexiletine. “I’d Buy Liddy’s M exican T acos.”	
MECHANISM	↓ AP duration. Preferentially affect ischemic or depolarized Purkinje and ventricular tissue. Phenytoin can also fall into the IB category.	
CLINICAL USE	Acute ventricular arrhythmias (especially post-MI), digitalis-induced arrhythmias. IB is B est post-MI.	
ADVERSE EFFECTS	CNS stimulation/depression, cardiovascular depression.	
Class IC	Flecainide, Propafenone. “Can I have F ries, P lease.”	
MECHANISM	Significantly prolongs ERP in AV node and accessory bypass tracts. No effect on ERP in Purkinje and ventricular tissue. Minimal effect on AP duration.	
CLINICAL USE	SVTs, including atrial fibrillation. Only as a last resort in refractory VT.	
ADVERSE EFFECTS	Proarrhythmic, especially post-MI (contraindicated). IC is C ontraindicated in structural and ischemic heart disease.	

**Antiarrhythmics—
β-blockers (class II)**

Metoprolol, propranolol, esmolol, atenolol, timolol, carvedilol.

MECHANISM

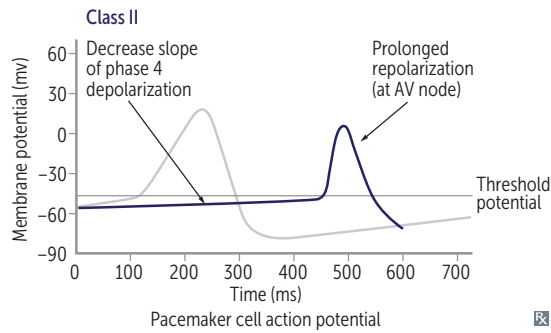
Decrease SA and AV nodal activity by ↓ cAMP, ↓ Ca²⁺ currents. Suppress abnormal pacemakers by ↓ slope of phase 4.
AV node particularly sensitive—↑ PR interval. Esmolol very short acting.

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 Prinzmetal angina.
β-blockers (except the nonselective α- and β-antagonists carvedilol and labetalol) cause unopposed α₁-agonism if given alone for pheochromocytoma or cocaine toxicity. Treat β-blocker overdose with saline, atropine, glucagon.



**Antiarrhythmics—
potassium channel
blockers (class III)**

Amiodarone, Ibutilide, Dofetilide, Sotalol.

AIDS.

MECHANISM

↑ AP duration, ↑ ERP, ↑ QT interval.

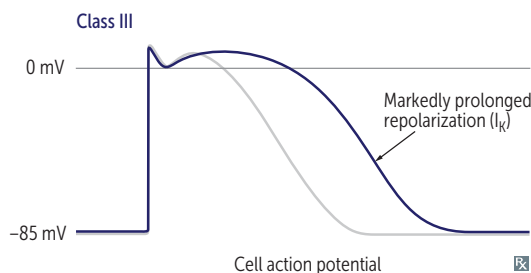
CLINICAL USE

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/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.



**Antiarrhythmics—
calcium channel
blockers (class IV)**

Verapamil, diltiazem.

MECHANISM

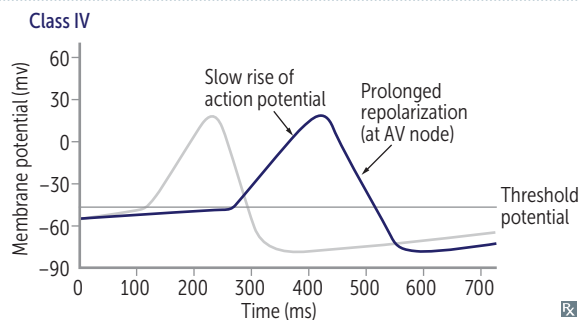
↓ conduction velocity, ↑ ERP, ↑ PR interval.

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} . 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.

 Mg^{2+}

Effective in torsades de pointes and digoxin toxicity.

Endocrine

“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.”

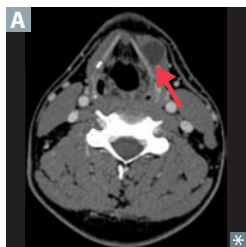
—Aldous (Leonard) Huxley

“Chocolate causes certain endocrine glands to secrete hormones that affect your feelings and behavior by making you happy.”

—Elaine Sherman, *Book of Divine Indulgences*

▶ Embryology	306
▶ Anatomy	306
▶ Physiology	308
▶ Pathology	317
▶ Pharmacology	334

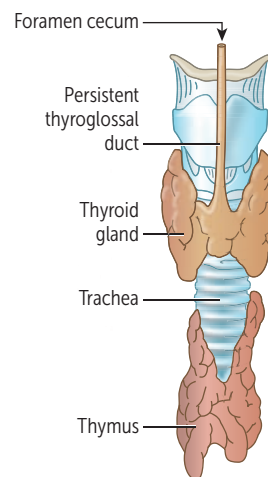
▶ ENDOCRINE—EMBRYOLOGY

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 branchial cleft cyst in lateral neck).

Thyroid tissue is derived from endoderm. Parafollicular cells (aka, C cells) of the thyroid are derived from neural crest.



▶ ENDOCRINE—ANATOMY

Adrenal cortex and medulla

Adrenal cortex (derived from mesoderm) and medulla (derived from neural crest).

	ANATOMY		PRIMARY REGULATORY CONTROL	SECRETORY PRODUCTS
CORTEX	Zona G lomerulosa		Renin-angiotensin	Aldosterone
	Zona F asciculata		ACTH, CRH	Cortisol
	Zona R eticularis		ACTH, CRH	Sex hormones (eg, androgens)
MEDULLA	Chromaffin cells		Preganglionic sympathetic fibers	Catecholamines (epinephrine, norepinephrine)

GFR corresponds with **S**alt (Na^+), **S**ugar (glucocorticoids), and **S**ex (androgens).

“The deeper you go, **the sweeter it gets.**”

Pituitary gland**Anterior pituitary
(adenohypophysis)**

Secretes FSH, LH, ACTH, TSH, prolactin, GH. 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.

ACTH and MSH are derivatives of proopiomelanocortin (POMC).

FLAT PiG: FSH, LH, ACTH, TSH, PRL, GH.

B-FLAT: Basophils—FSH, LH, ACTH, TSH.

Acidophils: GH, PRL.

**Posterior pituitary
(neurohypophysis)**

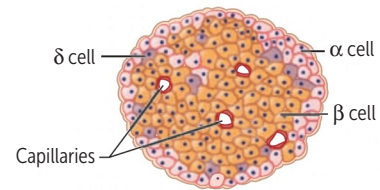
Stores and releases vasopressin (antidiuretic hormone, or ADH) and oxytocin, both made in the hypothalamus (supraoptic and paraventricular nuclei) and transported to posterior pituitary via neurophysins (carrier proteins). Derived from neuroectoderm.

**Endocrine pancreas
cell types**

Islets of Langerhans are collections of α , β , and δ endocrine cells. Islets arise from pancreatic buds.

- α = glucagon (peripheral)
- β = insulin (central)
- δ = somatostatin (interspersed)

Insulin (β cells) inside.

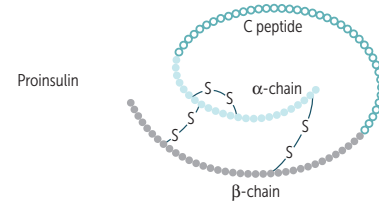


► ENDOCRINE—PHYSIOLOGY

Insulin

SYNTHESIS

Preproinsulin (synthesized in RER) → cleavage of “pre-signal” → proinsulin (stored in secretory granules) → cleavage of proinsulin → exocytosis of insulin and C-peptide equally. Insulin and C-peptide are ↑ in insulinoma and sulfonylurea use, whereas exogenous insulin lacks C-peptide.



SOURCE

Released from pancreatic β cells.

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⁺ retention (kidneys)
- ↑ protein synthesis (muscles)
- ↑ cellular uptake of K⁺ and amino acids
- ↓ glucagon release
- ↓ lipolysis in adipose tissue

Unlike glucose, insulin does not cross placenta.

Insulin-independent glucose transporters:

- GLUT-4: adipose tissue, striated muscle (exercise can also increase GLUT-4 expression)

Insulin-independent transporters:

- GLUT-1: RBCs, brain, cornea, placenta
- GLUT-2 (bidirectional): β islet cells, liver, kidney, small intestine
- GLUT-3: brain, placenta
- GLUT-5 (fructose): spermatocytes, GI tract

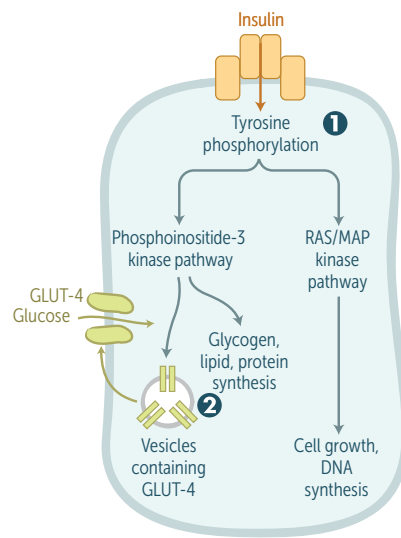
Brain utilizes glucose for metabolism normally and ketone bodies during starvation. RBCs always utilize glucose because they lack mitochondria for aerobic metabolism.

BRICK L (insulin-independent glucose uptake):
Brain, **R**BCs, **I**ntestine, **C**ornea, **K**idney, **L**iver.

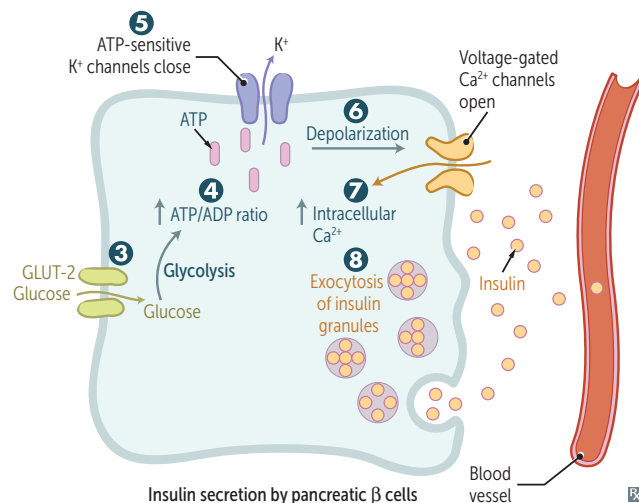
REGULATION

Glucose is the major regulator of insulin release. ↑ insulin response with oral vs IV glucose because of incretins such as glucagon-like peptide 1 (GLP-1), which are released after meals and ↑ β cell sensitivity to glucose.

Glucose enters β cells ③ → ↑ ATP generated from glucose metabolism ④ closes K⁺ channels (target of sulfonylureas) ⑤ and depolarizes β cell membrane ⑥. Voltage-gated Ca²⁺ channels open → Ca²⁺ influx ⑦ and stimulation of insulin exocytosis ⑧.



Insulin-dependent glucose uptake



Insulin secretion by pancreatic β cells

Glucagon

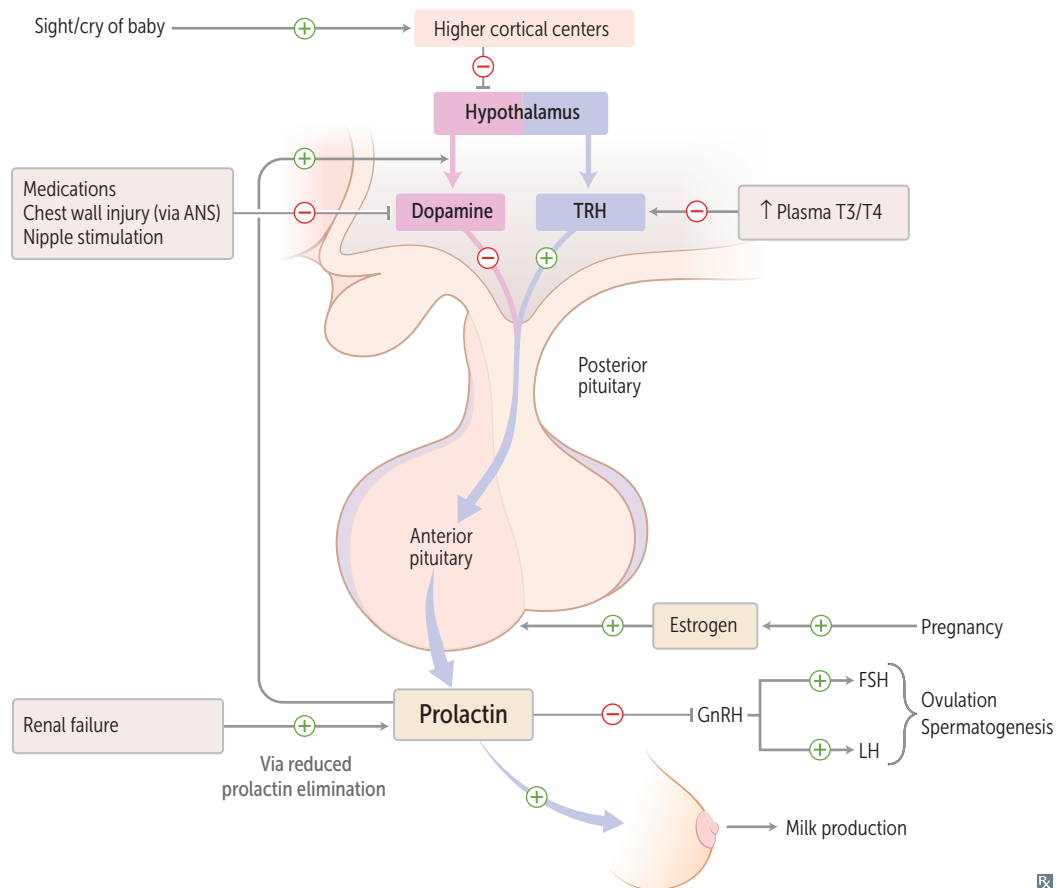
SOURCE	Made by α cells of pancreas.
FUNCTION	Catabolic effects of glucagon: <ul style="list-style-type: none"> ▪ Glycogenolysis, gluconeogenesis ▪ Lipolysis and ketone production
REGULATION	Secreted in response to hypoglycemia. Inhibited by insulin, hyperglycemia, and somatostatin.

Hypothalamic-pituitary hormones

HORMONE	FUNCTION	CLINICAL NOTES
CRH	↑ ACTH, MSH, β -endorphin	↓ in chronic exogenous steroid use
Dopamine	↓ prolactin, TSH	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 suppresses HPG axis Pulsatile GnRH leads to puberty, fertility
Prolactin	↓ GnRH	Pituitary prolactinoma → amenorrhea, osteoporosis, hypogonadism, galactorrhea
Somatostatin	↓ GH, TSH	Analogs used to treat acromegaly
TRH	↑ TSH, prolactin	

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 ↓ libido.
REGULATION	Prolactin secretion from anterior pituitary is tonically inhibited by dopamine from 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) and estrogens (eg, OCPs, pregnancy) stimulate prolactin secretion.



Growth hormone (somatotropin)

SOURCE	Secreted by anterior pituitary.	
FUNCTION	Stimulates linear growth and muscle mass through IGF-1 (somatomedin C) secretion by liver. ↑ insulin resistance (diabetogenic).	
REGULATION	Released in pulses in response to growth hormone–releasing hormone (GHRH). Secretion ↑ during exercise, deep sleep, puberty, hypoglycemia. Secretion inhibited by glucose and somatostatin release via negative feedback by somatomedin.	Excess secretion of GH (eg, pituitary adenoma) may cause acromegaly (adults) or gigantism (children). Treat with somatostatin analogs (eg, octreotide) or surgery.

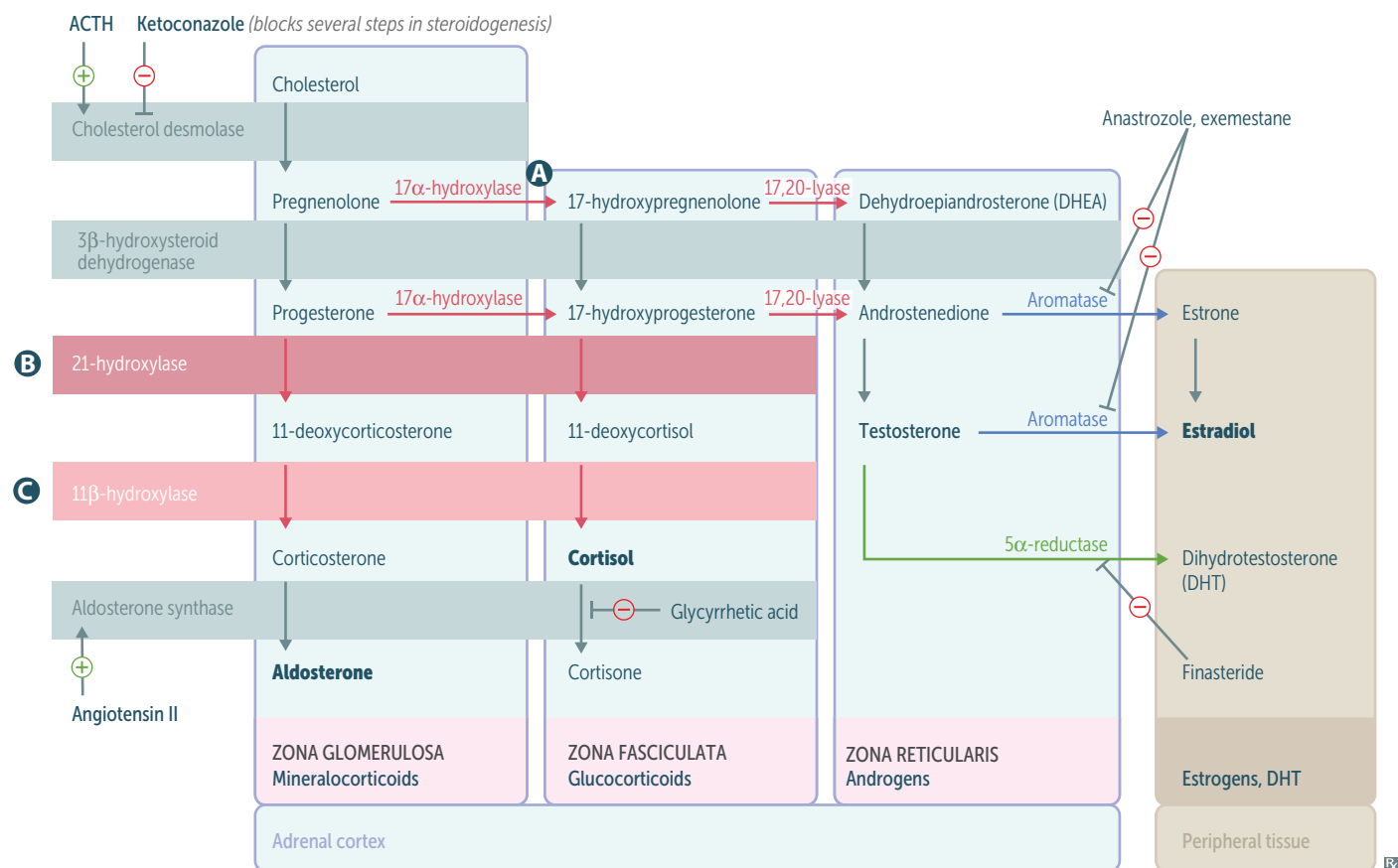
Appetite regulation

Ghrelin	Stimulates hunger (orexigenic effect) and GH release (via GH secretagog receptor). Produced by stomach. Sleep deprivation or Prader-Willi syndrome → ↑ ghrelin production.	Ghrelin makes you hunghre .
Leptin	Satiety hormone. Produced by adipose tissue. Mutation of leptin gene → congenital obesity. Sleep deprivation or starvation → ↓ leptin production.	Leptin keeps you thin .
Endocannabinoids	Act at cannabinoid receptors in hypothalamus and nucleus accumbens, two key brain areas for the homeostatic and hedonic control of food intake → ↑ appetite.	The munchies.

Antidiuretic hormone

SOURCE	Synthesized in hypothalamus (supraoptic nuclei), stored and secreted by posterior pituitary.	
FUNCTION	Regulates serum osmolarity (V ₂ -receptors) and blood pressure (V ₁ -receptors). Primary function is serum osmolarity regulation (ADH ↓ serum osmolarity, ↑ urine osmolarity) 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 V ₂ -receptor. Desmopressin acetate (ADH analog) is a treatment for central DI and nocturnal enuresis.
REGULATION	Osmoreceptors in hypothalamus; hypovolemia.	

Adrenal steroids and congenital adrenal hyperplasias



ENZYME DEFICIENCY	MINERALOCORTICOIDS	CORTISOL	SEX HORMONES	BP	[K ⁺]	LABS	PRESENTATION
A 17α-hydroxylase ^a	↑	↓	↓	↑	↓	↓ androstenedione	XY: ambiguous genitalia, undescended testes XX: lacks 2° sexual development
B 21-hydroxylase ^a	↓	↓	↑	↓	↑	↑ renin activity ↑ 17-hydroxyprogesterone	Most common Presents in infancy (salt wasting) or childhood (precocious puberty) XX: virilization
C 11β-hydroxylase ^a	↓ aldosterone ↑ 11-deoxycorticosterone (results in ↑ BP)	↓	↑	↑	↓	↓ renin activity	XX: virilization

^aAll congenital adrenal enzyme deficiencies are characterized by an enlargement of both adrenal glands due to ↑ ACTH stimulation (in response to ↓ cortisol).

Cortisol

SOURCE	Adrenal zona fasciculata.	Bound to corticosteroid-binding globulin.
FUNCTION	<p>↑ Blood pressure:</p> <ul style="list-style-type: none"> Upregulates α_1-receptors on arterioles → ↑ sensitivity to norepinephrine and epinephrine At high concentrations, can bind to mineralocorticoid (aldosterone) receptors <p>↑ Insulin resistance (diabetogenic)</p> <p>↑ Gluconeogenesis, lipolysis, and proteolysis</p> <p>↓ Fibroblast activity (causes striae)</p> <p>↓ Inflammatory and Immune responses:</p> <ul style="list-style-type: none"> Inhibits production of leukotrienes and prostaglandins Inhibits WBC adhesion → neutrophilia Blocks histamine release from mast cells Reduces eosinophils Blocks IL-2 production <p>↓ Bone formation (↓ osteoblast activity)</p>	<p>Cortisol is a BIG FIB.</p> <p>Exogenous corticosteroids can cause reactivation of TB and candidiasis (blocks IL-2 production).</p>
REGULATION	CRH (hypothalamus) stimulates ACTH release (pituitary) → cortisol production in adrenal zona fasciculata. Excess cortisol ↓ CRH, ACTH, and cortisol secretion.	Chronic stress induces prolonged secretion.

Calcium homeostasis

Plasma Ca^{2+} exists in three forms:	<ul style="list-style-type: none"> Ionized (~ 45%) Bound to albumin (~ 40%) Bound to anions (~ 15%) 	<p>↑ in pH → ↑ affinity of albumin (↑ negative charge) to bind Ca^{2+} → hypocalcemia (cramps, pain, paresthesias, carpopedal spasm).</p>
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Vitamin D (cholecalciferol)

SOURCE	D_3 from exposure of skin to sun, ingestion of fish and plants. D_2 from ingestion of plants, fungi, yeasts. Both converted to 25-OH in liver and to 1,25-(OH) $_2$ (active form) in kidney.	<p>Deficiency → rickets in kids, osteomalacia in adults. Caused by malabsorption, ↓ sunlight, poor diet, chronic kidney failure.</p> <p>24,25-(OH)$_2 \text{D}_3$ is an inactive form of vitamin D.</p>
FUNCTION	<p>↑ absorption of dietary Ca^{2+} and PO_4^{3-}.</p> <p>Enhances bone mineralization.</p>	<p>PTH leads to ↑ Ca^{2+} reabsorption and ↓ PO_4^{3-} reabsorption in the kidney, whereas 1,25-(OH)$_2 \text{D}_3$ leads to ↑ absorption of both Ca^{2+} and PO_4^{3-} in the gut.</p>
REGULATION	<p>↑ PTH, ↓ Ca^{2+}, ↓ PO_4^{3-} → ↑ 1,25-(OH)$_2$ production.</p> <p>1,25-(OH)$_2$ feedback inhibits its own production.</p>	

Parathyroid hormone

SOURCE

Chief cells of parathyroid.

FUNCTION

↑ bone resorption of Ca^{2+} and PO_4^{3-} .
 ↑ kidney reabsorption of Ca^{2+} in distal convoluted tubule.
 ↓ reabsorption of PO_4^{3-} in proximal convoluted tubule.
 ↑ $1,25\text{-(OH)}_2\text{D}_3$ (calcitriol) production by stimulating kidney 1α -hydroxylase in proximal convoluted tubule.

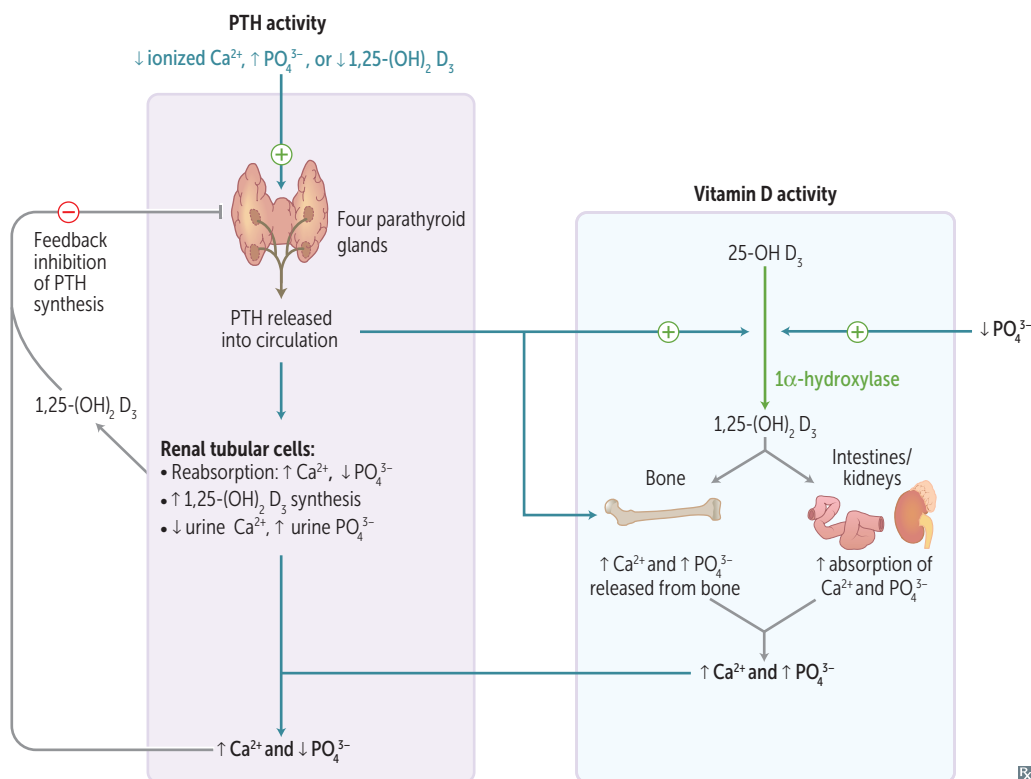
PTH ↑ serum Ca^{2+} , ↓ serum (PO_4^{3-}), ↑ urine (PO_4^{3-}), ↑ urine cAMP.
 ↑ RANK-L (receptor activator of $\text{NH-}\kappa\text{B}$ ligand) secreted by osteoblasts and osteocytes. Binds RANK (receptor) on osteoclasts and their precursors to stimulate osteoclasts and ↑ Ca^{2+} → bone resorption. 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^{2+} → ↑ PTH secretion.
 ↑ serum PO_4^{3-} → ↑ PTH secretion.
 ↓ serum Mg^{2+} → ↑ PTH secretion.
 ↓↓ serum Mg^{2+} → ↓ PTH secretion.
 Common causes of ↓ Mg^{2+} include diarrhea, aminoglycosides, diuretics, alcohol abuse.



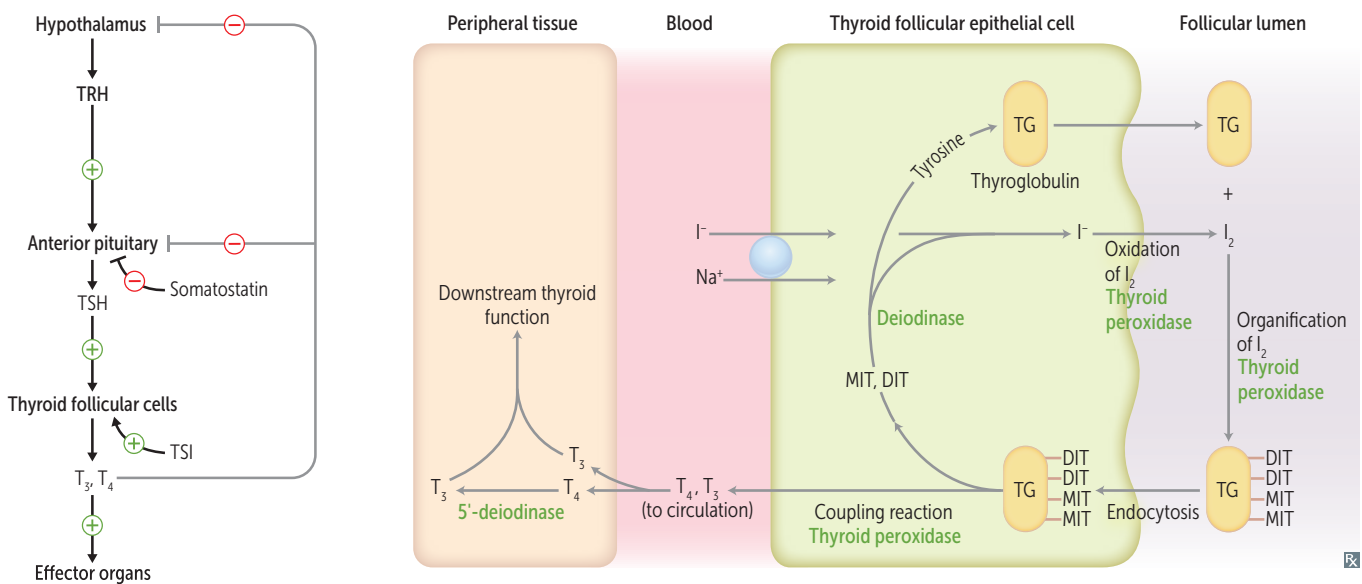
Calcitonin

SOURCE	Parafollicular cells (C cells) of thyroid.	Calcitonin opposes actions of PTH. Not important in normal Ca^{2+} homeostasis.
FUNCTION	↓ bone resorption of Ca^{2+} .	Calcitonin tones down Ca^{2+} levels.
REGULATION	↑ serum Ca^{2+} → calcitonin secretion.	

Thyroid hormones (T_3/T_4)

Iodine-containing hormones that control the body's metabolic rate.

SOURCE	Follicles of thyroid. Most T_3 formed in target tissues.	T_3 functions— 4 B's : B rain maturation B one growth β -adrenergic effects B asal metabolic rate ↑
FUNCTION	Bone growth (synergism with GH) CNS maturation ↑ β_1 receptors in heart = ↑ CO, HR, SV, contractility ↑ basal metabolic rate via ↑ Na^+/K^+ -ATPase activity → ↑ O_2 consumption, RR, body temperature ↑ glycogenolysis, gluconeogenesis, lipolysis	Thyroxine-binding globulin (TBG) binds most T_3/T_4 in blood; only free hormone is active. ↓ TBG in hepatic failure, steroids; ↑ TBG in pregnancy or OCP use (estrogen ↑ TBG). T_4 is major thyroid product; converted to T_3 in peripheral tissue by 5'-deiodinase. T_3 binds nuclear receptor with greater affinity than T_4 . Thyroid peroxidase is the enzyme responsible for oxidation and organification of iodide as well as coupling of monoiodotyrosine (MIT) and di-iodotyrosine (DIT). $DIT + DIT = T_4$. $DIT + MIT = T_3$. Propylthiouracil inhibits both thyroid peroxidase and 5'-deiodinase. Methimazole inhibits thyroid peroxidase only.
REGULATION	TRH (hypothalamus) stimulates TSH (pituitary), which stimulates follicular cells. May also be stimulated by thyroid-stimulating immunoglobulin (TSI) in Graves disease. Negative feedback by free T_3, T_4 to anterior pituitary ↓ sensitivity to TRH. Wolff-Chaikoff effect—excess iodine temporarily inhibits thyroid peroxidase → ↓ iodine organification → ↓ T_3/T_4 production.	



Signaling pathways of endocrine hormones

cAMP	FSH, LH, ACTH, TSH, CRH, hCG, ADH (V ₂ -receptor), MSH, PTH , calcitonin, GHRH, glucagon	FLAT ChAMP
cGMP	BNP, ANP, EDRF (NO)	BAD GraMPa Think vasodilators
IP₃	GnRH, Oxytocin, ADH (V₁-receptor), TRH, Histamine (H₁-receptor), Angiotensin II, Gastrin	GOAT HAG
Intracellular receptor	Progesterone, Estrogen, Testosterone, Cortisol, Aldosterone, T₃/T₄, Vitamin D	PET CAT on TV
Receptor tyrosine kinase	Insulin, IGF-1, FGF, PDGF, EGF	MAP kinase pathway Think growth factors
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

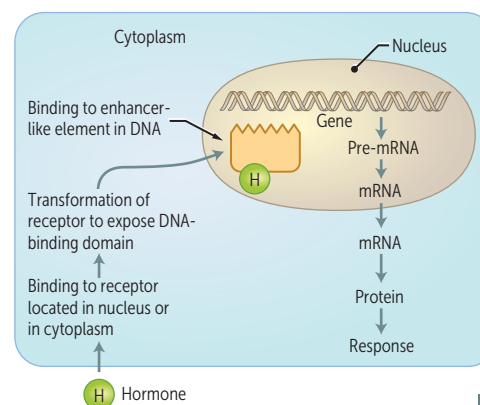
Signaling pathway of steroid hormones

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.

OCPs, pregnancy → ↑ SHBG.



▶ ENDOCRINE—PATHOLOGY

Cushing syndrome

ETIOLOGY

↑ cortisol due to a variety of causes:

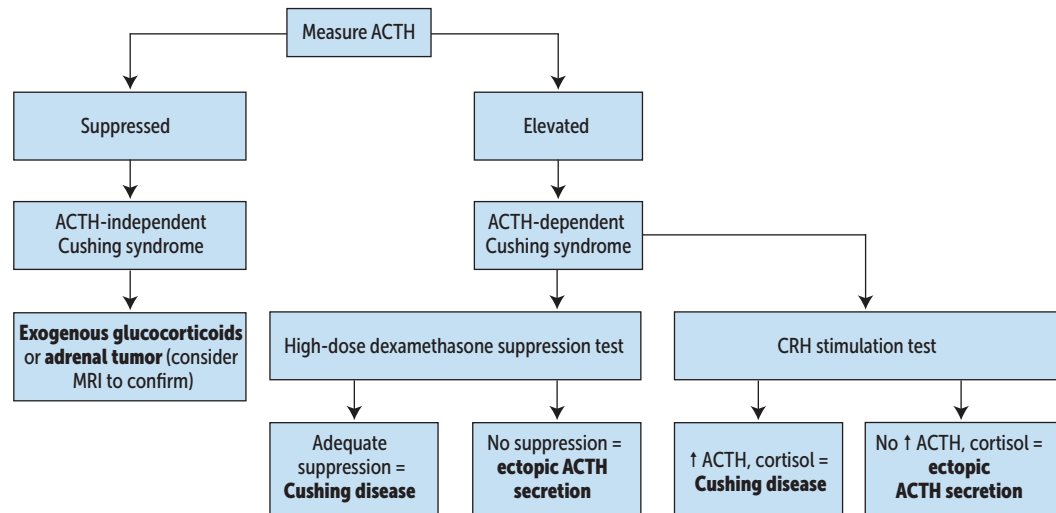
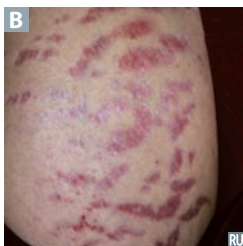
- Exogenous corticosteroids—result in ↓ ACTH, bilateral adrenal atrophy. Most common cause.
- Primary adrenal adenoma, hyperplasia, or carcinoma—result in ↓ ACTH, atrophy of uninvolved adrenal gland. Can also present with pseudohyperaldosteronism.
- ACTH-secreting pituitary adenoma (Cushing disease); paraneoplastic ACTH secretion (eg, small cell lung cancer, bronchial carcinoids)—result in ↑ ACTH, bilateral adrenal hyperplasia. Cushing disease is responsible for the majority of endogenous cases of Cushing syndrome.

FINDINGS

Hypertension, weight gain, moon facies **A**, abdominal striae **B** and truncal obesity, buffalo hump, skin changes (thinning, striae), osteoporosis, hyperglycemia (insulin resistance), amenorrhea, immunosuppression.

DIAGNOSIS

Screening tests include: ↑ free cortisol on 24-hr urinalysis, ↑ midnight salivary cortisol, and no suppression with overnight low-dose dexamethasone test. Measure serum ACTH. If ↓, suspect adrenal tumor or exogenous glucocorticoids. If ↑, distinguish between Cushing disease and ectopic ACTH secretion with a high-dose (8 mg) dexamethasone suppression test and CRH stimulation test. Ectopic secretion will not decrease with dexamethasone because the source is resistant to negative feedback; ectopic secretion will not increase with CRH because pituitary ACTH is suppressed.

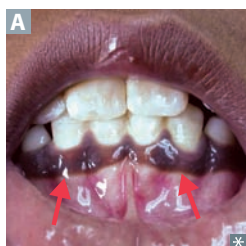


Adrenal insufficiency

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.

Diagnosis involves measurement of serum electrolytes, morning/random serum cortisol and ACTH (low cortisol, high ACTH in 1° adrenal insufficiency; low cortisol, low ACTH in 2°/3° adrenal insufficiency due to pituitary/hypothalamic disease), and response to ACTH stimulation test.

Alternatively, can use metyrapone stimulation test: metyrapone blocks last step of cortisol synthesis (11-deoxycortisol → cortisol). Normal response is ↓ cortisol and compensatory ↑ ACTH and 11-deoxycortisol. In 1° adrenal insufficiency, ACTH is ↑ but 11-deoxycortisol remains ↓ after test. In 2°/3° adrenal insufficiency, both ACTH and 11-deoxycortisol remain ↓ after test.

Primary adrenal insufficiency

Deficiency of aldosterone and cortisol production due to loss of gland function → hypotension (hyponatremic volume contraction), hyperkalemia, metabolic acidosis, skin and mucosal hyperpigmentation **A** (due to ↑ MSH, a byproduct of ACTH production from pro-opiomelanocortin [POMC]).

- **Acute**—sudden onset (eg, due to massive hemorrhage). May present with shock in acute adrenal crisis.
- **Chronic**—aka **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 **P**igments 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, no hyperkalemia (aldosterone synthesis preserved).

Secondary **S**pares the skin/mucosa.

Tertiary adrenal insufficiency

Seen in patients with chronic exogenous steroid use, precipitated by abrupt withdrawal. Aldosterone synthesis unaffected.

Tertiary from **T**reatment.

Hyperaldosteronism

Increased secretion of aldosterone from adrenal gland. Clinical features include hypertension, ↓ or normal K⁺, metabolic alkalosis. No edema due to aldosterone escape mechanism.

Primary hyperaldosteronism

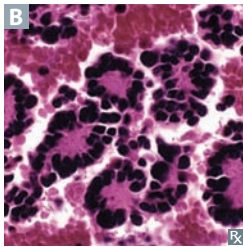
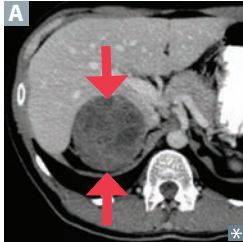
Seen with adrenal adenoma (Conn syndrome) or idiopathic adrenal hyperplasia. ↑ aldosterone, ↓ renin.

Secondary hyperaldosteronism

Seen in patients with renovascular hypertension, juxtaglomerular cell tumor (due to independent activation of renin-angiotensin-aldosterone system). ↑ aldosterone, ↑ renin.

Neuroendocrine tumors

Group of neoplasms originating from Kulchitsky and enterochromaffin-like cells. Occur in various organs (eg, thyroid: medullary carcinoma; lungs: small cell carcinoma; pancreas: islet cell tumor; adrenals: pheochromocytoma). Cells contain amine precursor uptake decarboxylase (APUD) and secrete different hormones (eg, 5-HIAA, neuron-specific enolase [NSE], chromogranin A).

Neuroblastoma

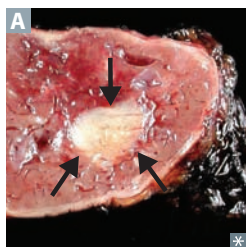
Most common tumor of the adrenal medulla in **children**, usually < 4 years old. Originates from neural crest cells. Occurs anywhere along the sympathetic chain **A**.

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. Can also present with opsoclonus-myoclonus syndrome (“dancing eyes-dancing feet”).

↑ HVA and VMA (catecholamine metabolites) in urine. Homer-Wright rosettes **B** characteristic of neuroblastoma and medulloblastoma. Bombesin and NSE ⊕. Associated with overexpression of N-myc oncogene. Classified as an APUD tumor.

Pheochromocytoma

ETIOLOGY



Most common tumor of the adrenal medulla in **adults** **A**. Derived from chromaffin cells (arise from neural crest).

Up to 25% of cases associated with germline mutations (eg, *NF-1*, *VHL*, *RET* [MEN 2A, 2B]).

Rule of 10's:

- 10% malignant
- 10% bilateral
- 10% extra-adrenal
- 10% calcify
- 10% kids

SYMPTOMS

Most tumors secrete epinephrine, norepinephrine, and dopamine, which can cause episodic hypertension. Symptoms occur in “spells”—relapse and remit.

Episodic hyperadrenergic symptoms (**5 P's**):

- P**ressure (↑ BP)
- P**ain (headache)
- P**erspiration
- P**alpitations (tachycardia)
- P**allor

FINDINGS

↑ catecholamines and metanephrines in urine and plasma.

TREATMENT

Irreversible α -antagonists (eg, phenoxybenzamine) followed by β -blockers prior to tumor resection. α -blockade must be achieved before giving β -blockers to avoid a hypertensive crisis.

Phenoxybenzamine (16 letters) is given for **pheochromocytoma** (also 16 letters).

Hypothyroidism vs hyperthyroidism

	Hypothyroidism	Hyperthyroidism
SIGNS/SYMPTOMS	Cold intolerance (↓ heat production) Weight gain, ↓ appetite Hypoactivity, lethargy, fatigue, weakness Constipation ↓ reflexes (delayed/slow relaxing) Hypothyroid myopathy (proximal muscle weakness, ↑ CK) Myxedema (facial/periorbital) Dry, cool skin; coarse, brittle hair Bradycardia, dyspnea on exertion	Heat intolerance (↑ heat production) Weight loss, ↑ appetite Hyperactivity, anxiety, insomnia, hand tremor Diarrhea ↑ reflexes (brisk) Thyrotoxic myopathy (proximal muscle weakness, normal CK) Pretibial myxedema (Graves disease), periorbital edema Warm, moist skin; fine hair Chest pain, palpitations, arrhythmias, ↑ number and sensitivity of β-adrenergic receptors
LAB FINDINGS	↑ TSH (if 1°) ↓ free T ₃ and T ₄ Hypercholesterolemia (due to ↓ LDL receptor expression)	↓ TSH (if 1°) ↑ free or total T ₃ and T ₄ Hypocholesterolemia (due to ↑ LDL receptor expression)

Causes of goiter

	Smooth/diffuse	Nodular
	Graves disease Hashimoto thyroiditis Iodine deficiency TSH-secreting pituitary adenoma	Toxic multinodular goiter Thyroid adenoma Thyroid cancer Thyroid cyst

Hypothyroidism

Hashimoto thyroiditis	<p>Most common cause of hypothyroidism in iodine-sufficient regions; an autoimmune disorder with antithyroid peroxidase (antimicrosomal) and antithyroglobulin antibodies. Associated with HLA-DR5. ↑ risk of non-Hodgkin lymphoma (typically of B-cell origin).</p> <p>May be hyperthyroid early in course due to thyrotoxicosis during follicular rupture.</p> <p>Histologic findings: Hürthle cells, lymphoid aggregates with germinal centers A.</p> <p>Findings: moderately enlarged, nontender thyroid.</p>
Congenital hypothyroidism (cretinism)	<p>Severe fetal hypothyroidism due to maternal hypothyroidism, thyroid agenesis, thyroid dysgenesis (most common cause in US), iodine deficiency, dysmorphogenetic goiter.</p> <p>Findings: Pot-bellied, Pale, Puffy-faced child with Protruding umbilicus, Protuberant tongue, and Poor brain development: the 6 P's B C.</p>
Subacute granulomatous thyroiditis (de Quervain)	<p>Self-limited disease often following a flu-like illness (eg, viral infection).</p> <p>May be hyperthyroid early in course, followed by hypothyroidism.</p> <p>Histology: granulomatous inflammation.</p> <p>Findings: ↑ ESR, jaw pain, very tender thyroid. (de Quervain is associated with pain.)</p>
Riedel thyroiditis	<p>Thyroid replaced by fibrous tissue with inflammatory infiltrate D. Fibrosis may extend to local structures (eg, trachea, esophagus), mimicking anaplastic carcinoma. ⅓ are hypothyroid.</p> <p>Considered a manifestation of IgG₄-related systemic disease (eg, autoimmune pancreatitis, retroperitoneal fibrosis, noninfectious aortitis).</p> <p>Findings: fixed, hard (rock-like), painless goiter.</p>
Other causes	<p>Iodine deficiency E, goitrogens (eg, amiodarone, lithium), Wolff-Chaikoff effect (thyroid gland downregulation in response to ↑ iodide).</p>



Hyperthyroidism**Graves disease**

Most common cause of hyperthyroidism. Thyroid-stimulating immunoglobulin (IgG; type II hypersensitivity) stimulates TSH receptors on thyroid (hyperthyroidism, diffuse goiter) and dermal fibroblasts (pretibial myxedema). Infiltration of retroorbital space by activated T-cells → ↑ cytokines (eg, TNF- α , IFN- γ) → ↑ fibroblast secretion of hydrophilic GAGs → ↑ osmotic muscle swelling, muscle inflammation, and adipocyte count → exophthalmos **A**. Often presents during stress (eg, pregnancy).

Tall, crowded follicular epithelial cells; scalloped colloid **B**.

Toxic multinodular goiter

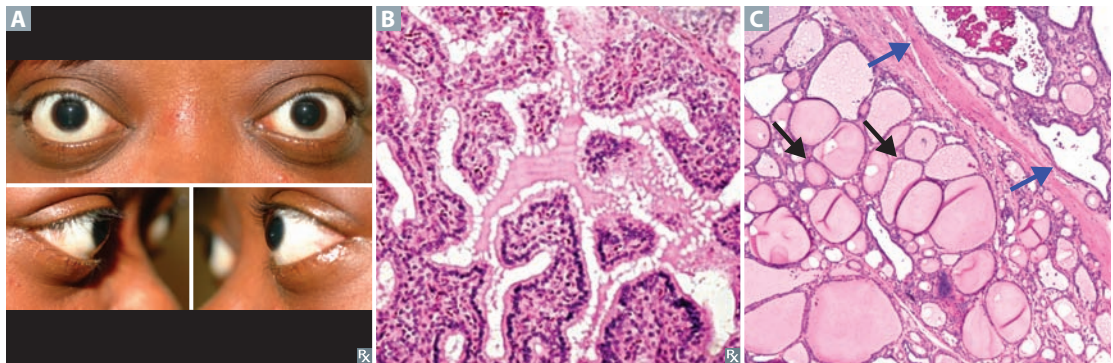
Focal patches of hyperfunctioning follicular cells **C** working independently of TSH (due to TSH receptor mutations in 60% of cases). ↑ release of T₃ and T₄. Hot nodules are rarely malignant.

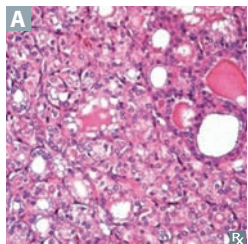
Thyroid storm

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**: β -blockers (eg, **P**ropranolol), **P**ropylthiouracil, corticosteroids (eg, **P**rednisolone), **P**otassium iodide (Lugol iodine).

Jod-Basedow phenomenon

Thyrotoxicosis if a patient with iodine deficiency and partially autonomous thyroid tissue (eg, autonomous nodule) is made iodine replete. Opposite of Wolff-Chaikoff effect.

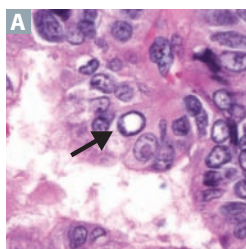


Thyroid adenoma

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 **A**; absence of capsular or vascular invasion (unlike follicular carcinoma).

Thyroid cancer

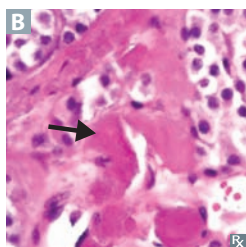
Treated with thyroidectomy. Complications of surgery include hoarseness (due to recurrent laryngeal nerve damage), hypocalcemia (due to removal of parathyroid glands), and transection of recurrent and superior laryngeal nerves (during ligation of inferior thyroid artery and superior laryngeal artery, respectively).

Papillary carcinoma

Most common, excellent prognosis. Empty-appearing nuclei with central clearing (“Orphan Annie” eyes) **A**, psammoma bodies, nuclear grooves. ↑ risk with *RET* and *BRAF* mutations, childhood irradiation.

Follicular carcinoma

Good prognosis, invades thyroid capsule and vasculature (unlike follicular adenoma), uniform follicles; hematogenous spread is common. Associated with *RAS* mutation.

Medullary carcinoma

From parafollicular “C cells”; produces calcitonin, sheets of cells in an amyloid stroma (stains with Congo red **B**). Associated with MEN 2A and 2B (*RET* mutations).

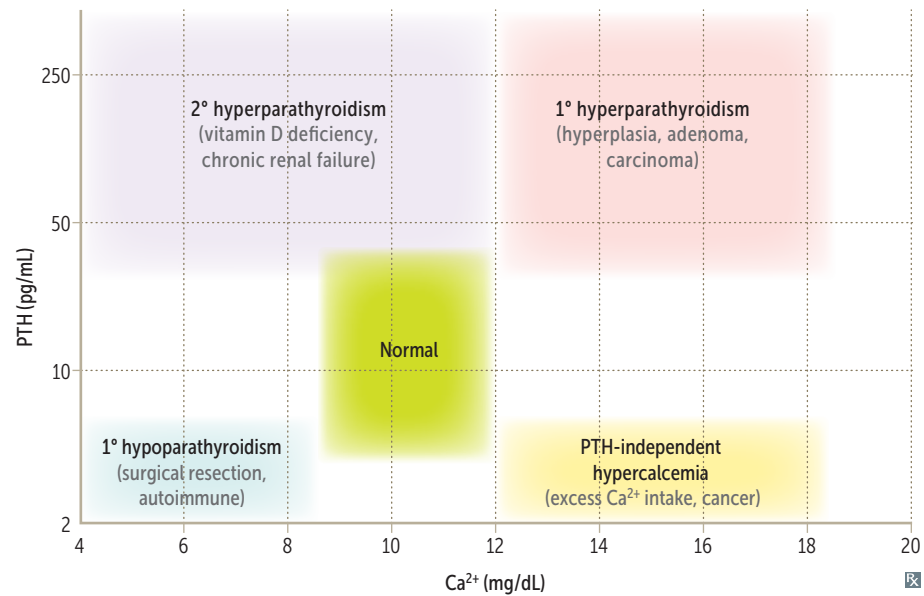
**Undifferentiated/
anaplastic carcinoma**

Older patients; invades local structures, very poor prognosis.

Lymphoma

Associated with Hashimoto thyroiditis.

Diagnosis of parathyroid disease



Hypoparathyroidism

Due to accidental surgical excision of parathyroid glands, autoimmune destruction, or DiGeorge syndrome. Findings: tetany, hypocalcemia, hyperphosphatemia.

Chvostek sign—tapping of facial nerve (tap the **C**heek) → contraction of facial muscles.

Trousseau sign—occlusion of brachial artery with BP cuff (cuff the **T**riceps) → carpal spasm.

Pseudohypoparathyroidism type 1A (Albright hereditary osteodystrophy)—unresponsiveness of kidney to PTH → hypocalcemia despite ↑ PTH levels. Characterized by shortened 4th/5th digits, short stature. Autosomal dominant. Due to defective G_s protein α-subunit causing end-organ resistance to PTH. Defect must be inherited from mother due to imprinting.

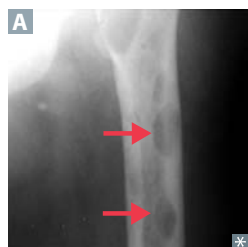
Pseudopseudohypoparathyroidism—physical exam features of Albright hereditary osteodystrophy but without end-organ PTH resistance. Occurs when defective G_s protein α-subunit is inherited from father.

Familial hypocalciuric hypercalcemia

Defective Ca²⁺-sensing receptor (CaSR) in multiple tissues (eg, parathyroids, kidneys). Higher than normal Ca²⁺ levels required to suppress PTH. Excessive renal Ca²⁺ reuptake → mild hypercalcemia and hypocalciuria with normal to ↑ PTH levels.

Hyperparathyroidism

Primary hyperparathyroidism



Usually due to parathyroid adenoma or hyperplasia. **Hypercalcemia**, hypercalciuria (renal **stones**), hypophosphatemia, ↑ PTH, ↑ ALP, ↑ cAMP in urine. Most often asymptomatic. May present with weakness and constipation (“**groans**”), abdominal/flank pain (kidney stones, acute pancreatitis), depression (“**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).

“**Stones, bones, groans, and psychiatric overtones.**”

Secondary hyperparathyroidism

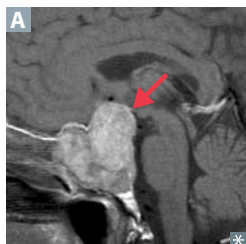
2° hyperplasia due to ↓ Ca²⁺ absorption and/or ↑ PO₄³⁻, most often in chronic renal disease (causes hypovitaminosis D → ↓ Ca²⁺ absorption). **Hypocalcemia**, hyperphosphatemia in chronic renal failure (vs hypophosphatemia with most other causes), ↑ ALP, ↑ PTH.

Renal osteodystrophy—renal disease → 2° and 3° hyperparathyroidism → bone lesions.

Tertiary hyperparathyroidism

Refractory (autonomous) hyperparathyroidism resulting from chronic renal disease. ↑↑ PTH, ↑ Ca²⁺.

Pituitary adenoma



Benign tumor, most commonly prolactinoma (arises from lactotrophs). Adenoma **A** may be functional (hormone producing) or nonfunctional (silent). Nonfunctional tumors present with mass effect (bitemporal hemianopia, hypopituitarism, headache). Functional tumor presentation is based on the hormone produced.

Treatment for prolactinoma: dopamine agonists (eg, ergot alkaloids such as bromocriptine, cabergoline), transsphenoidal resection.

Nelson syndrome

Enlargement of existing ACTH-secreting pituitary adenoma after bilateral adrenalectomy for refractory Cushing disease (due to removal of cortisol feedback mechanism). Presents with hyperpigmentation, headaches and bitemporal hemianopia. Treatment: pituitary irradiation or surgical resection.

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). ↑ risk of colorectal polyps and cancer.

↑ GH in children → gigantism (↑ linear bone growth). HF most common cause of death.

DIAGNOSIS

↑ serum IGF-1; failure to suppress serum GH following oral glucose tolerance test; pituitary mass seen on brain MRI.

TREATMENT

Pituitary adenoma resection. If not cured, treat with octreotide (somatostatin analog) or pegvisomant (growth hormone receptor antagonist).

**Laron syndrome (dwarfism)**

Defective growth hormone receptors → ↓ linear growth. ↑ GH, ↓ IGF-1. Clinical features include short height, small head circumference, characteristic facies with saddle nose and prominent forehead, delayed skeletal maturation, small genitalia.

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 DI	Nephrogenic DI
ETIOLOGY	Pituitary tumor, autoimmune, trauma, surgery, ischemic encephalopathy, idiopathic	Hereditary (ADH receptor mutation), 2° to hypercalcemia, hypokalemia, lithium, demeclocycline (ADH antagonist)
FINDINGS	↓ ADH Urine specific gravity < 1.006 Serum osmolality > 290 mOsm/kg Hyperosmotic volume contraction	Normal or ↑ ADH levels Urine specific gravity < 1.006 Serum osmolality > 290 mOsm/kg Hyperosmotic volume contraction
WATER DEPRIVATION TEST ^a	> 50% ↑ in urine osmolality only after administration of ADH analog	Minimal change in urine osmolality, even after administration of ADH analog
TREATMENT	Desmopressin acetate Hydration	HCTZ, indomethacin, amiloride Hydration, avoidance of offending agent

^aNo water intake for 2–3 hr followed by hourly measurements of urine volume and osmolality and plasma Na⁺ concentration and osmolality. ADH analog (desmopressin acetate) is administered if serum osmolality > 295–300 mOsm/kg, plasma Na⁺ ≥ 145, or urine osmolality does not rise despite a rising plasma osmolality.

Syndrome of inappropriate antidiuretic hormone secretion

Characterized by:

- Excessive free water retention
- Euvolemic hyponatremia with continued urinary Na⁺ excretion
- Urine osmolality > serum osmolality

Body responds to water retention with ↓ aldosterone and ↑ ANP and BNP → ↑ urinary Na⁺ secretion → normalization of extracellular fluid volume → euvolemic hyponatremia. Very low serum Na⁺ levels can lead to cerebral edema, seizures. Correct slowly to prevent osmotic demyelination syndrome (formerly known as central pontine myelinolysis).

Causes include:

- Ectopic ADH (eg, small cell lung cancer)
- CNS disorders/head trauma
- Pulmonary disease
- Drugs (eg, cyclophosphamide)

Treatment: fluid restriction, salt tablets, IV hypertonic saline, diuretics, conivaptan, tolvaptan, demeclocycline.

Hypopituitarism

Undersecretion of pituitary hormones due to:

- Nonsecreting pituitary adenoma, craniopharyngioma
- **Sheehan syndrome**—ischemic infarct of pituitary following postpartum bleeding; pregnancy-induced 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
- **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).

Diabetes mellitus

ACUTE MANIFESTATIONS

Polydipsia, polyuria, polyphagia, weight loss, DKA (type 1), hyperosmolar coma (type 2). Rarely, can be caused by unopposed secretion of GH and epinephrine. Also seen in patients on glucocorticoid therapy (steroid diabetes).

CHRONIC COMPLICATIONS

Nonenzymatic glycation:

- Small vessel disease (diffuse thickening of basement membrane) → retinopathy (hemorrhage, exudates, microaneurysms, vessel proliferation), glaucoma, neuropathy, nephropathy (nodular glomerulosclerosis, aka Kimmelstiel-Wilson nodules → progressive proteinuria [initially microalbuminuria; ACE inhibitors are renoprotective] and arteriosclerosis → hypertension; both lead to chronic renal failure).
- Large vessel atherosclerosis, CAD, peripheral vascular occlusive disease, gangrene → limb loss, cerebrovascular disease. MI most common cause of death.

Osmotic damage (sorbitol accumulation in organs with aldose reductase and ↓ or absent sorbitol dehydrogenase):

- Neuropathy (motor, sensory [glove and stocking distribution], and autonomic degeneration)
- Cataracts

DIAGNOSIS

TEST

HbA_{1c}

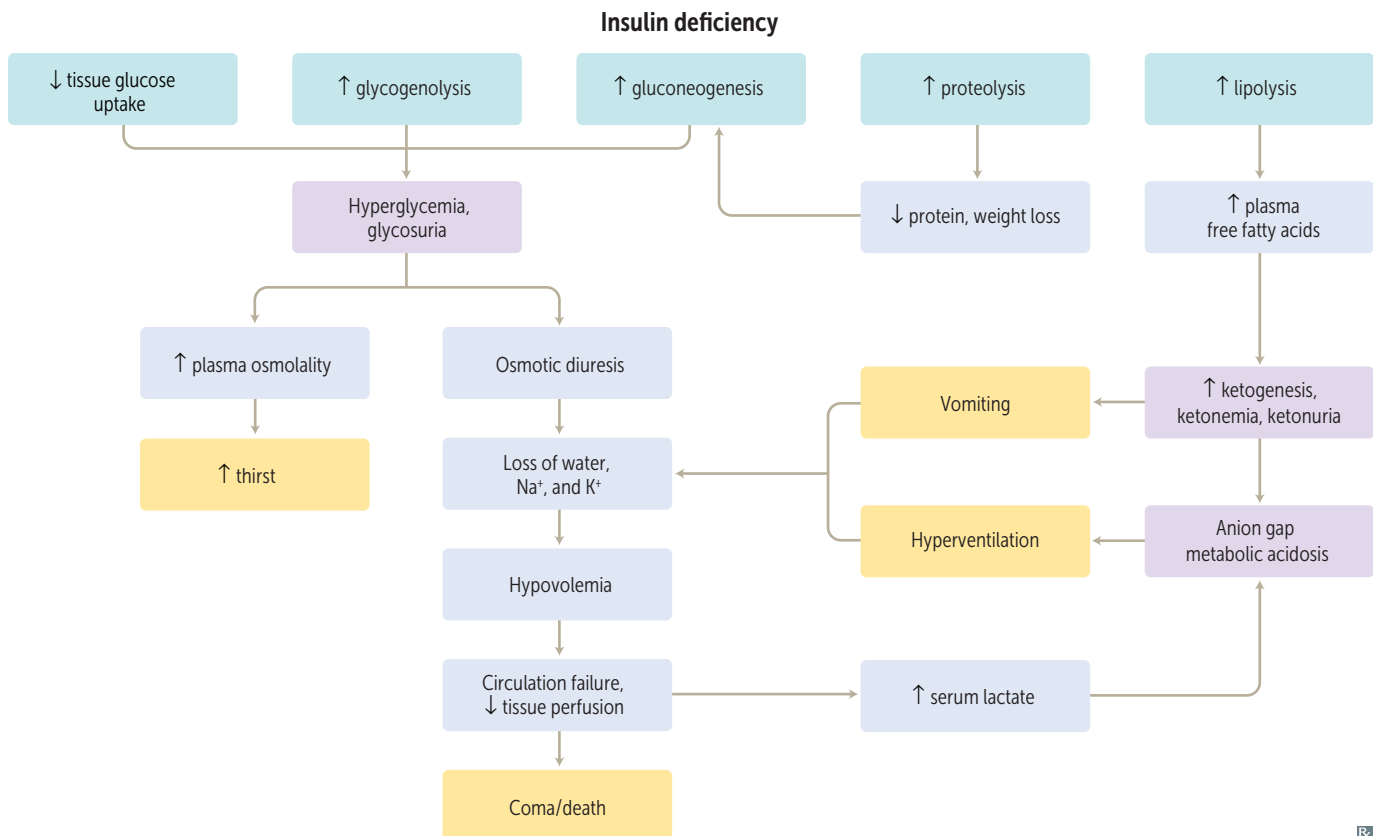
Fasting plasma glucose
2-hour oral glucose tolerance test

DIAGNOSTIC CUTOFF

≥ 6.5%
≥ 126 mg/dL
≥ 200 mg/dL

NOTES

Reflects average blood glucose over prior 3 months
Fasting for > 8 hours
2 hours after consumption of 75 g of glucose in water



Type 1 vs type 2 diabetes mellitus

Variable	Type 1	Type 2
1° DEFECT	Autoimmune destruction of β cells (eg, due to glutamic acid decarboxylase antibodies)	\uparrow resistance to insulin, progressive pancreatic β -cell failure
INSULIN NECESSARY IN TREATMENT	Always	Sometimes
AGE (EXCEPTIONS COMMONLY OCCUR)	< 30 yr	> 40 yr
ASSOCIATION WITH OBESITY	No	Yes
GENETIC PREDISPOSITION	Relatively weak (50% concordance in identical twins), polygenic	Relatively strong (90% concordance in identical twins), polygenic
ASSOCIATION WITH HLA SYSTEM	Yes (HLA-DR3 and -DR4)	No
GLUCOSE INTOLERANCE	Severe	Mild to moderate
INSULIN SENSITIVITY	High	Low
KETOACIDOSIS	Common	Rare
β -CELL NUMBERS IN THE ISLETS	\downarrow	Variable (with amyloid deposits)
SERUM INSULIN LEVEL	\downarrow	Variable
CLASSIC SYMPTOMS OF POLYURIA, POLYDIPSIA, POLYPHAGIA, WEIGHT LOSS	Common	Sometimes
HISTOLOGY	Islet leukocytic infiltrate	Islet amyloid polypeptide (IAPP) deposits

Diabetic ketoacidosis

One of the most feared complications of diabetes. Usually due to insulin noncompliance or \uparrow insulin requirements from \uparrow stress (eg, infection). Excess fat breakdown and \uparrow ketogenesis from \uparrow free fatty acids, which are then made into ketone bodies (β -hydroxybutyrate > acetoacetate). Usually occurs in type 1 diabetes, as endogenous insulin in type 2 diabetes usually prevents lipolysis.

SIGNS/SYMPTOMS	DKA is D eathly: D elirium/psychosis, K ussmaul respirations (rapid/deep breathing), A bdominal pain/nausea/vomiting, D ehydration. Fruity breath odor (due to exhaled acetone).
LABS	Hyperglycemia, \uparrow H^+ , \downarrow HCO_3^- (\uparrow anion gap metabolic acidosis), \uparrow blood ketone levels, leukocytosis. Hyperkalemia, but depleted intracellular K^+ due to transcellular shift from \downarrow insulin and acidosis (therefore total body K^+ is depleted).
COMPLICATIONS	Life-threatening mucormycosis (usually caused by <i>Rhizopus</i> infection), cerebral edema, cardiac arrhythmias, heart failure.
TREATMENT	IV fluids, IV insulin, and K^+ (to replete intracellular stores); glucose if necessary to prevent hypoglycemia.

Hyperosmolar hyperglycemia nonketotic syndrome

State of profound hyperglycemia-induced dehydration and ↑ serum osmolarity, classically seen in elderly type 2 diabetics with limited ability to drink. Hyperglycemia → excessive osmotic diuresis → dehydration → eventual onset of HHNS. Symptoms: thirst, polyuria, lethargy, focal neurological deficits (eg, seizures), can progress to coma and death if left untreated. Labs: hyperglycemia (often > 600 mg/dL), ↑ serum osmolarity (> 320 mOsm/kg), no acidosis (pH > 7.3, ketone production inhibited by presence of insulin). Treatment: aggressive IV fluids, insulin therapy.

Glucagonoma

Tumor of pancreatic α cells → overproduction of glucagon. Presents with dermatitis (necrolytic migratory erythema), diabetes (hyperglycemia), DVT, declining weight, depression. Treatment: octreotide, surgery.

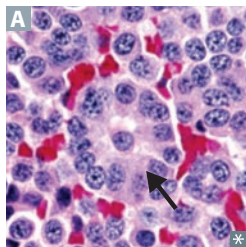
Insulinoma

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 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.

Somatostatinoma

Tumor of pancreatic δ cells → overproduction of somatostatin → ↓ secretion of secretin, cholecystokinin, glucagon, insulin, gastrin. May present with diabetes/glucose intolerance, steatorrhea, gallstones. Treatment: surgical resection; somatostatin analogs (eg, octreotide) for symptom control.

Carcinoid syndrome



Rare syndrome caused by carcinoid tumors (neuroendocrine cells **A**; note prominent rosettes [arrow]), especially metastatic small bowel tumors, which secrete high levels of serotonin (5-HT). Not seen if tumor is limited to GI tract (5-HT undergoes first-pass metabolism in liver). Results in recurrent diarrhea, cutaneous flushing, asthmatic wheezing, right-sided valvular heart disease (tricuspid regurgitation, pulmonic stenosis). ↑ 5-hydroxyindoleacetic acid (5-HIAA) in urine, niacin deficiency (pellagra). Treatment: surgical resection, somatostatin analog (eg, octreotide).

Rule of 1/3s:

- 1/3 metastasize
- 1/3 present with 2nd malignancy
- 1/3 are multiple

Most common malignancy in the small intestine.

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.

Multiple endocrine neoplasias

All **MEN** syndromes have autosomal **dominant** inheritance.
 “All **MEN** are **dominant**” (or so they think).

SUBTYPE	CHARACTERISTICS	COMMENTS
MEN 1	<p>Pituitary tumors (prolactin or GH)</p> <p>Pancreatic endocrine tumors—Zollinger-Ellison syndrome, insulinomas, VIPomas, glucagonomas (rare)</p> <p>Parathyroid adenomas</p> <p>Associated with mutation of <i>MEN1</i> (menin, a tumor suppressor, chromosome 11)</p>	
MEN 2A	<p>Parathyroid hyperplasia</p> <p>Medullary thyroid carcinoma—neoplasm of parafollicular or C cells; secretes calcitonin; prophylactic thyroidectomy required</p> <p>Pheochromocytoma (secretes catecholamines)</p> <p>Associated with mutation in <i>RET</i> (codes for receptor tyrosine kinase) in cells of neural crest origin</p>	
MEN 2B	<p>Medullary thyroid carcinoma</p> <p>Pheochromocytoma</p> <p>Mucosal neuromas (oral/intestinal ganglioneuromatosis)</p> <p>Associated with marfanoid habitus; mutation in <i>RET</i> gene</p>	

MEN 1 = 3 P's: Pituitary, Parathyroid, and Pancreas
MEN 2A = 2 P's: Parathyroids and Pheochromocytoma
MEN 2B = 1 P: Pheochromocytoma

▶ ENDOCRINE—PHARMACOLOGY

Diabetes mellitus drugs

Treatment strategies:

Type 1 DM—low-carbohydrate diet, insulin replacement

Type 2 DM—dietary modification and exercise for weight loss; oral agents, non-insulin injectables, insulin replacement

Gestational DM (GDM)—dietary modifications, exercise, insulin replacement if lifestyle modification fails

DRUG CLASSES	ACTION	CLINICAL USE	RISKS/CONCERNS
Insulin preparations			
Insulin, rapid acting Lispro, Aspart, Glulisine	Binds insulin receptor (tyrosine kinase activity) rapidly, no LAG . Liver: ↑ glucose stored as glycogen. Muscle: ↑ glycogen, protein synthesis; ↑ K ⁺ uptake. Fat: ↑ TG storage.	Type 1 DM, type 2 DM, GDM (postprandial glucose control).	Hypoglycemia, lipodystrophy, rare hypersensitivity reactions.
Insulin, short acting Regular		Type 1 DM, type 2 DM, GDM, DKA (IV), hyperkalemia (+ glucose), stress hyperglycemia.	
Insulin, intermediate acting NPH		Type 1 DM, type 2 DM, GDM.	
Insulin, long acting Detemir, glargine		Type 1 DM, type 2 DM, GDM (basal glucose control).	
Oral hypoglycemic drugs			
Biguanides Metformin	Exact mechanism unknown. ↓ gluconeogenesis, ↑ glycolysis, ↑ peripheral glucose uptake (↑ insulin sensitivity).	Oral. First-line therapy in type 2 DM, causes modest weight loss. Can be used in patients without islet function.	GI upset; most serious adverse effect is lactic acidosis (thus contraindicated in renal insufficiency).
Sulfonylureas First generation: chlorpropamide, tolbutamide Second generation: glimepiride, glipizide, glyburide	Close K ⁺ channel in β-cell membrane → cell depolarizes → insulin release via ↑ Ca ²⁺ influx.	Stimulate release of endogenous insulin in type 2 DM. Require some islet function, so useless in type 1 DM.	Risk of hypoglycemia ↑ in renal failure, weight gain. First generation: disulfiram-like effects. Second generation: hypoglycemia.
Glitazones/ thiazolidinediones Pioglitazone, rosiglitazone	↑ insulin sensitivity in peripheral tissue. Binds to PPAR-γ nuclear transcription regulator. ^a	Used as monotherapy in type 2 DM or combined with above agents. Safe to use in renal impairment.	Weight gain, edema. Hepatotoxicity, HF, ↑ risk of fractures.

Diabetes mellitus drugs (continued)

DRUG CLASSES	ACTION	CLINICAL USE	RISKS/CONCERNS
Oral hypoglycemic drugs (continued)			
Meglitinides Nateglinide, repaglinide	Stimulate postprandial insulin release by binding to K ⁺ channels on β-cell membranes (site differs from sulfonylureas).	Used as monotherapy in type 2 DM or combined with metformin.	Hypoglycemia (↑ risk with renal failure), weight gain.
GLP-1 analogs Exenatide, liraglutide (sc injection)	↑ glucose-dependent insulin release, ↓ glucagon release, ↓ gastric emptying, ↑ satiety.	Type 2 DM.	Nausea, vomiting, pancreatitis; modest weight loss.
DPP-4 inhibitors Linagliptin, saxagliptin, sitagliptin	Inhibits DPP-4 enzyme that deactivates GLP-1, thereby ↑ glucose-dependent insulin release, ↓ glucagon release, ↓ gastric emptying, ↑ satiety.	Type 2 DM.	Mild urinary or respiratory infections; weight neutral.
Amylin analogs Pramlintide (sc injection)	↓ gastric emptying, ↓ glucagon.	Type 1 DM, type 2 DM.	Hypoglycemia (in setting of mistimed prandial insulin), nausea.
Sodium-glucose co-transporter 2 (SGLT-2) inhibitors Canagliflozin, dapagliflozin, empagliflozin	Block reabsorption of glucose in PCT.	Type 2 DM.	Glucosuria, UTIs, vaginal yeast infections, hyperkalemia, dehydration (orthostatic hypotension).
α-glucosidase inhibitors Acarbose, miglitol	Inhibit intestinal brush-border α-glucosidases. Delayed carbohydrate hydrolysis and glucose absorption → ↓ postprandial hyperglycemia.	Type 2 DM.	GI disturbances.

^aGenes activated by PPAR-γ regulate fatty acid storage and glucose metabolism. Activation of PPAR-γ ↑ insulin sensitivity and levels of adiponectin.

Thionamides	Propylthiouracil (PTU), methimazole.
MECHANISM	Block thyroid peroxidase, inhibiting the oxidation of iodide and the organification (coupling) of iodine → inhibition of thyroid hormone synthesis. Propylthiouracil also blocks 5'-deiodinase → ↓ peripheral conversion of T ₄ to T ₃ .
CLINICAL USE	Hyperthyroidism. PTU blocks P eripheral conversion and is used in P regnancy.
ADVERSE EFFECTS	Skin rash, agranulocytosis (rare), aplastic anemia, hepatotoxicity. Methimazole is a possible teratogen (can cause aplasia cutis).

Levothyroxine (T₄), triiodothyronine (T₃)

MECHANISM	Thyroid hormone replacement.
CLINICAL USE	Hypothyroidism, myxedema. Used off-label as weight loss supplements.
ADVERSE EFFECTS	Tachycardia, heat intolerance, tremors, arrhythmias.

Hypothalamic/pituitary drugs

DRUG	CLINICAL USE
ADH antagonists (conivaptan, tolvaptan)	SIADH, block action of ADH at V ₂ -receptor.
Desmopressin acetate	Central (not nephrogenic) DI.
GH	GH deficiency, Turner syndrome.
Oxytocin	Stimulates labor, uterine contractions, milk let-down; controls uterine hemorrhage.
Somatostatin (octreotide)	Acromegaly, carcinoid syndrome, gastrinoma, glucagonoma, esophageal varices.

Demeclocycline

MECHANISM	ADH antagonist (member of tetracycline family).
CLINICAL USE	SIADH.
ADVERSE EFFECTS	Nephrogenic DI, photosensitivity, abnormalities of bone and teeth.

Glucocorticoids

MECHANISM	Beclomethasone, dexamethasone, hydrocortisone, methylprednisolone, prednisone, triamcinolone. Metabolic, catabolic, anti-inflammatory, and immunosuppressive effects mediated by interactions with glucocorticoid response elements, inhibition of phospholipase A ₂ , and inhibition of transcription factors such as NF-κB.
CLINICAL USE	Adrenal insufficiency, inflammation, immunosuppression, asthma.
ADVERSE EFFECTS	Iatrogenic Cushing syndrome (hypertension, weight gain, moon facies, truncal obesity, buffalo hump, thinning of skin, striae, acne, osteoporosis, hyperglycemia, amenorrhea, immunosuppression), adrenocortical atrophy, peptic ulcers, steroid diabetes, steroid psychosis, cataracts. Adrenal insufficiency when drug stopped abruptly after chronic use.

Fludrocortisone

MECHANISM	Synthetic analog of aldosterone with little glucocorticoid effects.
CLINICAL USE	Mineralocorticoid replacement in 1° adrenal insufficiency.
ADVERSE EFFECTS	Similar to glucocorticoids; also edema, exacerbation of heart failure, hyperpigmentation.

Cinacalcet

MECHANISM	Sensitizes Ca ²⁺ -sensing receptor (CaSR) in parathyroid gland to circulating Ca ²⁺ → ↓ PTH.
CLINICAL USE	1° or 2° hyperparathyroidism.
ADVERSE EFFECTS	Hypocalcemia.

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

“Is life worth living? It all depends on the liver.”

—William James

▶ Embryology	338
▶ Anatomy	339
▶ Physiology	350
▶ Pathology	353
▶ Pharmacology	374

▶ GASTROINTESTINAL—EMBRYOLOGY

Normal gastrointestinal embryology

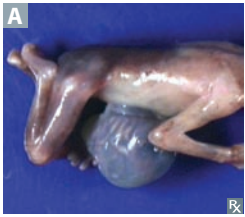
Foregut—pharynx to duodenum.

Midgut—duodenum to proximal $\frac{2}{3}$ of transverse colon.

Hindgut—distal $\frac{1}{3}$ of transverse colon to anal canal above pectinate line.

Midgut development:

- 6th week—physiologic midgut herniates 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—sternal defects
- Lateral fold closure—omphalocele, gastroschisis
- Caudal fold closure—bladder exstrophy

Gastroschisis—extrusion of abdominal contents through abdominal folds (typically right of umbilicus); not covered by peritoneum.

Omphalocele—persistence of herniation of abdominal contents into umbilical cord, sealed by peritoneum **A**.

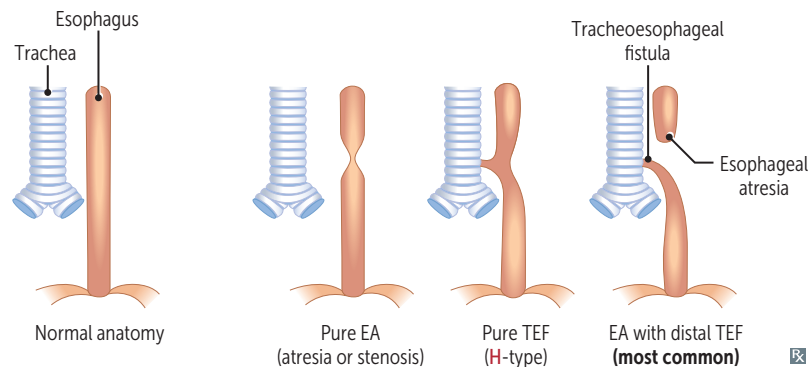
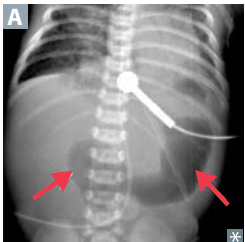
Tracheoesophageal anomalies

Esophageal atresia (EA) with distal tracheoesophageal fistula (TEF) is the most common (85%).

Polyhydramnios in utero. Neonates drool, choke, and vomit with first feeding. TEF allows 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 the CXR shows gasless abdomen.

**Intestinal atresia**

Presents with bilious vomiting and abdominal distension within first 1–2 days of life.

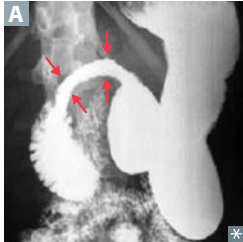
Duodenal atresia—failure to recanalize → dilation of stomach and proximal duodenum (“double bubble” on x-ray **A**). Associated with Down syndrome.

Jejunal and ileal atresia—disruption of mesenteric vessels → ischemic necrosis → segmental resorption (bowel discontinuity or “apple peel”).

Hypertrophic pyloric stenosis

Most common cause of gastric outlet obstruction in infants (1:600). Palpable “olive” mass in epigastric region and nonbilious projectile vomiting at ~ 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). Treatment is surgical incision (pyloromyotomy).

Pancreas and spleen embryology

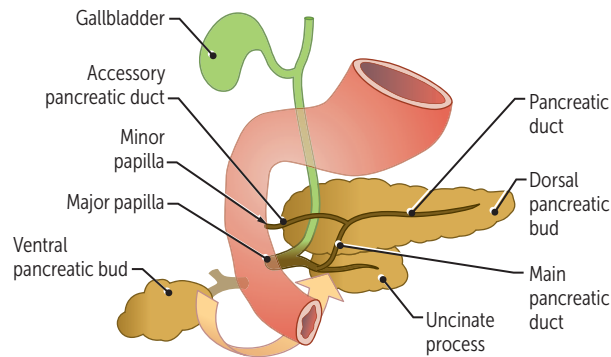


Pancreas—derived from foregut. Ventral pancreatic buds contribute to uncinate process and main pancreatic duct. The dorsal pancreatic bud alone becomes the body, tail, isthmus, and accessory pancreatic duct. Both the ventral and dorsal buds contribute to pancreatic head.

Annular pancreas—ventral pancreatic bud abnormally encircles 2nd part of duodenum; forms a ring of pancreatic tissue that may cause duodenal narrowing **A** and nonbilious 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 → splenic artery).



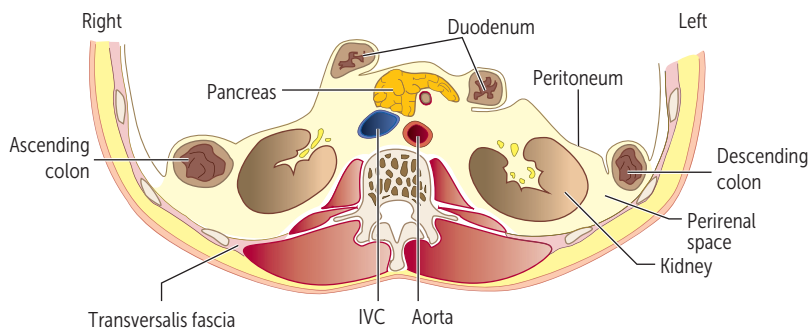
▶ GASTROINTESTINAL—ANATOMY

Retroperitoneal structures

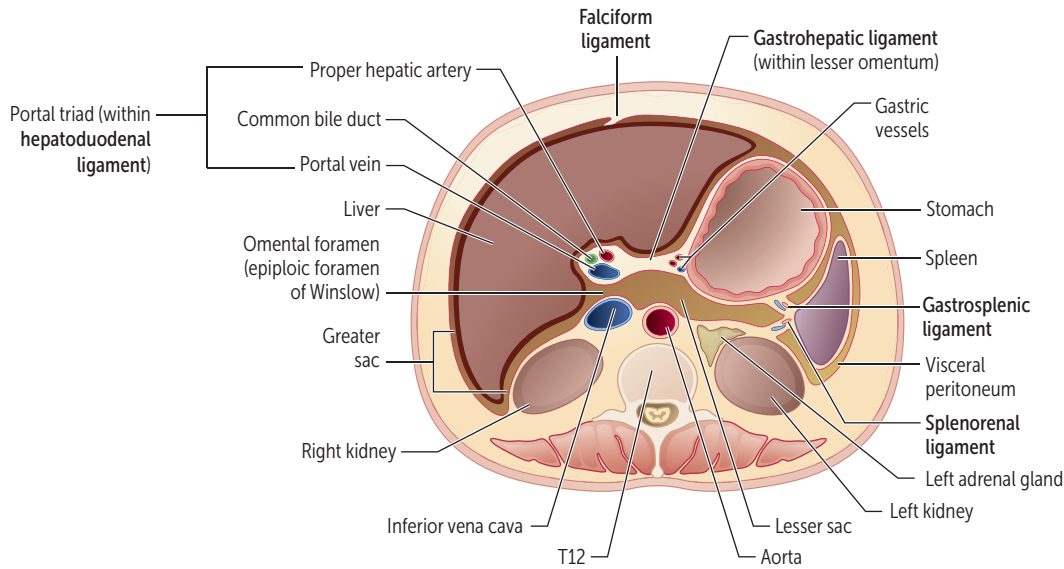
Retroperitoneal structures include GI structures that lack a mesentery and non-GI structures. Injuries to retroperitoneal structures can cause blood or gas accumulation in retroperitoneal space.

SAD PUCKER:

- Suprarenal (adrenal) glands [not shown]
- A**orta and IVC
- D**uodenum (2nd through 4th parts)
- P**ancreas (except tail)
- U**reters [not shown]
- C**olon (descending and ascending)
- K**idneys
- E**sophagus (thoracic portion) [not shown]
- R**ectum (partially) [not shown]



Important gastrointestinal ligaments



LIGAMENT	CONNECTS	STRUCTURES CONTAINED	NOTES
Falciform	Liver to anterior abdominal wall	Ligamentum teres hepatis (derivative of fetal umbilical vein)	Derivative of ventral mesentery
Hepatoduodenal	Liver to duodenum	Portal triad: proper hepatic artery, portal vein, common bile duct	Pringle maneuver—ligament may be compressed between thumb and index finger placed in omental foramen to control bleeding Borders the omental foramen, which connects the greater and lesser sacs
Gastrohepatic	Liver to lesser curvature of stomach	Gastric arteries	Separates greater and lesser sacs on the right May be cut during surgery to access lesser sac
Gastrocolic (not shown)	Greater curvature and transverse colon	Gastroepiploic arteries	Part of greater omentum
Gastrosplenic	Greater curvature and spleen	Short gastrics, left gastroepiploic vessels	Separates greater and lesser sacs on the left Part of greater omentum
Splenorenal	Spleen to posterior abdominal wall	Splenic artery and vein, tail of pancreas	

Digestive tract anatomy

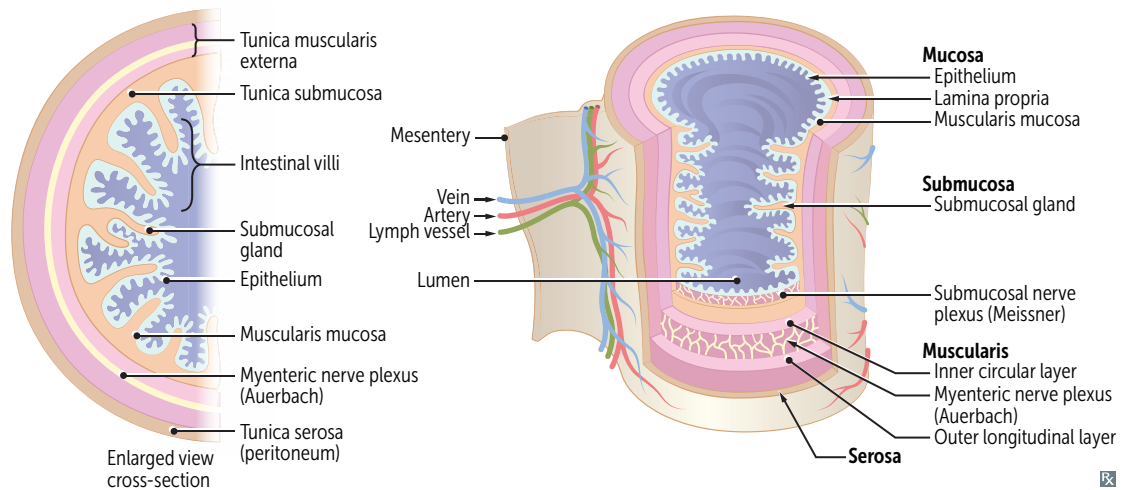
Layers of gut wall (inside to outside—**MSMS**):

- **M**ucosa—epithelium, lamina propria, muscularis mucosa
- **S**ubmucosa—includes **S**ubmucosal nerve plexus (**M**eissner), **S**ecretes fluid
- **M**uscularis externa—includes **M**yenteric nerve plexus (**A**uerbach), **M**otility
- **S**erosa (when intraperitoneal), adventitia (when retroperitoneal)

Ulcers can extend into submucosa, inner or outer muscular layer. Erosions are in the mucosa only.

Frequencies of basal electric rhythm (slow waves):

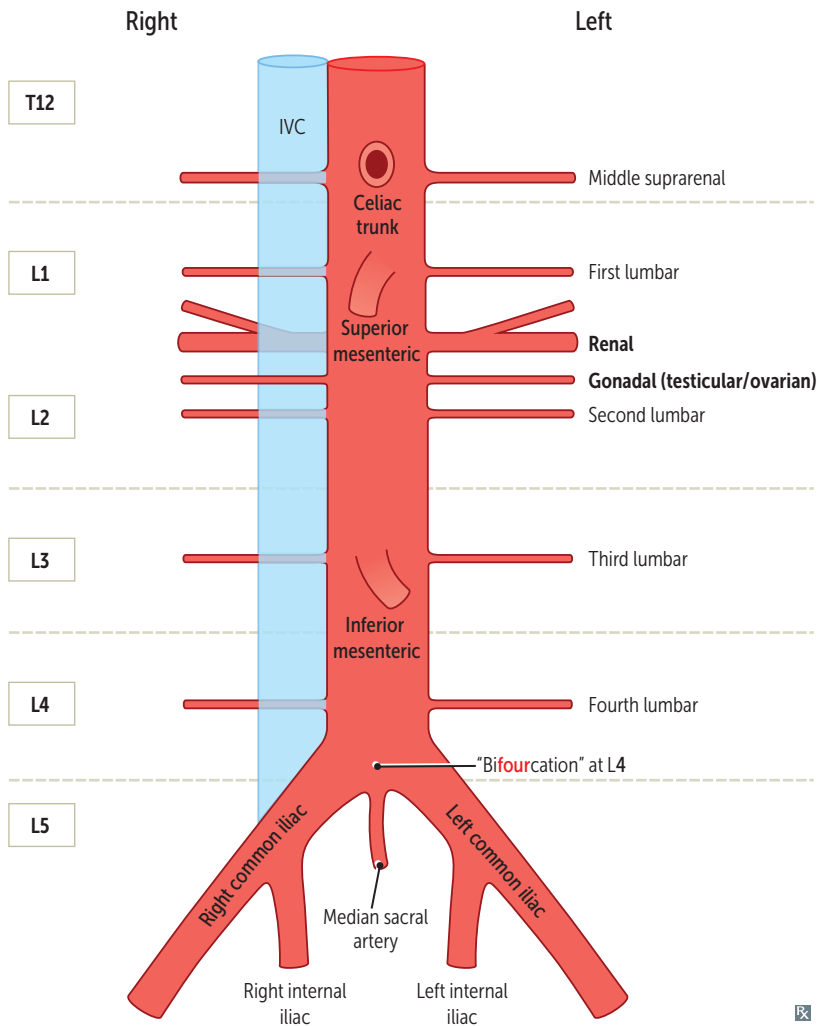
- Stomach—3 waves/min
- Duodenum—12 waves/min
- Ileum—8–9 waves/min



Digestive tract histology

Esophagus	Nonkeratinized stratified squamous epithelium.
Stomach	Gastric glands.
Duodenum	Villi and microvilli ↑ absorptive surface. Brunner glands (HCO_3^- -secreting cells of submucosa) and crypts of Lieberkühn.
Jejunum	Plicae circulares and crypts of Lieberkühn.
Ileum	Peyer patches (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 but no villi; abundant goblet cells.

Abdominal aorta and branches



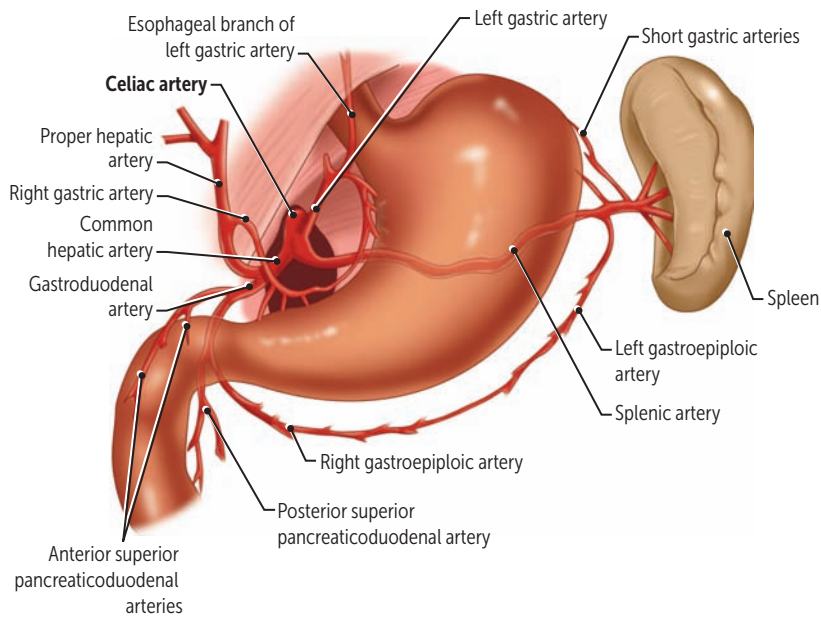
Arteries supplying GI structures branch **anteriorly**. Arteries supplying non-GI structures branch **laterally** and **posteriorly**.

Superior mesenteric artery syndrome

Characterized by intermittent intestinal obstruction symptoms (primarily postprandial pain) when transverse (third) portion of duodenum is compressed between SMA and aorta. Typically occurs in conditions associated with diminished mesenteric fat (eg, low body weight/malnutrition).

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	L1	Distal duodenum to proximal $\frac{2}{3}$ of transverse colon
Hindgut	IMA	Pelvic	L3	Distal $\frac{1}{3}$ of transverse colon to upper portion of rectum

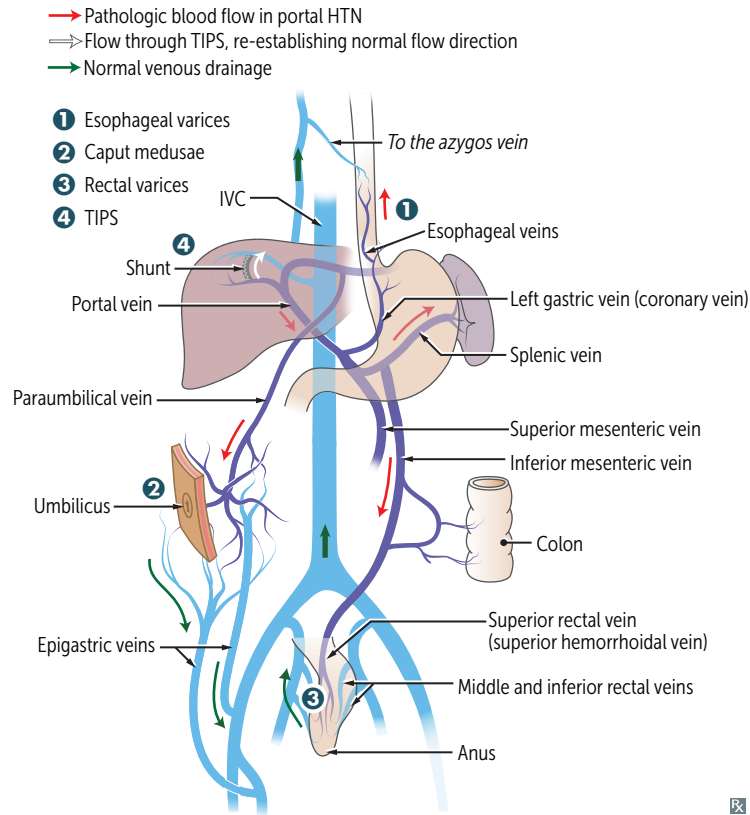
Celiac trunk

Branches of celiac trunk: common hepatic, splenic, and left gastric. These constitute the main blood supply of the stomach.

Strong anastomoses exist between:

- Left and right gastroepiploics
- Left and right gastrics

Portosystemic anastomoses



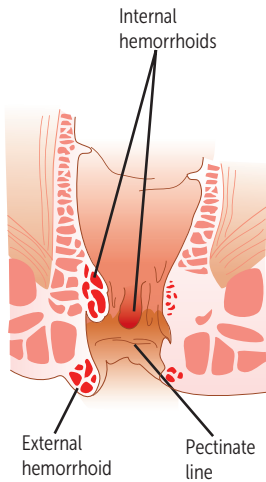
SITE OF ANASTOMOSIS	CLINICAL SIGN	PORTAL ↔ SYSTEMIC
① Esophagus	Esophageal varices	Left gastric ↔ azygos
② Umbilicus	Caput medusae	Paraumbilical ↔ small epigastric veins of the anterior abdominal wall.
③ Rectum	Anorectal varices	Superior rectal ↔ middle and inferior rectal

Varices of **gut**, **butt**, and **caput** (medusae) are commonly seen with portal hypertension.

Treatment with a **transjugular intrahepatic portosystemic shunt (TIPS)** ④ between the portal vein and hepatic vein relieves portal hypertension by shunting blood to the systemic circulation, bypassing the liver.

Pectinate (dentate) line

Formed where endoderm (hindgut) meets ectoderm.



Above pectinate line—internal hemorrhoids, adenocarcinoma.

Arterial supply from superior rectal artery (branch of IMA).

Venous drainage: superior rectal vein → inferior mesenteric vein → portal system.

Below pectinate line—external hemorrhoids, anal fissures, squamous cell carcinoma.

Arterial supply from inferior rectal artery (branch of internal pudendal artery).

Venous drainage: inferior rectal vein → internal pudendal vein → internal iliac vein → common iliac vein → IVC.

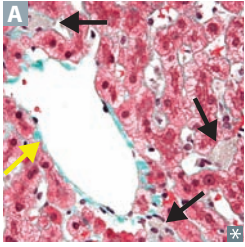
Internal hemorrhoids receive visceral innervation and are therefore **not painful**.

Lymphatic drainage to internal iliac lymph nodes.

External hemorrhoids receive somatic innervation (inferior rectal branch of pudendal nerve) and are therefore **painful** if thrombosed. Lymphatic drainage to superficial inguinal nodes.

Anal fissure—tear in the anal mucosa below the Pectinate line. **P**ain while **P**ooping; blood on toilet **P**aper. Located **P**osteriorly because this area is **P**oorly **P**erfused. Associated with low-fiber diets and constipation.

Liver tissue architecture



Apical surface of hepatocytes faces bile canaliculi. Basolateral surface faces sinusoids.

Kupffer cells, which are specialized macrophages, form the lining of these sinusoids (black arrows in **A**; yellow arrow shows hepatic venule).

Hepatic stellate (Ito) cells in space of Disse store vitamin A (when quiescent) and produce extracellular matrix (when activated).

Zone I—periportal zone:

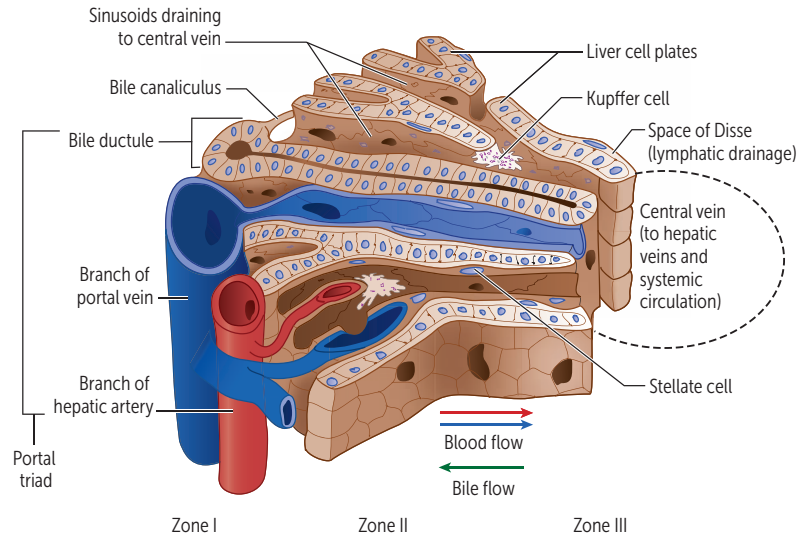
- Affected 1st by viral hepatitis
- Ingested toxins (eg, cocaine)

Zone II—intermediate zone:

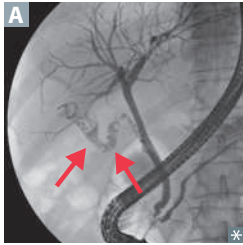
- Yellow fever

Zone III—pericentral vein (centrilobular) zone:

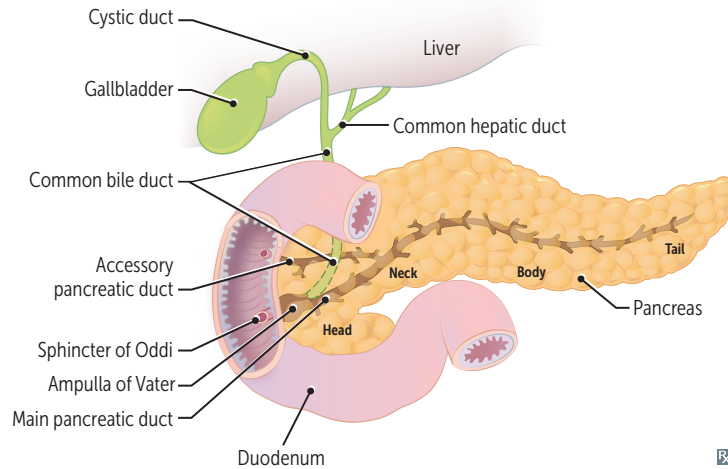
- Affected 1st by ischemia
- Contains cytochrome P-450 system
- Most sensitive to metabolic toxins
- Site of alcoholic hepatitis



Biliary structures



Gallstones (filling defects, red arrows in **A**) 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 → painless jaundice.



Femoral region

ORGANIZATION

Lateral to medial: Nerve-Artery-Vein-Lymphatics.

You go from **lateral to medial** to find your **NAVeL**.

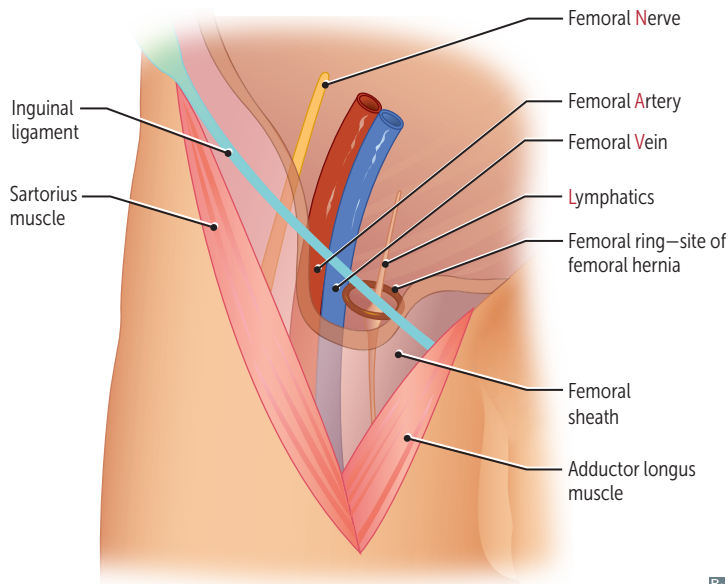
Femoral triangle

Contains femoral nerve, artery, vein.

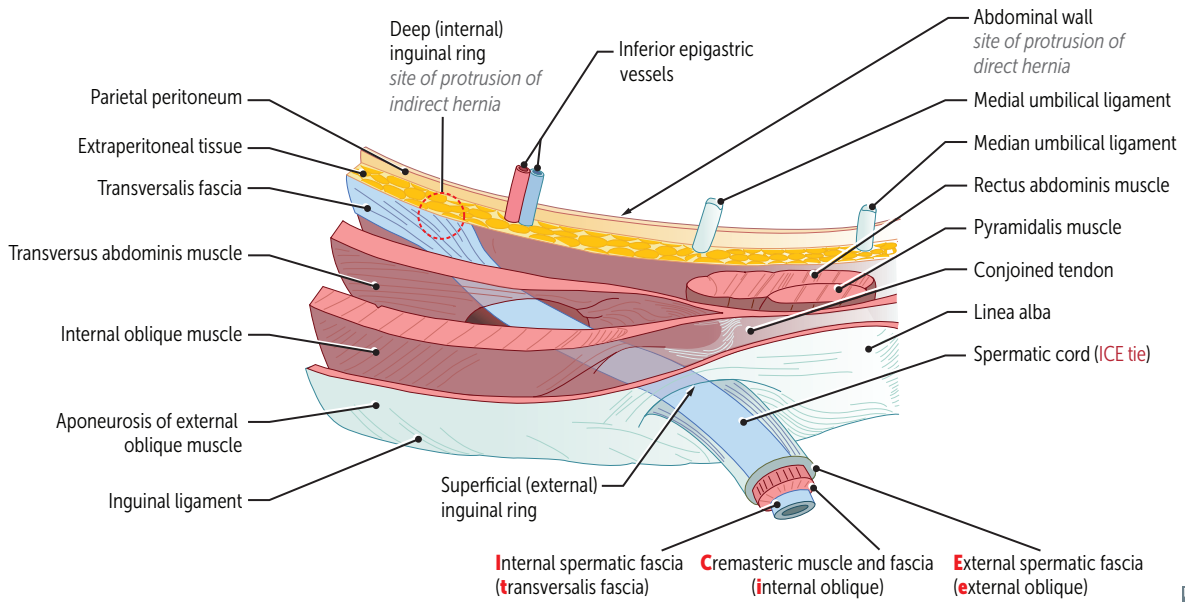
Venous near the penis.

Femoral sheath

Fascial tube 3–4 cm below inguinal ligament. Contains femoral vein, artery, and canal (deep inguinal lymph nodes) but not femoral nerve.



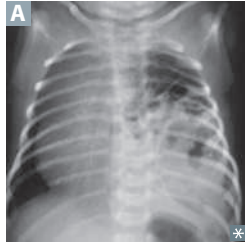
Inguinal canal



Hernias

A 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; may occur due to congenital defect of pleuroperitoneal membrane **A**, or as a result of 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 is most common.

Gastroesophageal junction is displaced upward; “hourglass stomach.”

Paraesophageal hernia—gastroesophageal junction is usually normal. Fundus protrudes into the thorax.

Indirect inguinal hernia



Goes through the **internal** (deep) inguinal ring, external (superficial) inguinal ring, and **into** the scrotum. Enters internal inguinal ring lateral to inferior epigastric vessels. Occurs in **infants** owing to failure of processus vaginalis to close (can form hydrocele). Much more common in males **B**.

An indirect inguinal hernia follows the path of descent of the testes. Covered by all 3 layers of spermatic fascia.

Direct inguinal hernia

Protrudes through the inguinal (Hesselbach) triangle. Bulges directly through abdominal wall medial to inferior epigastric vessels. Goes through the external (superficial) inguinal ring only. Covered by external spermatic fascia. Usually in older men.

MDs don't LIe:

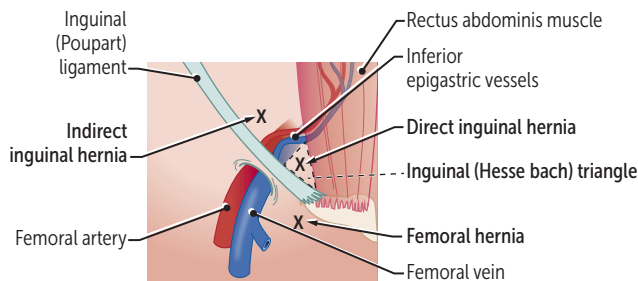
Medial to inferior epigastric vessels = **D**irect hernia.

Lateral to inferior epigastric vessels = **I**ndirect hernia.

Femoral hernia

Protrudes below inguinal ligament through femoral canal below and lateral to pubic tubercle. More common in **females**.

More likely to present with incarceration or strangulation than inguinal hernias.



Inguinal (Hesselbach) triangle:

- Inferior epigastric vessels
- Lateral border of rectus abdominis
- Inguinal ligament

▶ GASTROINTESTINAL—PHYSIOLOGY

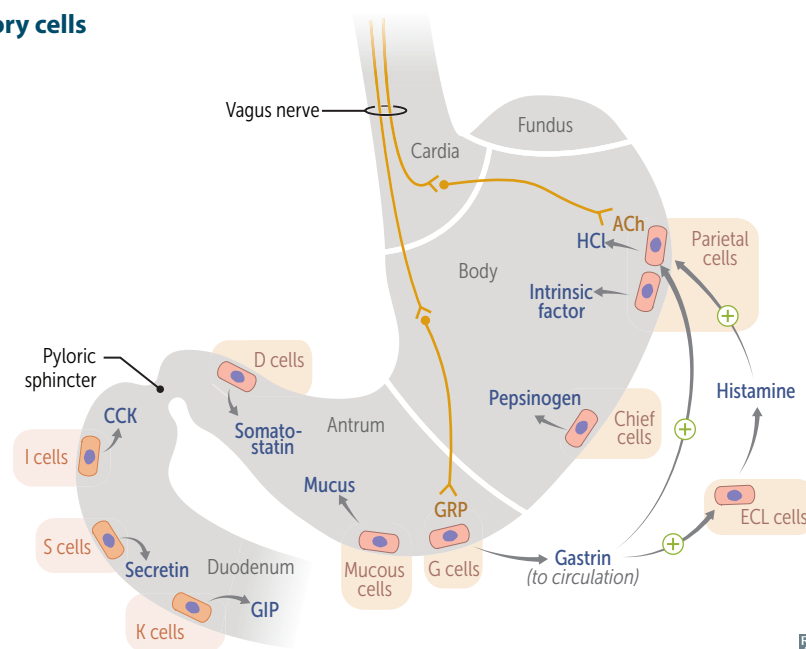
Gastrointestinal regulatory substances

REGULATORY SUBSTANCE	SOURCE	ACTION	REGULATION	NOTES
Gastrin	G cells (antrum of stomach, duodenum)	<ul style="list-style-type: none"> ↑ gastric H⁺ secretion ↑ growth of gastric mucosa ↑ gastric motility 	<ul style="list-style-type: none"> ↑ by stomach distention/alkalinization, amino acids, peptides, vagal stimulation via gastrin-releasing peptide (GRP) ↓ by pH < 1.5 	<ul style="list-style-type: none"> ↑ 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 style="list-style-type: none"> ↓ gastric acid and pepsinogen secretion ↓ pancreatic and small intestine fluid secretion ↓ gallbladder contraction ↓ insulin and glucagon release 	<ul style="list-style-type: none"> ↑ 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 style="list-style-type: none"> ↑ pancreatic secretion ↑ gallbladder contraction ↓ gastric emptying ↑ sphincter of Oddi relaxation 	<ul style="list-style-type: none"> ↑ by fatty acids, amino acids 	Acts on neural muscarinic pathways to cause pancreatic secretion.
Secretin	S cells (duodenum)	<ul style="list-style-type: none"> ↑ pancreatic HCO₃⁻ secretion ↓ gastric acid secretion ↑ bile secretion 	<ul style="list-style-type: none"> ↑ by acid, fatty acids in lumen of duodenum 	↑ HCO ₃ ⁻ neutralizes gastric acid in duodenum, allowing pancreatic enzymes to function.
Glucose-dependent insulinotropic peptide	K cells (duodenum, jejunum)	<p>Exocrine:</p> <ul style="list-style-type: none"> ↓ gastric H⁺ secretion <p>Endocrine:</p> <ul style="list-style-type: none"> ↑ insulin release 	<ul style="list-style-type: none"> ↑ by fatty acids, amino acids, oral glucose 	Also known as gastric inhibitory peptide (GIP). Oral glucose load leads to ↑ insulin compared to IV equivalent due to GIP secretion.
Motilin	Small intestine	Produces migrating motor complexes (MMCs)	<ul style="list-style-type: none"> ↑ 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 style="list-style-type: none"> ↑ intestinal water and electrolyte secretion ↑ relaxation of intestinal smooth muscle and sphincters 	<ul style="list-style-type: none"> ↑ by distention and vagal stimulation ↓ by adrenergic input 	VIPoma —non-α, non-β islet cell pancreatic tumor that secretes VIP. Watery Diarrhea, Hypokalemia, and Achlorhydria (WDHA syndrome) .
Nitric oxide		<ul style="list-style-type: none"> ↑ smooth muscle relaxation, including lower esophageal sphincter (LES) 		Loss of NO secretion is implicated in ↑ LES tone of achalasia.
Ghrelin	Stomach	<ul style="list-style-type: none"> ↑ appetite 	<ul style="list-style-type: none"> ↑ in fasting state ↓ by food 	<ul style="list-style-type: none"> ↑ in Prader-Willi syndrome. ↓ after gastric bypass surgery.

Gastrointestinal secretory products

PRODUCT	SOURCE	ACTION	REGULATION	NOTES
Intrinsic factor	Parietal cells (stomach)	Vitamin B ₁₂ -binding protein (required for B ₁₂ uptake in terminal ileum)		Autoimmune destruction of parietal cells → chronic gastritis and pernicious anemia.
Gastric acid	Parietal cells (stomach)	↓ stomach pH	↑ by histamine, ACh, gastrin ↓ by somatostatin, GIP, prostaglandin, secretin	
Pepsin	Chief cells (stomach)	Protein digestion	↑ by vagal stimulation, local acid	Pepsinogen (inactive) is converted to pepsin (active) in the presence of H ⁺ .
Bicarbonate	Mucosal cells (stomach, duodenum, salivary glands, pancreas) and Brunner glands (duodenum)	Neutralizes acid	↑ by pancreatic and biliary secretion with secretin	Trapped in mucus that covers the gastric epithelium.

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.

Pancreatic secretions Isotonic fluid; low flow → high Cl^- , high flow → high HCO_3^- .

ENZYME	ROLE	NOTES
α-amylase	Starch digestion	Secreted in active form
Lipases	Fat digestion	
Proteases	Protein digestion	Includes trypsin, chymotrypsin, elastase, carboxypeptidases Secreted as proenzymes also known as zymogens
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^+ dependent). Fructose is taken up by facilitated diffusion by GLUT-5. All are transported to blood by GLUT-2.
D-xylose absorption test: distinguishes GI mucosal damage from other causes of malabsorption.

Vitamin/mineral absorption

Iron	Absorbed as Fe^{2+} in duodenum.	Iron F ist, B ro
Folate	Absorbed in small bowel.	Clinically relevant in patients with small bowel disease or after resection.
B₁₂	Absorbed in terminal ileum along with bile salts, requires intrinsic factor.	

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 **I**ntra-gut **A**ntibody. And always say “secretory IgA.”

Bile

Composed of bile salts (bile acids conjugated to glycine or taurine, making them water soluble), phospholipids, cholesterol, bilirubin, water, and ions. Cholesterol 7 α -hydroxylase catalyzes rate-limiting step of bile acid synthesis.

Functions:

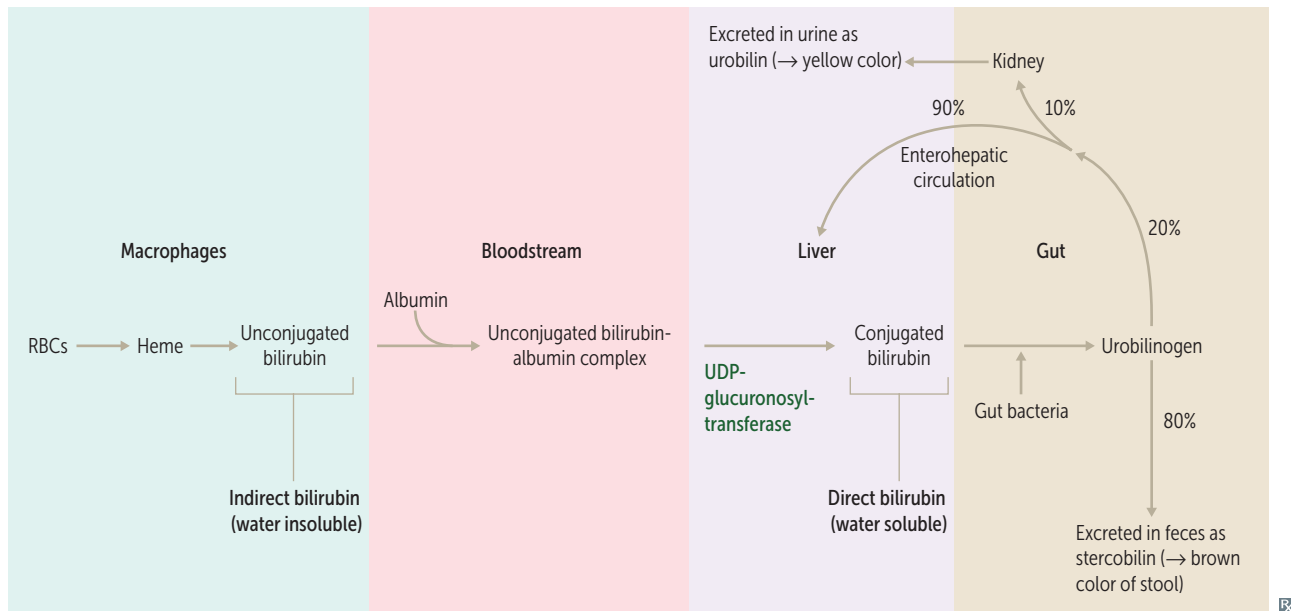
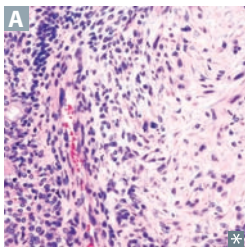
- Digestion and absorption of lipids and fat-soluble vitamins
- Cholesterol excretion (body's only means of eliminating cholesterol)
- Antimicrobial activity (via membrane disruption)

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.

Indirect bilirubin—unconjugated; water **ins**oluble.

**► GASTROINTESTINAL—PATHOLOGY****Salivary gland tumors**

Most commonly benign and in parotid gland. Tumors in smaller glands more likely malignant. Typically present as painless mass/swelling. Facial pain or paralysis suggests malignant involvement of CN VII.

- **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.
- **Mucoepidermoid carcinoma**—most common malignant tumor, has mucinous and squamous components.
- **Warthin tumor** (papillary cystadenoma lymphomatosum)—benign cystic tumor with germinal centers.

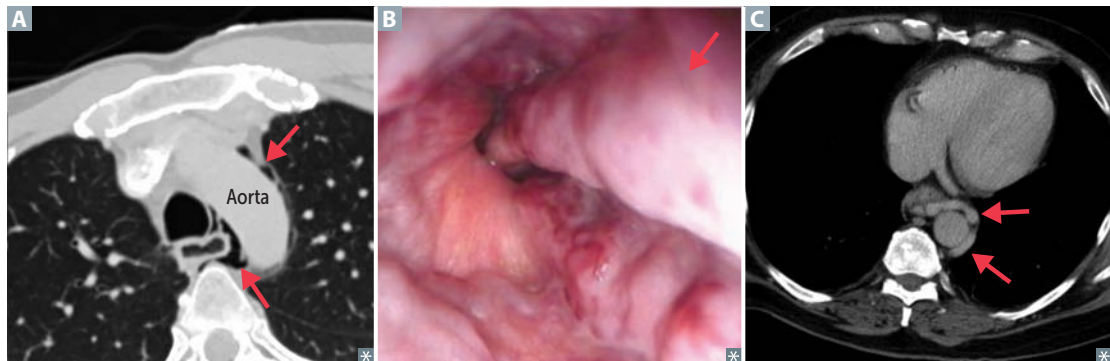
Achalasia

Failure of relaxation of LES due to loss of myenteric (Auerbach) plexus. High LES resting pressure and uncoordinated or absent peristalsis → progressive dysphagia to solids and liquids (vs obstruction—solids only). Barium swallow shows dilated esophagus with an area of distal stenosis. Associated with ↑ risk of esophageal cancer, especially squamous cell carcinoma.

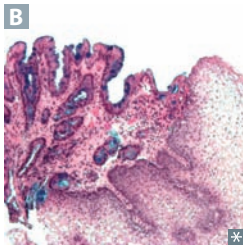
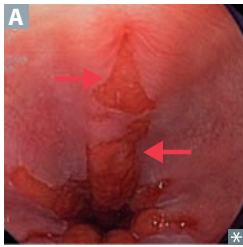
Achalasia = absence of relaxation.
 “Bird’s beak” on barium swallow **A**.
 2° achalasia may arise from Chagas disease (*T. cruzi* infection) or extraesophageal malignancies (mass effect or paraneoplastic).

Esophageal pathologies

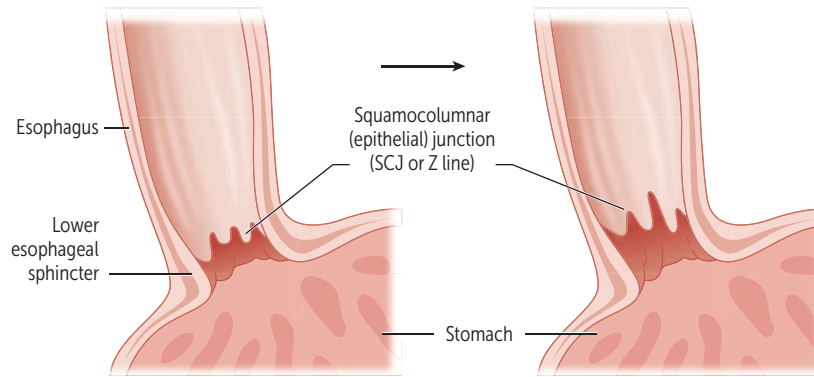
Boerhaave syndrome	Transmural, usually distal esophageal rupture with pneumomediastinum (arrows in A) due to violent retching; surgical emergency.
Eosinophilic esophagitis	Infiltration of eosinophils in the esophagus often in atopic patients. Food allergens → dysphagia, food impaction. Esophageal rings and linear furrows often seen on endoscopy. Unresponsive to GERD therapy.
Esophageal strictures	Associated with caustic ingestion and acid reflux.
Esophageal varices	Dilated submucosal veins B C 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; HSV-1: punched-out ulcers; CMV: linear ulcers), caustic ingestion, or medications.
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.
Mallory-Weiss syndrome	Mucosal lacerations at the gastroesophageal junction due to severe vomiting. Leads to hematemesis that can be painful. Usually found in alcoholics and bulimics.
Plummer-Vinson syndrome	Triad of D ysphagia, I ron deficiency anemia, and E sophageal webs. May be associated with glossitis. Increased risk of esophageal squamous cell carcinoma (“ Plumbers ” DIE).
Scleroderma esophageal dysmotility	Esophageal smooth muscle atrophy → ↓ LES pressure and dysmotility → acid reflux and dysphagia → stricture, Barrett esophagus, and aspiration. Part of CREST syndrome.



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 reflux esophagitis (GERD). Associated with ↑ risk of esophageal adenocarcinoma.



Esophageal cancer

Typically presents with progressive dysphagia (first solids, then liquids) and weight loss; poor prognosis.

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

Gastritis**Acute gastritis**

Erosions can be caused by:

- NSAIDs— \downarrow PGE₂ \rightarrow \downarrow gastric mucosa protection
- Burns (Curling ulcer)—hypovolemia \rightarrow mucosal ischemia
- Brain injury (Cushing ulcer)— \uparrow vagal stimulation \rightarrow \uparrow ACh \rightarrow \uparrow H⁺ production

Especially common among alcoholics and patients taking daily NSAIDs (eg, patients with rheumatoid arthritis).

Burned by the **Curling** iron.

Always **Cushion** the **brain**.

Chronic gastritis

Mucosal inflammation, often leading to atrophy (hypochlorhydria \rightarrow hypergastrinemia) and intestinal metaplasia (\uparrow risk of gastric cancers).

H pylori

Most common. \uparrow risk of peptic ulcer disease, MALT lymphoma.

Affects antrum first and spreads to body of stomach.

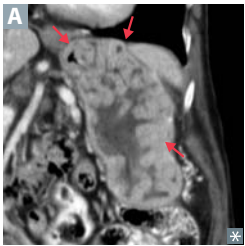
Autoimmune

Autoantibodies to parietal cells and intrinsic factor. \uparrow risk of pernicious anemia.

Affects body/fundus of stomach.

Ménétrier disease

Gastric hyperplasia of mucosa \rightarrow hypertrophied rugae (looking like brain gyri **A**), excess mucus production with resultant protein loss and parietal cell atrophy with \downarrow acid production. Precancerous.

**Gastric cancer**

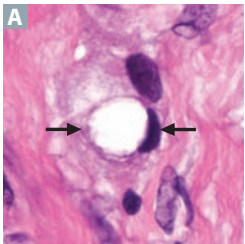
Most commonly gastric adenocarcinoma; lymphoma, GI stromal tumor, carcinoid (rare). Early aggressive local spread with node/liver metastases. Often presents late, with weight loss, early satiety, and in some cases acanthosis nigricans or Leser-Trélat sign.

- **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*; 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.



Peptic ulcer disease

	Gastric ulcer	Duodenal ulcer
PAIN	Can be G reater with meals—weight loss	D ecreases 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	↑	Generally benign
OTHER	Biopsy margins to rule out malignancy	Hypertrophy of Brunner glands

Ulcer complications**Hemorrhage**

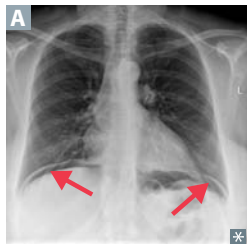
Gastric, duodenal (posterior > anterior). Most common complication.
 Ruptured gastric ulcer on the lesser curvature of stomach → bleeding from left gastric artery.
 An ulcer on the posterior wall of duodenum → bleeding from gastroduodenal artery.

Obstruction

Pyloric channel, duodenal

Perforation

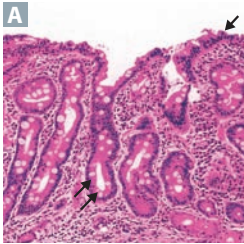
Duodenal (anterior > posterior).
 May see free air under diaphragm **A** with referred pain to the shoulder via phrenic nerve.



Malabsorption syndromes

Can cause diarrhea, steatorrhea, weight loss, weakness, vitamin and mineral deficiencies. Screen for fecal fat (eg, Sudan stain).

Celiac disease



Gluten-sensitive enteropathy, celiac sprue. Autoimmune-mediated intolerance of gliadin (gluten protein found in wheat) → malabsorption and steatorrhea. Associated with HLA-DQ2, HLA-DQ8, northern European descent, dermatitis herpetiformis, ↓ bone density. Findings: IgA anti-tissue transglutaminase, anti-endomysial, anti-deamidated gliadin peptide antibodies; villous atrophy (arrow in **A** shows blunting), crypt hyperplasia (double arrows in **A**), and intraepithelial lymphocytosis. Moderately ↑ risk of malignancy (eg, T-cell lymphoma).

↓ mucosal absorption primarily affects distal duodenum and/or proximal jejunum.
D-xylose test: passively absorbed in proximal small intestine; blood and urine levels ↓ with mucosa defects or bacterial overgrowth, normal in pancreatic insufficiency.
Treatment: gluten-free diet.

Lactose intolerance

Lactase deficiency. Normal-appearing villi, except when 2° to injury at tips of villi (eg, viral enteritis). Osmotic diarrhea with ↓ stool pH (colonic bacteria ferment lactose).

Lactose hydrogen breath test: ⊕ for lactose malabsorption if postlactose breath hydrogen value rises > 20 ppm compared with baseline.

Pancreatic insufficiency

Due to chronic pancreatitis, cystic fibrosis, obstructing cancer. Causes malabsorption of fat and fat-soluble vitamins (A, D, E, K) as well as vitamin B₁₂.

↓ duodenal pH (bicarbonate) and fecal elastase.

Tropical sprue

Similar findings as celiac sprue (affects small bowel), but responds to antibiotics. Cause is unknown, but seen in residents of or recent visitors to tropics.

↓ mucosal absorption affecting duodenum and jejunum but can involve ileum with time. Associated with megaloblastic anemia due to folate deficiency and, later, B₁₂ deficiency.

Whipple disease



Infection with *Tropheryma whipplei* (intracellular gram ⊕); PAS ⊕ **foamy** macrophages in intestinal lamina propria **B**, mesenteric nodes. **C**ardiac symptoms, **A**rthralgias, and **N**eurologic symptoms are common. Most often occurs in older men.

Foamy Whipped cream in a **CAN**.

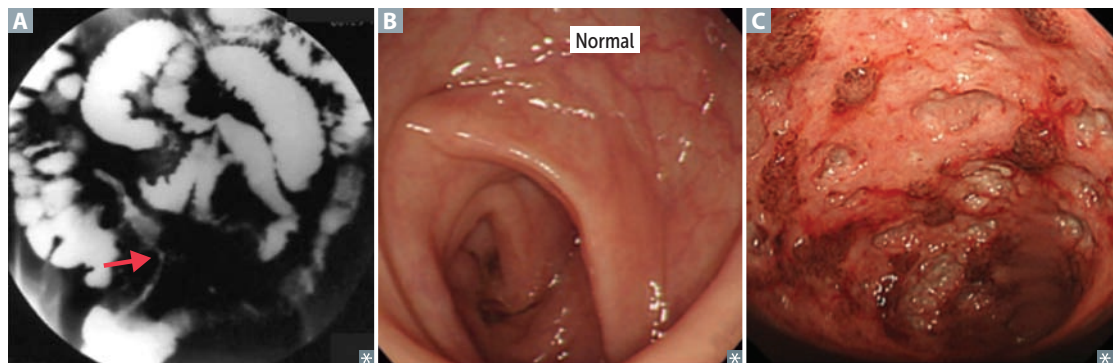
Inflammatory bowel diseases

	Crohn disease	Ulcerative colitis
LOCATION	Any portion of the GI tract, usually the terminal ileum and colon. Skip lesions, rectal 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 mucosal pseudopolyps (compare normal B with diseased C) with freely hanging mesentery. Loss of haustra → “lead pipe” appearance on imaging.
MICROSCOPIC MORPHOLOGY	Noncaseating granulomas and lymphoid aggregates.	Crypt abscesses and ulcers, bleeding, no granulomas.
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.	Malabsorption/malnutrition, colorectal cancer (↑ risk with pancolitis). Fulminant colitis, toxic megacolon, perforation.
INTESTINAL MANIFESTATION	Diarrhea that may or may not be bloody.	Bloody diarrhea.
EXTRAIESTINAL MANIFESTATIONS	Rash (pyoderma gangrenosum, erythema nodosum), eye inflammation (episcleritis, uveitis), oral ulcerations (aphthous stomatitis), arthritis (peripheral, spondylitis). Kidney stones (usually calcium oxalate), gallstones.	1° sclerosing cholangitis. Associated with p-ANCA.
TREATMENT	Corticosteroids, azathioprine, antibiotics (eg, ciprofloxacin, metronidazole), 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).

Ulcerative colitis causes **ULCCERS**:

Ulcers
Large intestine
Continuous, **C**olorectal carcinoma, **C**rypt abscesses
Extends proximally
Red diarrhea
Sclerosing cholangitis



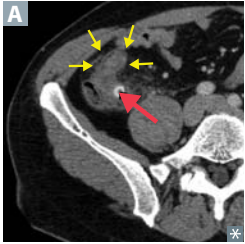
Irritable bowel syndrome

Recurrent abdominal pain associated with ≥ 2 of the following:

- Pain improves with defecation
- Change in stool frequency
- Change in appearance of stool

No structural abnormalities. Most common in middle-aged women. Chronic symptoms may be diarrhea-predominant, constipation-predominant, or mixed. Pathophysiology is multifaceted.

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).

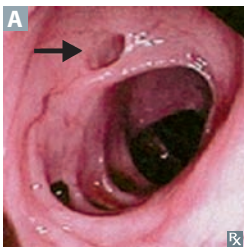
Initial diffuse periumbilical pain migrates to McBurney point ($\frac{1}{3}$ the distance from right anterior superior iliac spine to umbilicus). Nausea, fever; may perforate \rightarrow peritonitis; may elicit psoas, obturator, and Rovsing signs, guarding and rebound tenderness on exam.

Differential: diverticulitis (elderly), ectopic pregnancy (use β -hCG to rule out).

Treatment: appendectomy.

Diverticula of the GI tract

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” in that they lack or have an attenuated muscularis externa. Most often in sigmoid colon.

“True” diverticulum—all 3 gut wall layers outpouch (eg, Meckel).

“False” diverticulum or pseudodiverticulum—only mucosa and submucosa outpouch.

Occur especially where vasa recta perforate muscularis externa.

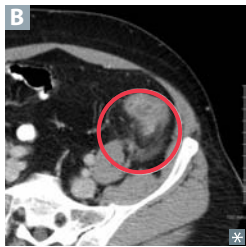
Diverticulosis

Many false diverticula of the colon, commonly sigmoid. Common (in $\sim 50\%$ of people > 60 years). Caused by \uparrow intraluminal pressure and focal weakness in colonic wall. Associated with low-fiber diets.

Often asymptomatic or associated with vague discomfort.

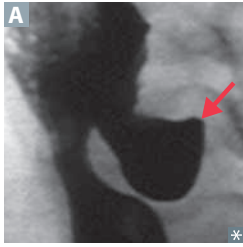
Complications include diverticular bleeding (painless hematochezia), diverticulitis.

Diverticulitis



Diverticulosis with inflamed microperforations **B** classically causing LLQ pain, fever, leukocytosis. Treat with antibiotics.

Complications: abscess, fistula (colovesical fistula \rightarrow pneumaturia), obstruction (inflammatory stenosis), perforation (\rightarrow peritonitis). Treat with percutaneous drainage or surgery.

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

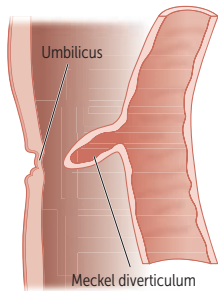
Males

Inferior pharyngeal constrictor

Killian triangle

Esophageal dysmotility

Halitosis

Meckel diverticulum

True diverticulum. Persistence of the vitelline duct. May contain ectopic acid-secreting gastric mucosa and/or pancreatic tissue. Most common congenital anomaly of GI tract. Can cause melena, RLQ pain, intussusception, volvulus, or obstruction near terminal ileum. Contrast with omphalomesenteric cyst = cystic dilation of vitelline duct.

Diagnosis: pertechnetate study for uptake by ectopic gastric mucosa.

The **six 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 mutations in *RET*.

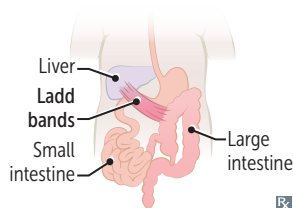
Presents with bilious emesis, abdominal distention, and failure to pass meconium within 48 hours → chronic constipation.

Normal portion of the colon proximal to the aganglionic segment is dilated, resulting in a “transition zone.”

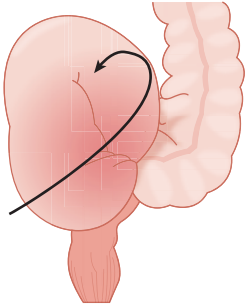
Think of Hirschsprung as a giant spring that has **sprung** in the colon. Risk ↑ with Down syndrome.

Diagnosed by rectal suction biopsy.

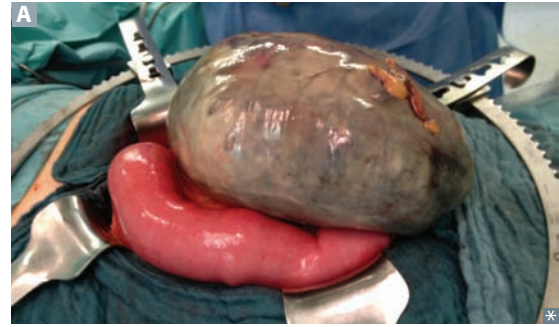
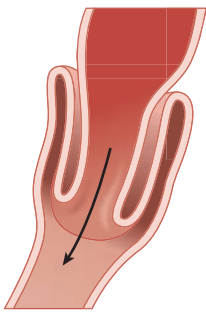
Treatment: resection.

Malrotation

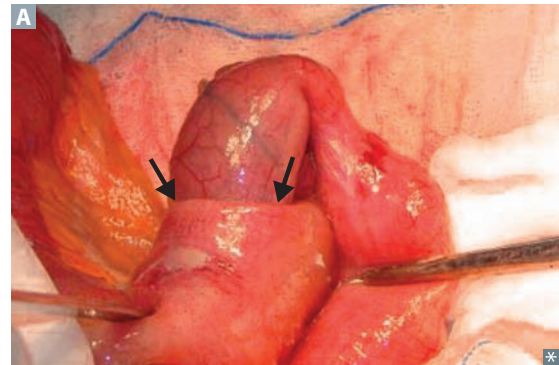
Anomaly of midgut rotation during fetal development → improper positioning of bowel, formation of fibrous bands (Ladd bands). Can lead to volvulus, duodenal obstruction.

Volvulus

Twisting of portion of bowel around its mesentery; can lead to obstruction and infarction **A**. Can occur throughout the GI tract. Midgut volvulus more common in infants and children. Sigmoid volvulus more common in elderly.

**Intussusception**

Telescoping **A** of proximal bowel segment into distal segment, commonly at ileocecal junction. Compromised blood supply → intermittent abdominal pain often with “currant jelly” stools. Unusual in adults (associated with intraluminal mass or tumor that acts as lead point that is pulled into the lumen). Majority of cases occur in children (usually idiopathic; may be associated with recent viral infection, such as adenovirus → Peyer patch hypertrophy → lead point; most common pathologic lead point is Meckel diverticulum). Abdominal emergency in early childhood, with bull’s-eye appearance on ultrasound.

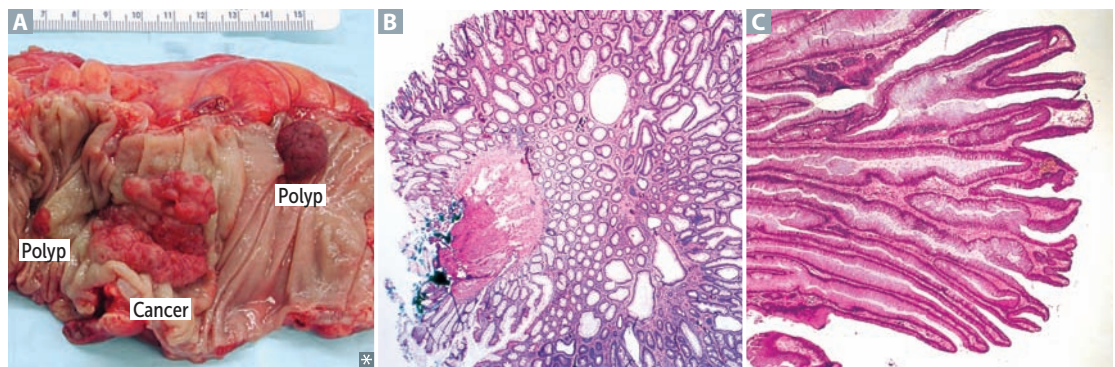
**Other intestinal disorders**

Acute mesenteric ischemia	Critical blockage of intestinal blood flow (often embolic occlusion of SMA) → small bowel necrosis → abdominal pain out of proportion to physical findings. May see red “currant jelly” stools.
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, distal colon). Typically affects elderly.
Angiodysplasia	Tortuous dilation of vessels → hematochezia. Most often found in cecum, terminal ileum, ascending colon. More common in older patients. Confirmed by angiography.
Adhesion	Fibrous band of scar tissue; commonly forms after surgery; most common cause of small bowel obstruction. Can have well-demarcated necrotic zones.
Ileus	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	In cystic fibrosis, meconium plug obstructs intestine, preventing stool passage at birth.
Necrotizing enterocolitis	Seen in premature, formula-fed infants with immature immune system. Necrosis of intestinal mucosa (primarily colonic) with possible perforation, which can lead to pneumatosis intestinalis, free air in abdomen, portal venous gas.

Colonic polyps

Growths of tissue within the colon **A**. May be neoplastic or non-neoplastic. Grossly characterized as flat, sessile, or pedunculated (on a stalk) on the basis of protrusion into colonic lumen. Generally classified by histologic type.

HISTOLOGIC TYPE	CHARACTERISTICS
Hyperplastic	Non-neoplastic. Generally smaller and majority located in rectosigmoid area.
Hamartomatous	Generally non-neoplastic; solitary lesions do not have a significant risk of malignant transformation. Growths of normal colonic tissue with distorted architecture. Associated with Peutz-Jeghers syndrome and juvenile polyposis.
Adenomatous	Neoplastic, via chromosomal instability pathway with mutations in <i>APC</i> and <i>KRAS</i> . Tubular B histology has less malignant potential than villous C ; tubulovillous has intermediate malignant potential. Usually asymptomatic; may present with occult bleeding.
Serrated	Premalignant, via CpG hypermethylation phenotype pathway with microsatellite instability and mutations in <i>BRAF</i> . “Saw-tooth” pattern of crypts on biopsy. Up to 20% of cases of sporadic CRC.

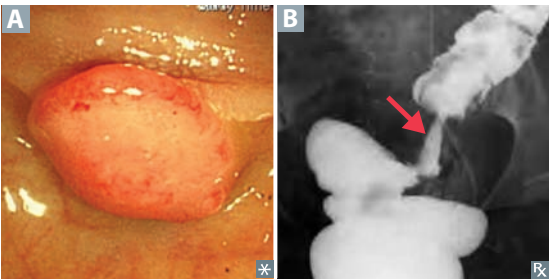
**Polyposis syndromes**

Familial adenomatous polyposis	Autosomal dominant mutation of <i>APC</i> tumor suppressor gene on chromosome 5q. 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, congenital hypertrophy of retinal pigment epithelium, impacted/supernumerary teeth.
Turcot syndrome	FAP + malignant CNS tumor. Turcot = Turban .
Peutz-Jeghers syndrome	Autosomal dominant syndrome featuring numerous hamartomas throughout GI tract, along with hyperpigmented 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.

Lynch syndrome

Previously known as hereditary nonpolyposis colorectal cancer (HNPCC). Autosomal dominant mutation of DNA mismatch repair genes with subsequent microsatellite instability. ~ 80% progress to CRC. Proximal colon is always involved. Associated with endometrial, ovarian, and skin cancers.

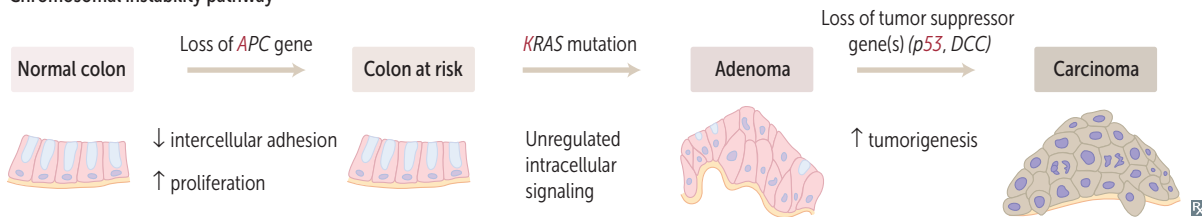
Colorectal cancer

EPIDEMIOLOGY	Most patients are > 50 years old. ~ 25% have a family history.	
RISK FACTORS	Adenomatous and serrated polyps, familial cancer syndromes, IBD, tobacco use, diet of processed meat with low fiber.	
PRESENTATION	Rectosigmoid > ascending > descending. Ascending—exophytic mass, iron deficiency anemia, weight loss. Descending—infiltrating mass, partial obstruction, colicky pain, hematochezia. Rarely, presents with <i>Streptococcus bovis</i> bacteremia.	Right side bleeds; left side obstructs.
DIAGNOSIS	Iron deficiency anemia in males (especially > 50 years old) and postmenopausal females raises suspicion. Screen patients > 50 years old with colonoscopy A , flexible sigmoidoscopy, fecal occult blood test, or fecal DNA test. “Apple core” lesion seen on barium enema x-ray B . CEA tumor marker: good for monitoring recurrence, should not be used for screening.	

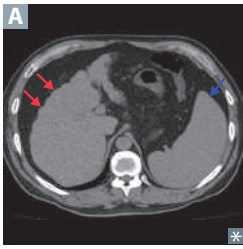
Molecular pathogenesis of colorectal cancer

Chromosomal instability pathway: mutations in *APC* cause FAP and most sporadic CRC (via adenoma-carcinoma sequence; **(fring)** 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).

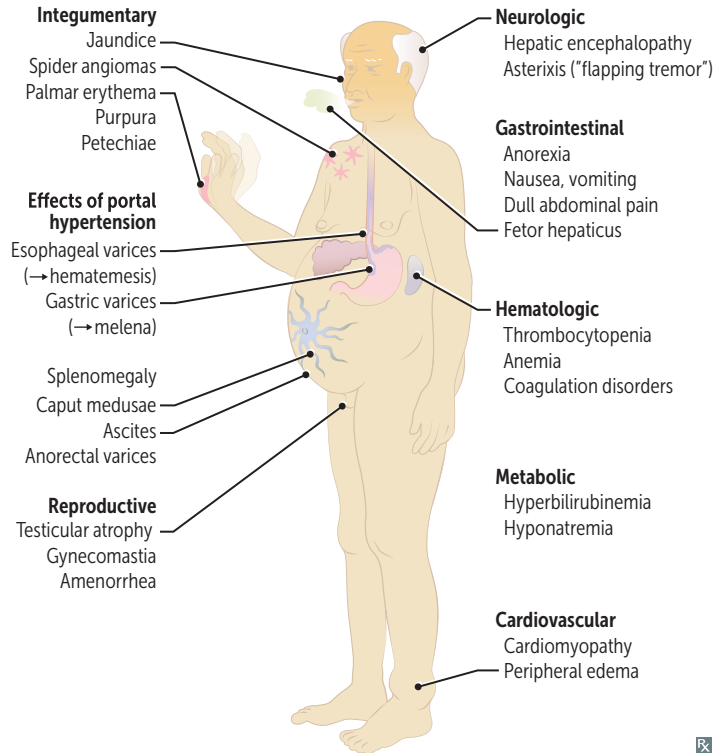
Chromosomal instability pathway

Cirrhosis and portal hypertension



Cirrhosis—diffuse bridging fibrosis (via stellate cells) and regenerative nodules (red arrows in **A**; blue arrow shows splenomegaly) disrupt normal architecture of liver; ↑ risk for hepatocellular carcinoma (HCC). Etiologies include alcohol (60–70% of cases in the US), 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.



Serum markers of liver pathology

ENZYMES RELEASED IN LIVER DAMAGE

Aspartate aminotransferase and alanine aminotransferase	<p>↑ in most liver disease: ALT > AST</p> <p>↑ in alcoholic liver disease: AST > ALT</p> <p>AST > ALT in nonalcoholic liver disease suggests progression to advanced fibrosis or cirrhosis</p>
Alkaline phosphatase	↑ in cholestasis (eg, biliary obstruction), infiltrative disorders, bone disease
γ-glutamyl transpeptidase	↑ in various liver and biliary diseases (just as ALP can), but not in bone disease; associated with alcohol use

FUNCTIONAL LIVER MARKERS

Bilirubin	↑ in various liver diseases (eg, biliary obstruction, alcoholic or viral hepatitis, cirrhosis), hemolysis
Albumin	↓ in advanced liver disease
Prothrombin	↑ in advanced liver disease (↓ production of clotting factors)
Platelets	↓ in advanced liver disease (↓ thrombopoietin, liver sequestration) and portal hypertension (splenomegaly/splenic sequestration)

Reye syndrome

Rare, often fatal childhood hepatic encephalopathy. Findings: mitochondrial abnormalities, fatty liver (microvesicular fatty change), hypoglycemia, vomiting, hepatomegaly, coma. Associated with viral infection (especially VZV and influenza B) that has been treated with aspirin. Mechanism: aspirin metabolites ↓ β-oxidation by reversible inhibition of mitochondrial enzymes. Avoid aspirin in children, except in those with Kawasaki disease.

Alcoholic liver disease**Hepatic steatosis**

Macrovesicular fatty change **A** that may be reversible with alcohol cessation.

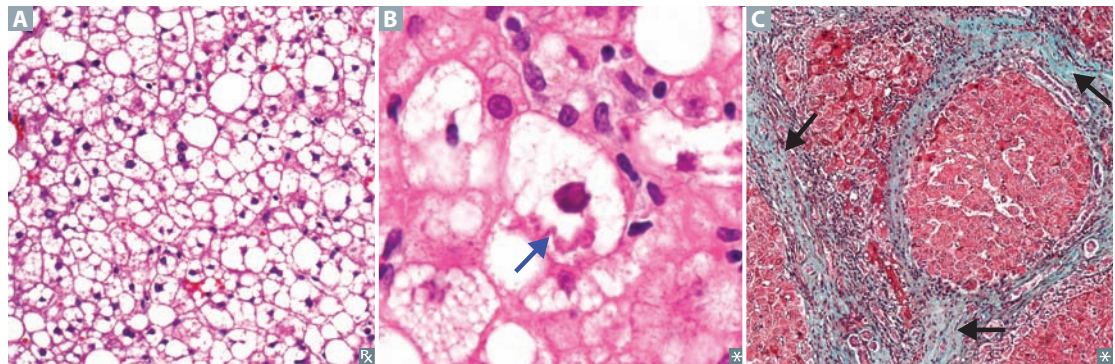
Alcoholic hepatitis

Requires sustained, long-term consumption. Swollen and necrotic hepatocytes with neutrophilic infiltration. Mallory bodies **B** (intracytoplasmic eosinophilic inclusions of damaged keratin filaments).

Make a toAST with alcohol:
AST > ALT (ratio usually > 2:1).

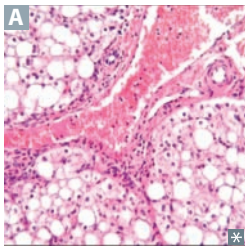
Alcoholic cirrhosis

Final and irreversible form. Micronodular, irregularly shrunken liver with “hobnail” appearance. Sclerosis (arrows in **C**) around central vein (zone III). Manifestations of chronic liver disease (eg, jaundice, hypoalbuminemia).

**Non-alcoholic 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 → ↓ NH₃ metabolism → neuropsychiatric dysfunction. Spectrum from disorientation/asterixis (mild) to difficult arousal or coma (severe). Triggers:

- ↑ NH₃ production and absorption (due to dietary protein, GI bleed, constipation, infection).
- ↓ NH₃ removal (due to renal failure, diuretics, bypassed hepatic blood flow post-TIPS).

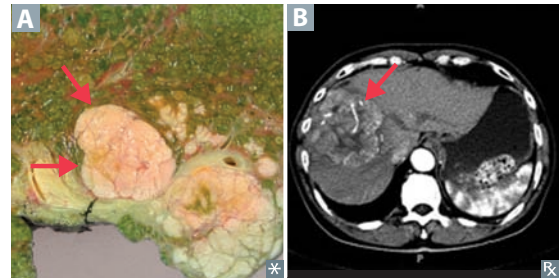
Treatment: lactulose (↑ NH₄⁺ generation) and rifaximin or neomycin (↓ NH₄⁺ producing gut bacteria).

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 non-alcoholic fatty liver disease, autoimmune disease, hemochromatosis, α_1 -antitrypsin deficiency) and specific carcinogens (eg, aflatoxin from *Aspergillus*). May lead to Budd-Chiari syndrome.

Findings: jaundice, tender hepatomegaly, ascites, polycythemia, anorexia. Spreads hematogenously.

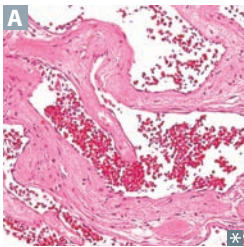
Diagnosis: \uparrow α -fetoprotein; ultrasound or contrast CT/MRI **B**, biopsy.



Other liver tumors

Cavernous hemangioma

Common, benign liver tumor **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).

Angiosarcoma

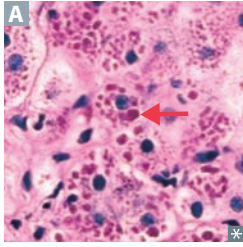
Malignant tumor of endothelial origin; associated with exposure to arsenic, vinyl chloride.

Metastases

GI malignancies, breast and lung cancer. Most common overall.

Budd-Chiari syndrome

Thrombosis or compression of hepatic veins with centrilobular congestion and necrosis \rightarrow 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).

α_1 -antitrypsin deficiency

Misfolded gene product protein aggregates in hepatocellular ER → cirrhosis with PAS ⊕ globules **A** in liver. Codominant trait.

In lungs, ↓ α_1 -antitrypsin → uninhibited elastase in alveoli → ↓ elastic tissue → panacinar emphysema.

Jaundice

Abnormal yellowing of the skin and/or sclera **A** due to bilirubin deposition. Hyperbilirubinemia 2° to ↑ production or ↓ disposition (impaired hepatic uptake, conjugation, excretion).

Unconjugated (indirect) hyperbilirubinemia

Hemolytic, physiologic (newborns), Crigler-Najjar, Gilbert syndrome.

Conjugated (direct) hyperbilirubinemia

Biliary tract obstruction: gallstones, cholangiocarcinoma, pancreatic or liver cancer, liver fluke.

Biliary tract disease:

- 1° sclerosing cholangitis
- 1° biliary cirrhosis

Excretion defect: Dubin-Johnson syndrome, Rotor syndrome.

Mixed (direct and indirect) hyperbilirubinemia

Hepatitis, cirrhosis.

Physiologic neonatal jaundice

At birth, immature UDP-glucuronosyltransferase → unconjugated hyperbilirubinemia → jaundice/kernicterus (bilirubin deposition in 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.

Hereditary hyperbilirubinemias

All autosomal recessive.

1 Gilbert syndrome

Mildly ↓ UDP-glucuronosyltransferase conjugation and impaired bilirubin uptake. Asymptomatic or mild jaundice. ↑ unconjugated bilirubin without overt hemolysis. Bilirubin ↑ with fasting and stress.

Very common. No clinical consequences.

2 Crigler-Najjar syndrome, type I

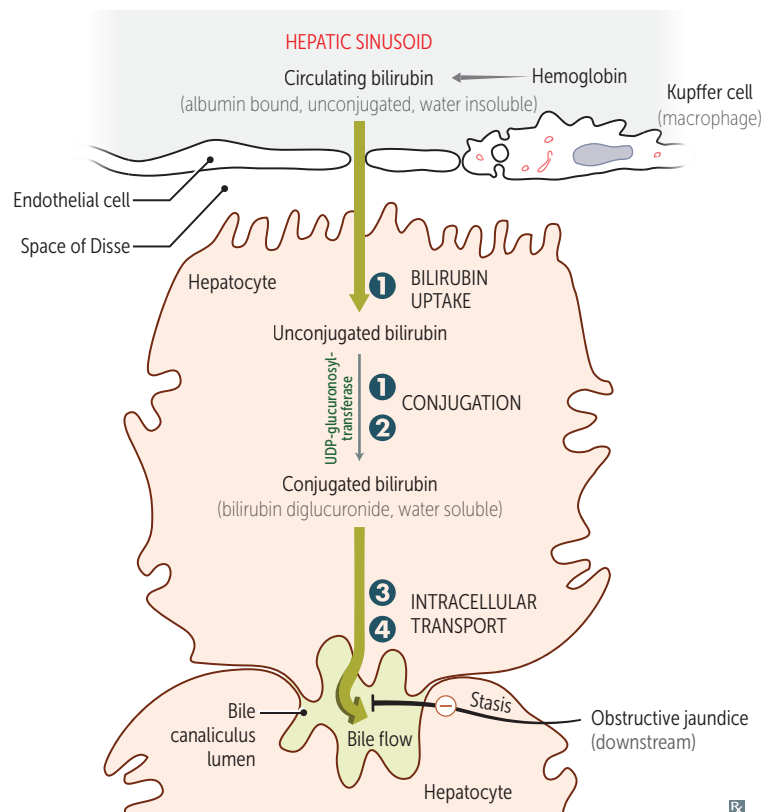
Absent UDP-glucuronosyltransferase. Presents early in life; patients die within a few years. Findings: jaundice, kernicterus (bilirubin deposition in brain), ↑ unconjugated bilirubin. Treatment: plasmapheresis and phototherapy.

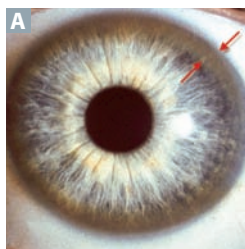
Type II is less severe and responds to phenobarbital, which ↑ liver enzyme synthesis.

3 Dubin-Johnson syndrome

Conjugated hyperbilirubinemia due to defective liver excretion. Grossly black liver. Benign.

4 Rotor syndrome is similar, but milder in presentation without black liver. Due to impaired hepatic uptake and excretion.

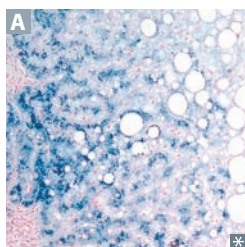


**Wilson disease
(hepatolenticular
degeneration)**

Recessive mutations in hepatocyte copper-transporting ATPase (*ATP7B* gene; chromosome 13) → inadequate copper excretion into bile and blood (↓ serum ceruloplasmin, ↑ urine copper). Copper accumulates, especially in liver, brain, cornea, kidneys, joints.

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 syndrome).

Treatment: chelation with penicillamine or trientine, oral zinc.

Hemochromatosis

Recessive mutations in *HFE* gene (C282Y > H63D, chromosome 6) → 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 dilated cardiomyopathy (reversible), hypogonadism, arthropathy (calcium pyrophosphate deposition; especially metacarpophalangeal joints). HCC is common cause of death.

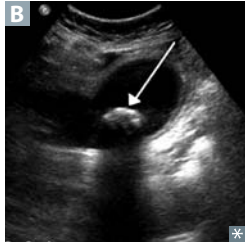
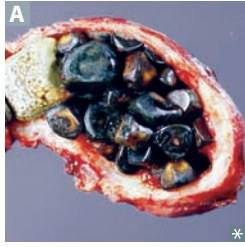
Treatment: repeated phlebotomy, chelation with deferasirox, deferoxamine, oral deferiprone.

Biliary tract disease

May present with pruritus, jaundice, dark urine, light-colored stool, hepatosplenomegaly. Typically with cholestatic pattern of LFTs (↑ conjugated bilirubin, ↑ cholesterol, ↑ ALP).

	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 IBD.	Associated with ulcerative colitis. p-ANCA ⊕. ↑ IgM. Can lead to 2° biliary cirrhosis. ↑ risk of cholangiocarcinoma and gallbladder cancer.
Primary biliary cirrhosis	Autoimmune reaction → lymphocytic infiltrate + granulomas → destruction of intralobular bile ducts.	Classically in middle-aged women.	Anti-mitochondrial antibody ⊕, ↑ IgM. Associated with other autoimmune conditions (eg, Sjögren syndrome, Hashimoto thyroiditis, CREST, rheumatoid arthritis, celiac disease).
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.

Gallstones (cholelithiasis)



↑ cholesterol and/or bilirubin, ↓ bile salts, and gallbladder stasis all cause stones **A**.

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 (black = radiopaque, Ca^{2+} bilirubinate, hemolysis; brown = radiolucent, infection)—seen in patients with Crohn disease, chronic hemolysis, alcoholic cirrhosis, advanced age, biliary infections, total parenteral nutrition (TPN).

Uncomplicated disease manifests as **biliary colic**—neurohormonal activation (eg, by CCK after a fatty meal) triggers contraction of gallbladder, forcing a stone into the cystic duct. May present without pain (eg, in diabetics).

Diagnose with ultrasound **B**. Treat with cholecystectomy if symptomatic.

Risk factors (**4 F**'s):

1. **F**emale
2. **F**at
3. **F**ertile (pregnant)
4. **F**orty

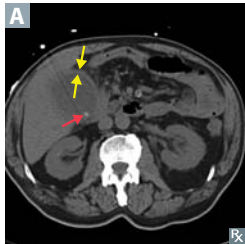
Most common complication is cholecystitis; also acute pancreatitis, ascending cholangitis.

Charcot triad of cholangitis:

- Jaundice
- Fever
- RUQ pain

Can cause fistula between gallbladder and gastrointestinal tract → air in biliary tree (pneumobilia) → passage of gallstones into intestinal tract → obstruction of ileocecal valve (gallstone ileus).

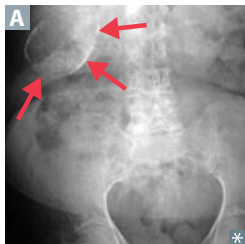
Cholecystitis



Acute or chronic inflammation of gallbladder usually from cholelithiasis (stone at neck of gallbladder [red arrow in **A**] with gallbladder wall thickening [yellow arrows]). Gallstones most commonly blocking the cystic duct → 2° infection; rarely acalculous due to ischemia and stasis, or 1° infection (CMV). Murphy sign ⊕: inspiratory arrest on RUQ palpation due to pain. ↑ ALP if bile duct becomes involved (eg, ascending cholangitis).

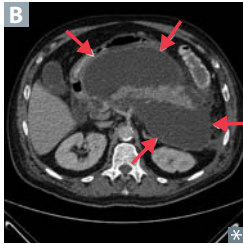
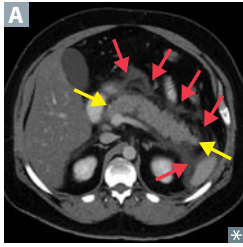
Diagnose with ultrasound or cholescintigraphy (HIDA, or hepatobiliary iminodiacetic acid scan).

Porcelain gallbladder



Calcified gallbladder due to chronic cholecystitis; usually found incidentally on imaging **A**.

Treatment: prophylactic cholecystectomy due to high rates of gallbladder cancer (mostly adenocarcinoma).

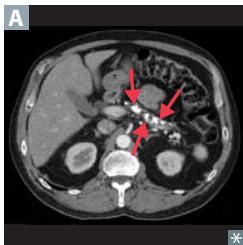
Acute pancreatitis

Autodigestion of pancreas by pancreatic enzymes (**A** shows pancreas [yellow arrows] surrounded by edema [red arrows]).

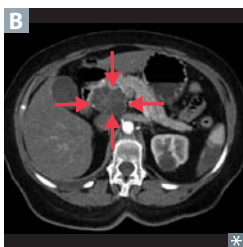
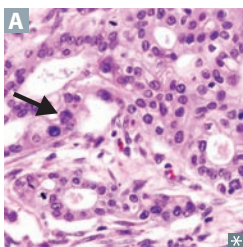
Causes: **I**diopathic, **G**allstones, **E**thanol, **T**rauma, **S**teroids, **M**umps, **A**utoimmune disease, **S**corpion sting, **H**ypercalcemia/**H**ypertriglyceridemia (> 1000 mg/dL), **E**RCP, **D**rugs (eg, sulfa drugs, NRTIs, protease inhibitors). **I GET SMASHED**.

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), necrosis, hemorrhage, infection, organ failure (ARDS, shock, renal failure), hypocalcemia (precipitation of Ca^{2+} soaps).

Chronic pancreatitis

Chronic inflammation, atrophy, calcification of the pancreas **A**. Major causes are alcohol abuse and idiopathic. Mutations in *CFTR* (cystic fibrosis) can cause chronic pancreatic insufficiency. Can lead to pancreatic insufficiency → steatorrhea, fat-soluble vitamin deficiency, diabetes mellitus. Amylase and lipase may or may not be elevated (almost always elevated in acute pancreatitis).

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** (→ 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

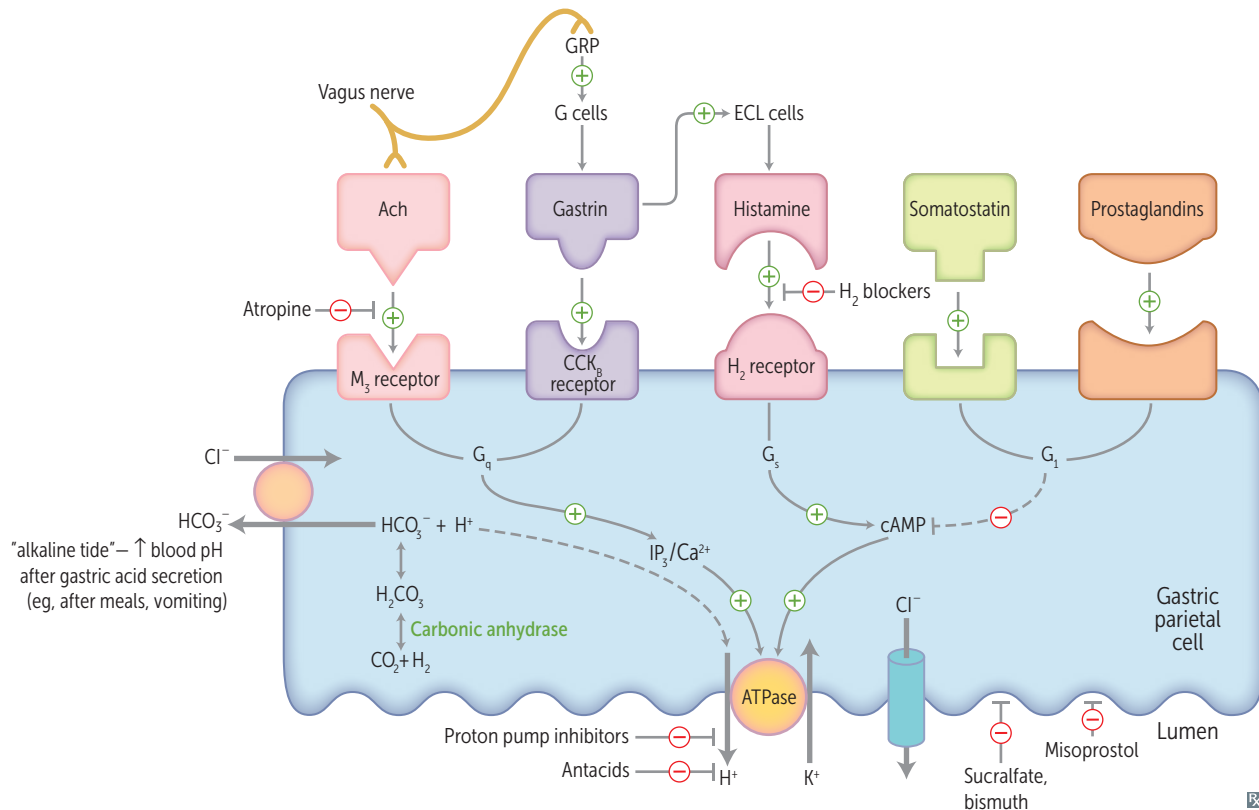
Often presents with:

- 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, chemotherapy, radiation therapy.

▶ GASTROINTESTINAL—PHARMACOLOGY

Acid suppression therapy

**H₂ blockers**

Cimetidine, ranitidine, famotidine, nizatidine. Take H₂ blockers before you **dine**. Think “**table for 2**” to remember **H₂**.

MECHANISM

Reversible block of histamine H₂-receptors → ↓ H⁺ 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, pantoprazole, dexlansoprazole.

MECHANISM

Irreversibly inhibit H⁺/K⁺ ATPase in stomach parietal cells.

CLINICAL USE

Peptic ulcer, gastritis, esophageal reflux, Zollinger-Ellison syndrome.

ADVERSE EFFECTS

↑ risk of *C difficile* infection, pneumonia. ↓ serum Mg²⁺ with long-term use.

Antacid use	Can affect absorption, bioavailability, or urinary excretion of other drugs by altering gastric and urinary pH or by delaying gastric emptying. All can cause hypokalemia. Overuse can also cause the following problems.	
Aluminum hydroxide	Constipation and hypophosphatemia; proximal muscle weakness, osteodystrophy, seizures	Aluminum amount of feces.
Calcium carbonate	Hypercalcemia (milk-alkali syndrome), rebound acid ↑	Can chelate and ↓ effectiveness of other drugs (eg, tetracycline).
Magnesium hydroxide	Diarrhea, hyporeflexia, hypotension, cardiac arrest	Mg²⁺ = Must go to the bathroom.

Bismuth, sucralfate

MECHANISM	Bind to ulcer base, providing physical protection and allowing HCO ₃ ⁻ secretion to reestablish pH gradient in the mucous layer.	
CLINICAL USE	↑ ulcer healing, travelers' diarrhea.	

Misoprostol

MECHANISM	A PGE ₁ analog. ↑ production and secretion of gastric mucous barrier, ↓ acid production.	
CLINICAL USE	Prevention of NSAID-induced peptic ulcers (NSAIDs block PGE ₁ production); maintenance of a PDA. Also used off-label for induction of labor (ripens cervix).	
ADVERSE EFFECTS	Diarrhea. Contraindicated in women of childbearing potential (abortifacient).	

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.	

Osmotic laxatives

MECHANISM	Magnesium hydroxide, magnesium citrate, polyethylene glycol, lactulose.	
MECHANISM	Provide osmotic load to draw water into the GI lumen.	
CLINICAL USE	Constipation. Lactulose also treats hepatic encephalopathy since gut flora degrade it into metabolites (lactic acid and acetic acid) that promote nitrogen excretion as NH ₄ ⁺ .	
ADVERSE EFFECTS	Diarrhea, dehydration; may be abused by bulimics.	

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 μ -opioid receptors; slows gut motility. Poor CNS penetration (low addictive potential).
CLINICAL USE	Diarrhea.
ADVERSE EFFECTS	Constipation, nausea.

Ondansetron

MECHANISM	5-HT ₃ antagonist; ↓ vagal stimulation. Powerful central-acting antiemetic.	At a party but feeling queasy? Keep on dancing with ondansetron !
CLINICAL USE	Control vomiting postoperatively and in patients undergoing cancer chemotherapy.	
ADVERSE EFFECTS	Headache, constipation, QT interval prolongation.	

Metoclopramide

MECHANISM	D ₂ receptor antagonist. ↑ resting tone, contractility, LES tone, motility. Does not influence colon transport time.
CLINICAL USE	Diabetic and postsurgery gastroparesis, antiemetic.
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 or Parkinson disease (due to D ₂ -receptor blockade).

Orlistat

MECHANISM	Inhibits gastric and pancreatic lipase → ↓ breakdown and absorption of dietary fats.
CLINICAL USE	Weight loss.
ADVERSE EFFECTS	Steatorrhea, ↓ absorption of fat-soluble vitamins.

Ursodiol (ursodeoxycholic acid)

MECHANISM	Nontoxic bile acid. ↑ bile secretion, ↓ cholesterol secretion and reabsorption.
CLINICAL USE	Primary biliary cirrhosis, gallstone prevention or dissolution.

Hematology and Oncology

“Of all that is written, I love only what a person has written with his own blood.”

—Friedrich Nietzsche

“I used to get stressed out, but my cancer has put everything into perspective.”

—Delta Goodrem

“The best blood will at some time get into a fool or a mosquito.”

—Austin O’Malley

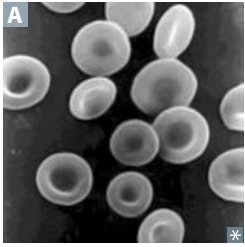
“Carcinoma works cunningly from the inside out. Detection and treatment often work more slowly and gropingly, from the outside in.”

—Christopher Hitchens

▶ Anatomy	378
▶ Physiology	381
▶ Pathology	386
▶ Pharmacology	405

Study tip: When reviewing oncologic drugs, focus on mechanisms and side effects rather than details of clinical uses, which may be lower yield.

▶ HEMATOLOGY AND ONCOLOGY—ANATOMY

Erythrocyte

Carries O₂ to tissues and CO₂ to lungs.

Anucleate and lacks 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). Membrane contains Cl⁻/HCO₃⁻ antiporter, which allows RBCs to export HCO₃⁻ and transport CO₂ from the periphery to the lungs for elimination.

Eryth = red; *cyte* = cell.

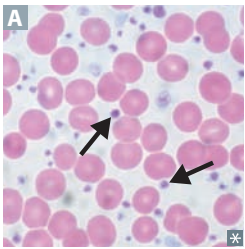
Erythrocytosis = polycythemia = ↑ hematocrit.

Anisocytosis = varying sizes.

Poikilocytosis = varying shapes.

Reticulocyte = immature RBC; reflects erythroid proliferation.

Bluish color on Wright-Giemsa stain of reticulocytes represents residual ribosomal RNA.

Thrombocyte (platelet)

Involved in 1° hemostasis. Small cytoplasmic fragment **A** derived from megakaryocytes.

Life span of 8–10 days. When activated by endothelial injury, aggregates with other platelets and interacts with fibrinogen to form platelet plug. Contains dense granules (ADP, Ca²⁺) and α granules (vWF, fibrinogen, fibronectin). 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.

Leukocyte

Divided into granulocytes (neutrophil, eosinophil, basophil) and mononuclear cells (monocytes, lymphocytes).

WBC differential from highest to lowest (normal ranges per USMLE):

Neutrophils (54–62%)

Lymphocytes (25–33%)

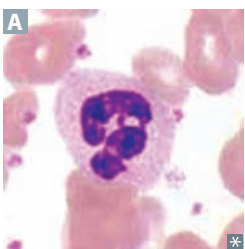
Monocytes (3–7%)

Eosinophils (1–3%)

Basophils (0–0.75%)

Leuk = white; *cyte* = cell.

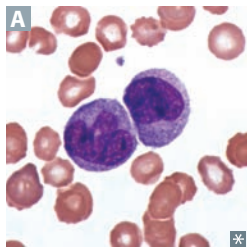
Neutrophils **L**ike **M**aking **E**verything **B**etter.

Neutrophil

Acute inflammatory response cell. Increased 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.

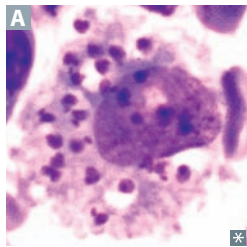
Hypersegmented neutrophils (nucleus has 6+ lobes) are seen in vitamin B₁₂/folate deficiency. ↑ band cells (immature neutrophils) reflect states of ↑ myeloid proliferation (bacterial infections, CML).

Important neutrophil chemotactic agents: C5a, IL-8, LTB₄, kallikrein, platelet-activating factor.

Monocyte

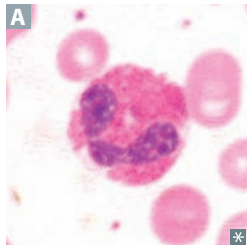
Differentiates into macrophage in tissues.
Large, kidney-shaped nucleus **A**. Extensive
“frosted glass” cytoplasm.

Mono = one (nucleus); *cyte* = cell.
Monocyte: in the blood.

Macrophage

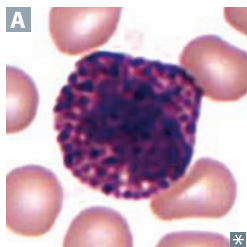
Phagocytoses bacteria, cellular debris, and
senescent RBCs. Long life in tissues.
Macrophages differentiate from circulating
blood monocytes **A**. Activated by γ -interferon.
Can function as antigen-presenting cell via
MHC II.

Macro = large; *phage* = eater.
Macrophage: in the tissue.
Important component of granuloma formation
(eg, TB, sarcoidosis).
Lipid A from bacterial LPS binds CD14 on
macrophages to initiate septic shock.

Eosinophil

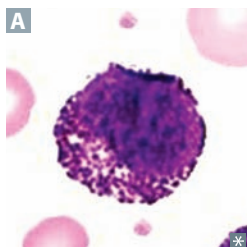
Defends against helminthic infections (major
basic protein). Bilobate nucleus. Packed
with large eosinophilic granules of uniform
size **A**. Highly phagocytic for antigen-
antibody complexes.
Produces histaminase and major basic protein
(MBP, a helminthotoxin).

Eosin = pink dye; *philic* = loving.
Causes of eosinophilia = **NAACP**:
Neoplasia
Asthma
Allergic processes
Chronic adrenal insufficiency
Parasites (invasive)

Basophil

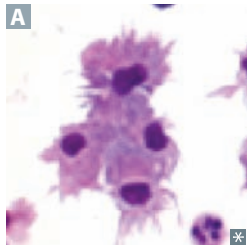
Mediates allergic reaction. Densely basophilic
granules **A** contain heparin (anticoagulant)
and histamine (vasodilator). Leukotrienes
synthesized and released on demand.

Basophilic—staining readily with **basic** stains.
Basophilia is uncommon, but can be a sign of
myeloproliferative disease, particularly CML.

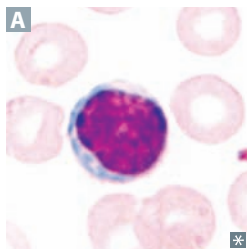
Mast cell

Mediates allergic reaction in local tissues.
Mast cells contain basophilic granules **A** and
originate from the same precursor as basophils
but are not the same cell type. Can bind the
Fc portion of IgE to membrane. IgE cross-
links upon antigen binding → degranulation
→ release of histamine, heparin, tryptase, and
eosinophil chemotactic factors.

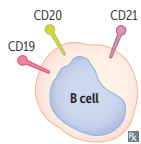
Involved in type I hypersensitivity reactions.
Cromolyn sodium prevents mast cell
degranulation (used for asthma prophylaxis).

Dendritic cell

Highly phagocytic APC **A**. Functions as link between innate and adaptive immune systems. Expresses MHC class II and Fc receptors on surface. Called Langerhans cell in the skin.

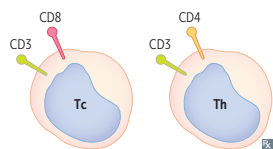
Lymphocyte

Refers 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**.

B cell

Part of humoral immune response. Originates from stem cells in bone marrow and matures in marrow. Migrates 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 via MHC II.

B = **B**one marrow.

T cell

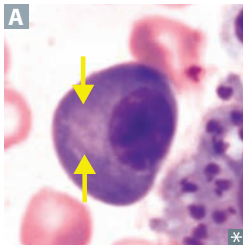
Mediates cellular immune response. Originates from stem cells in the bone marrow, but matures in the thymus. T cells differentiate into cytotoxic T cells (express CD8, recognize MHC I), helper T cells (express CD4, recognize MHC II), and regulatory T cells. CD28 (costimulatory signal) necessary for T-cell activation. The majority of circulating lymphocytes are T cells (80%).

T is for **T**hymus.

CD4+ helper T cells are the primary target of HIV.

MHC × **CD** = **8** (eg, MHC 2 × CD4 = 8, and MHC 1 × CD8 = 8).

Plasma cell



Produces large amounts of antibody specific to a particular antigen. “Clock-face” chromatin distribution and eccentric nucleus, abundant RER, and well-developed Golgi apparatus (yellow arrows in **A**). Found in bone marrow and normally do not circulate in peripheral blood.

Multiple myeloma is a plasma cell cancer.

▶ HEMATOLOGY AND ONCOLOGY—PHYSIOLOGY

Fetal erythropoiesis

Fetal erythropoiesis occurs in:

- Yolk sac (3–8 weeks)
- Liver (6 weeks–birth)
- Spleen (10–28 weeks)
- Bone marrow (18 weeks to adult)

Young Liver Synthesizes Blood.

Hemoglobin development

Embryonic globins: ζ and ϵ .

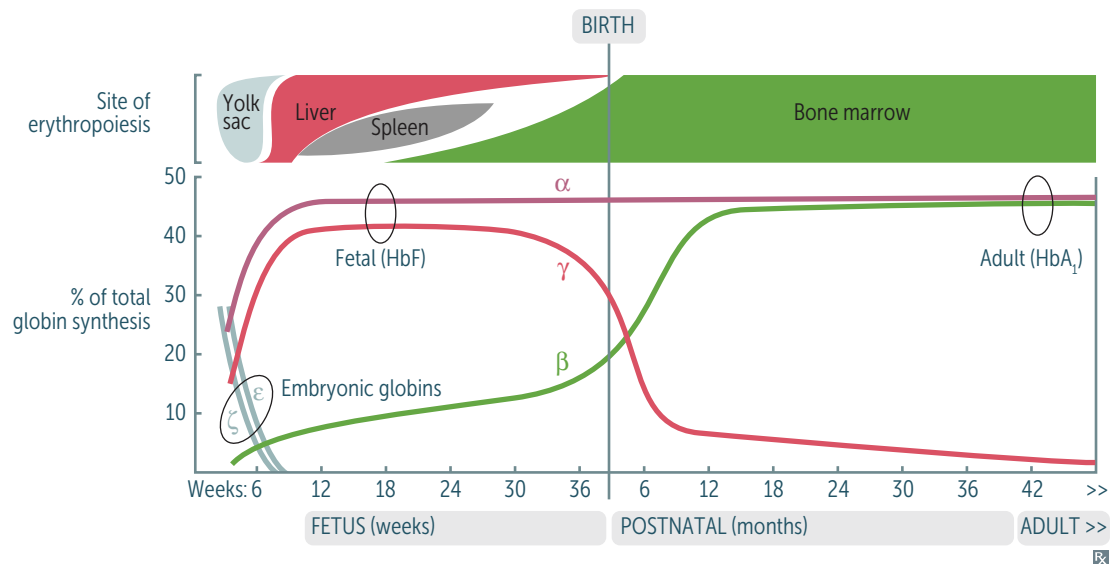
Fetal hemoglobin (HbF) = $\alpha_2\gamma_2$.

Adult hemoglobin (HbA₁) = $\alpha_2\beta_2$.

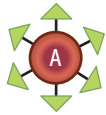
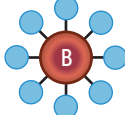
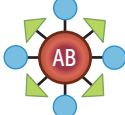

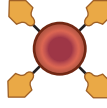









HbF has higher affinity for O₂ due to less avid binding of 2,3-BPG, allowing HbF to extract O₂ from maternal hemoglobin (HbA₁ and HbA₂) across the placenta.

From fetal to adult hemoglobin:

Alpha Always; Gamma Goes, Becomes Beta.



Blood groups

	ABO classification				Rh classification	
	A	B	AB	O	Rh ⁺	Rh ⁻
RBC type						
Group antigens on RBC surface	A 	B 	A & B 	NONE	Rh (D) 	NONE
Antibodies in plasma	Anti-B  IgM	Anti-A  IgM	NONE	Anti-A Anti-B  IgM	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	Universal recipient of RBCs	Treat mother with anti-D Ig (RhoGAM) during and after each pregnancy to prevent anti-D IgG formation

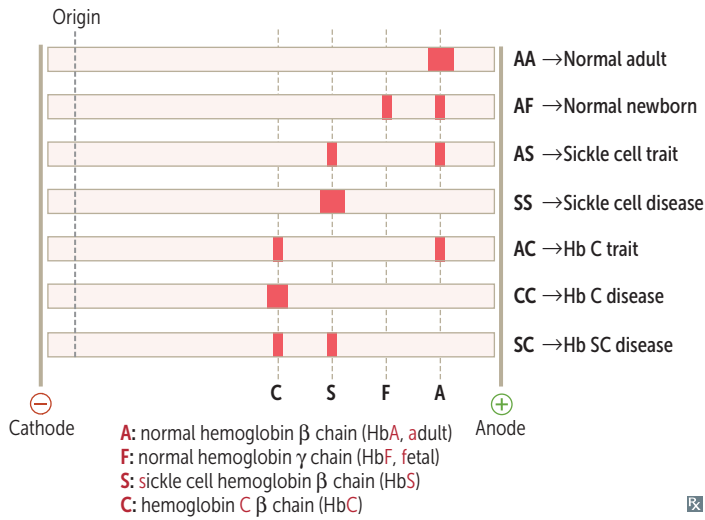
Rh hemolytic disease of the newborn

IgM does not cross placenta; IgG does cross placenta. Rh⁻ mothers exposed to fetal Rh⁺ blood (often during delivery) may make anti-D IgG. In subsequent pregnancies, anti-D IgG crosses the placenta → hemolytic disease of the newborn (erythroblastosis fetalis) in the next fetus that is Rh⁺. Administration of anti-D IgG (RhoGAM) to Rh⁻ pregnant women during third trimester prevents maternal anti-D IgG production. Rh⁻ mothers have anti-D IgG only if previously exposed to Rh⁺ blood.

ABO hemolytic disease of the newborn

Most common form. Usually occurs in a type O mother with a type A, B, or AB fetus. Can occur in a first pregnancy as maternal anti-A and/or anti-B IgG antibodies are formed early in life. Does not worsen with future pregnancies. Presents as mild jaundice in the neonate within 24 hours of birth; treatment is phototherapy or exchange transfusion.

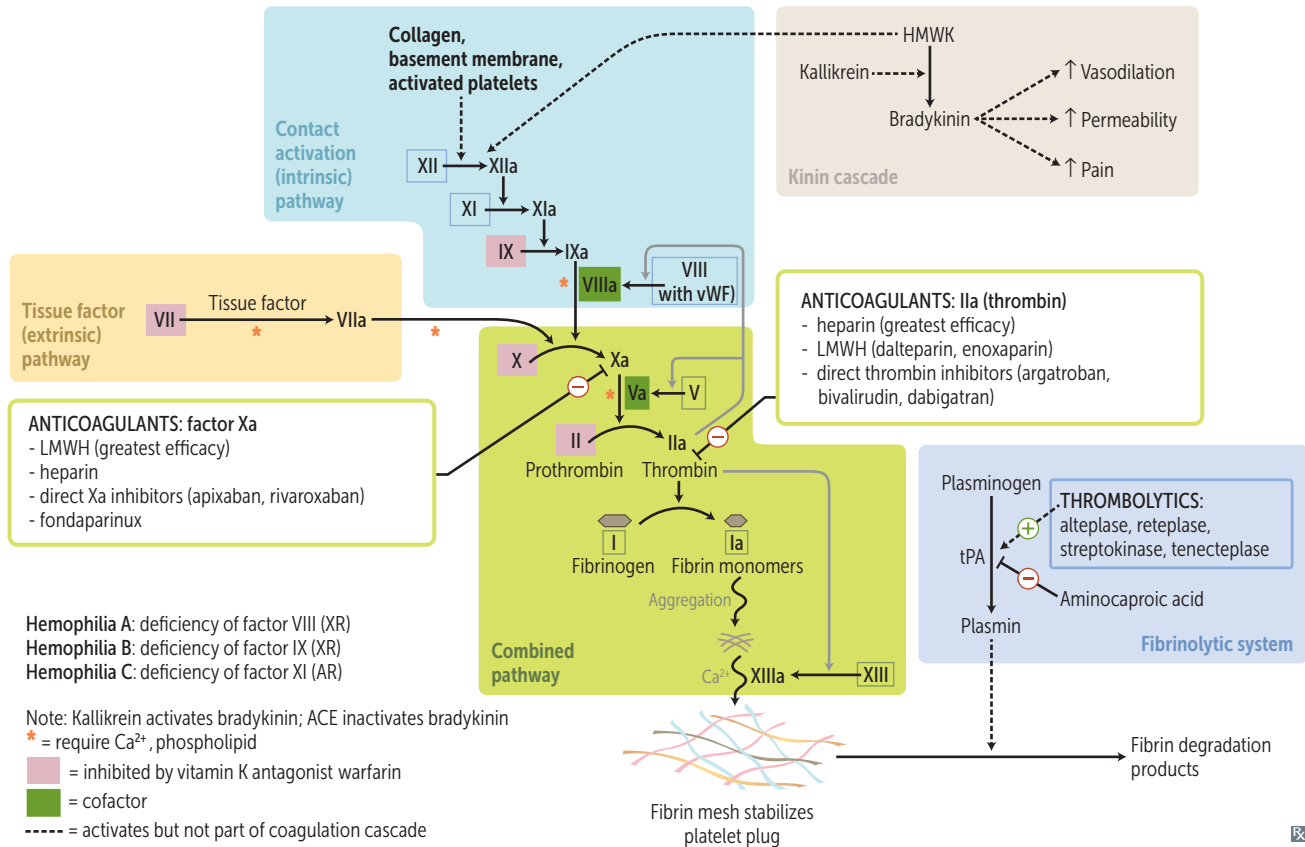
Hemoglobin electrophoresis



On a gel, hemoglobin migrates from the negatively charged cathode to the positively charged anode. HbA migrates the farthest, followed by HbS, followed by HbC. This is because the missense mutations in HbS and HbC replace glutamic acid \ominus with valine (neutral) and lysine \oplus , respectively, impacting the net protein charge.

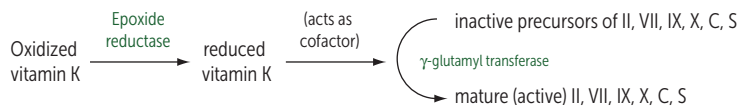
A Fat Santa Claus

Coagulation and kinin pathways

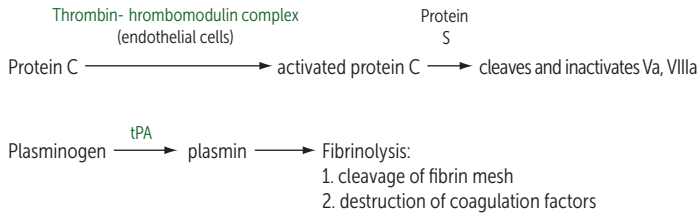


Coagulation cascade components

Procoagulation



Anticoagulation



Warfarin inhibits the enzyme vitamin K epoxide reductase.

Neonates lack enteric bacteria, which produce vitamin K.

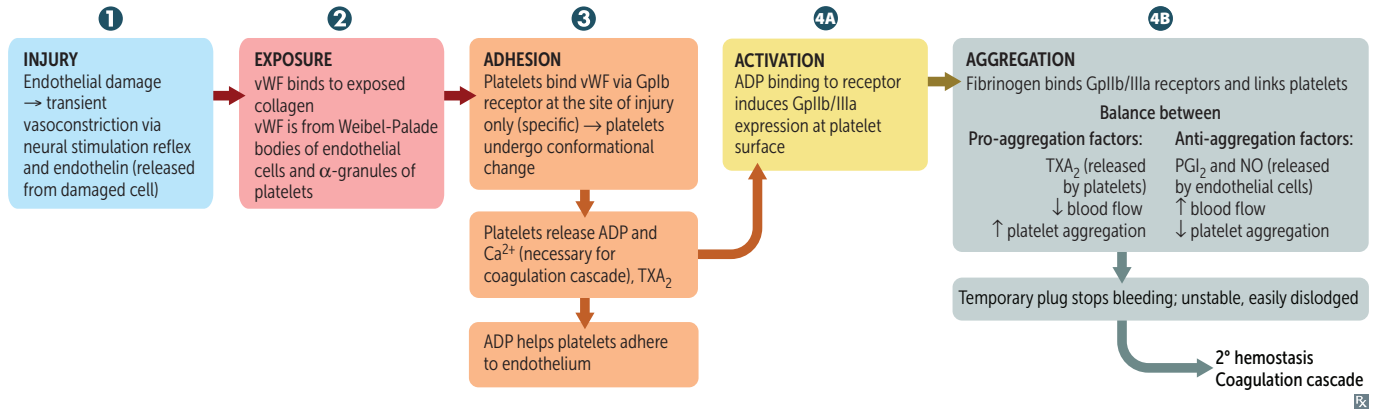
Vitamin K deficiency: ↓ synthesis of factors II, VII, IX, X, protein C, protein S. vWF carries/protects VIII.

Antithrombin inhibits activated forms of factors II, VII, IX, X, XI, XII.

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.

Platelet plug formation (primary hemostasis)



Thrombogenesis

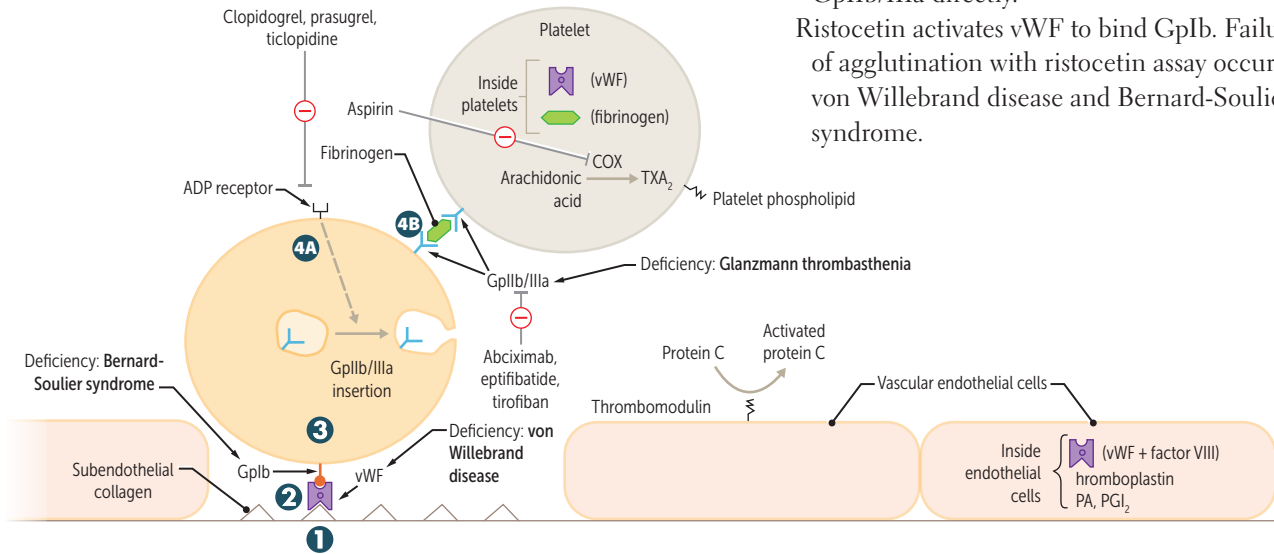
Formation of insoluble fibrin mesh.

Aspirin irreversibly inhibits cyclooxygenase (TXA_2 synthesis).

Clopidogrel, prasugrel, and ticlopidine inhibit ADP-induced expression of GpIIb/IIIa.

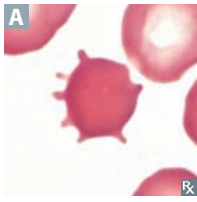
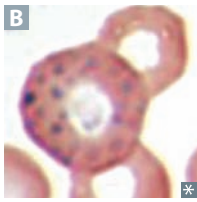


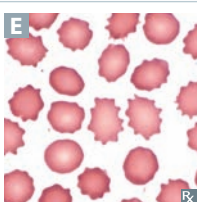
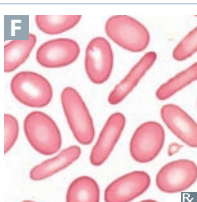

Abciximab, eptifibatide, and tirofiban inhibit GpIIb/IIIa directly.

Ristocetin activates vWF to bind GpIb. Failure of agglutination with ristocetin assay occurs in von Willebrand disease and Bernard-Soulier syndrome.

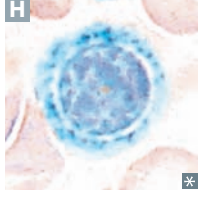
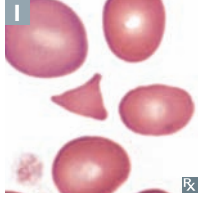


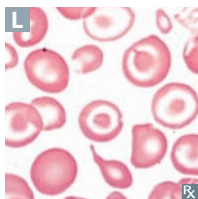


▶ HEMATOLOGY AND ONCOLOGY—PATHOLOGY

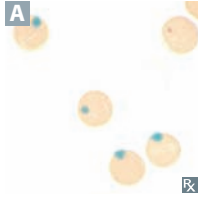
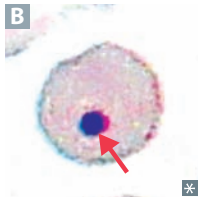
Pathologic RBC forms

TYPE	EXAMPLE	ASSOCIATED PATHOLOGY	NOTES
Acanthocyte ("spur cell")		Liver disease, abetalipoproteinemia (states of cholesterol dysregulation).	<i>Acantho</i> = spiny.
Basophilic stippling		Lead poisoning, sideroblastic anemias, myelodysplastic syndromes.	
Dacrocyte ("teardrop cell")		Bone marrow infiltration (eg, myelofibrosis).	RBC "sheds a tear " because it's mechanically squeezed out of its home in the bone marrow.
Degmacyte ("bite cell")		G6PD deficiency.	
Echinocyte ("burr cell")		End-stage renal disease, liver disease, pyruvate kinase deficiency.	Different from acanthocyte; its projections are more uniform and smaller.
Elliptocyte		Hereditary elliptocytosis, usually asymptomatic; caused by mutation in genes encoding RBC membrane proteins (eg, spectrin).	
Macro-ovalocyte		Megaloblastic anemia (also hypersegmented PMNs), marrow failure.	

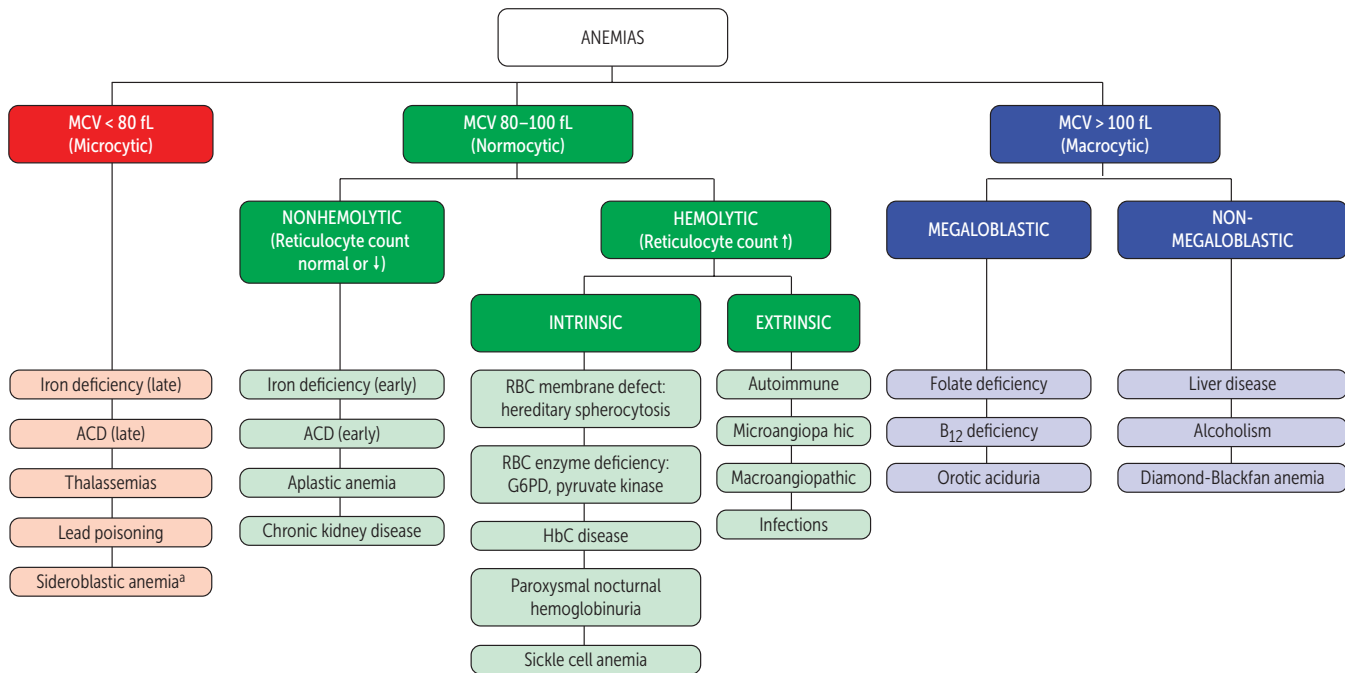
Pathologic RBC forms (continued)

TYPE	EXAMPLE	ASSOCIATED PATHOLOGY	NOTES
Ringed sideroblast		Sideroblastic anemia. Excess iron in mitochondria.	
Schistocyte		DIC, TTP/HUS, HELLP syndrome, mechanical hemolysis (eg, heart valve prosthesis).	Examples include helmet cell.
Sickle cell		Sickle cell anemia.	Sickling occurs with dehydration, deoxygenation, and at high altitude.
Spherocyte		Hereditary spherocytosis, drug- and infection-induced hemolytic anemia.	
Target cell		HbC disease, Asplenia, Liver disease, Thalassemia.	“ HALT ,” said the hunter to his target .

Other RBC abnormalities

TYPE	EXAMPLE	ASSOCIATED PATHOLOGY	NOTES
Heinz bodies		Seen in G6PD deficiency.	Oxidation of Hb -SH groups to -S-S- → Hb precipitation (Heinz bodies), with subsequent phagocytic damage to RBC membrane → bite cells.
Howell-Jolly bodies		Seen in patients with functional hyposplenia or asplenia.	Basophilic nuclear remnants found in RBCs. Howell-Jolly bodies are normally removed from RBCs by splenic macrophages.

Anemias



On a peripheral blood smear, a lymphocyte nucleus is approximately the same size as a normocytic RBC. If RBC is larger than lymphocyte nucleus, consider macrocytosis; if RBC is smaller, consider microcytosis.

^aCopper deficiency can cause a microcytic sideroblastic anemia.

Microcytic (MCV < 80 fL), hypochromic anemia

Iron deficiency

↓ iron due to chronic bleeding (eg, GI loss, menorrhagia), malnutrition, absorption disorders, or ↑ demand (eg, pregnancy) → ↓ final step in heme synthesis.

Labs: ↓ iron, ↑ TIBC, ↓ ferritin. Microcytosis and hypochromasia (central pallor) **A**.

Symptoms: fatigue, conjunctival pallor **B**, pica (consumption of nonfood substances), spoon nails (koilonychia).

May manifest as **Plummer-Vinson syndrome** (triad of iron deficiency anemia, esophageal webs, and dysphagia).

α-thalassemia

Defect: α-globin gene deletions → ↓ α-globin synthesis. *cis* deletion (both deletions occur on same chromosome) prevalent in Asian populations; *trans* deletion (deletions occur on separate chromosomes) prevalent in African populations.

4 allele deletion: No α-globin. Excess γ-globin forms γ₄ (Hb Barts). Incompatible with life (causes hydrops fetalis).

3 allele deletion: inheritance of chromosome with *cis* deletion + a chromosome with 1 allele deleted → HbH disease. Very little α-globin. Excess β-globin forms β₄ (HbH).

2 allele deletion: less clinically severe anemia.

1 allele deletion: no anemia (clinically silent).

Microcytic (MCV < 80 fL), hypochromic anemia (continued)**β-thalassemia**

Point mutations in splice sites and promoter sequences → ↓ β-globin synthesis. Prevalent in Mediterranean populations.

β-thalassemia minor (heterozygote): β chain is underproduced. Usually asymptomatic. Diagnosis confirmed by ↑ HbA₂ (> 3.5%) on electrophoresis.

β-thalassemia major (homozygote): β chain is absent → severe microcytic, hypochromic anemia with target cells and increased anisopoikilocytosis **C** requiring blood transfusion (2° hemochromatosis). Marrow expansion (“crew cut” on skull x-ray) → skeletal deformities. “Chipmunk” facies. Extramedullary hematopoiesis → hepatosplenomegaly. ↑ risk of parvovirus B19–induced aplastic crisis. ↑ HbF (α₂γ₂). HbF is protective in the infant and disease becomes symptomatic only after 6 months, when fetal hemoglobin declines.

HbS/β-thalassemia heterozygote: mild to moderate sickle cell disease depending on amount of β-globin production.

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:

- **L**ead **L**ines on gingivae (Burton lines) and on metaphyses of long bones **D** on x-ray.
- **E**ncephalopathy and **E**rythrocyte basophilic stippling.
- **A**bdominal colic and sideroblastic **A**nemia.
- **D**rops—wrist and foot drop. **D**imercaprol and **E**DTA are 1st line of treatment.

Succimer used for chelation for kids (It “**sucks**” to be a kid who eats lead).

Exposure risk ↑ in old houses with chipped paint.

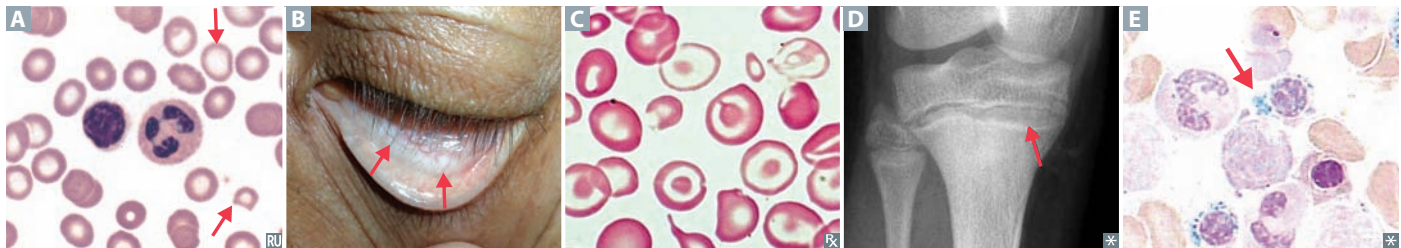
Sideroblastic anemia

Defect in heme synthesis due to X-linked defect in δ-ALA synthase gene.

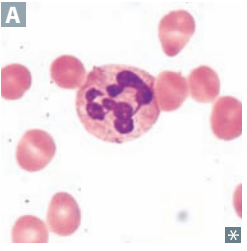
Causes: genetic, acquired (myelodysplastic syndromes), and reversible (alcohol is most common; also lead, vitamin B₆ deficiency, copper deficiency, isoniazid).

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.

Treatment: pyridoxine (B₆, cofactor for δ-ALA synthase).



Macrocytic (MCV > 100 fL) anemia

	DESCRIPTION	FINDINGS
Megaloblastic anemia 	Impaired DNA synthesis → maturation of nucleus of precursor cells in bone marrow delayed relative to maturation of cytoplasm.	RBC macrocytosis, hypersegmented neutrophils A , glossitis.
Folate deficiency	Causes: malnutrition (eg, alcoholics), malabsorption, drugs (eg, methotrexate, trimethoprim, phenytoin), ↑ requirement (eg, hemolytic anemia, pregnancy).	↑ homocysteine, normal methylmalonic acid. No neurologic symptoms (vs B ₁₂ deficiency).
Vitamin B₁₂ (cobalamin) deficiency	Causes: insufficient intake (eg, veganism), malabsorption (eg, Crohn disease), pernicious anemia, <i>Diphyllobothrium latum</i> (fish tapeworm), gastrectomy.	↑ homocysteine, ↑ methylmalonic acid. Neurologic symptoms: subacute combined degeneration (due to involvement of B ₁₂ in fatty acid pathways and myelin synthesis): spinocerebellar tract, lateral corticospinal tract, dorsal column dysfunction. Historically diagnosed with the Schilling test, a 4-stage test that determines if the cause is dietary insufficiency vs malabsorption.
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 B ₁₂ . No hyperammonemia (vs ornithine transcarbamylase deficiency—↑ orotic acid with hyperammonemia).	Orotic acid in urine. Treatment: uridine monophosphate to bypass mutated enzyme.
Diamond-Blackfan anemia	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.
Nonmegaloblastic anemia	Macrocytic anemia in which DNA synthesis is unimpaired. Causes: alcoholism, liver disease.	RBC macrocytosis without hypersegmented neutrophils.

Normocytic, normochromic anemia

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).

Intravascular hemolysis

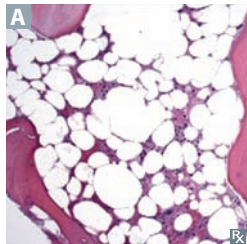
Findings: ↓ haptoglobin, ↑ LDH, schistocytes and ↑ reticulocytes on blood smear. Characteristic hemoglobinuria, hemosiderinuria, and urobilinogen in urine. May also see ↑ unconjugated bilirubin. Notable causes are mechanical hemolysis (eg, prosthetic valve), paroxysmal nocturnal hemoglobinuria, microangiopathic hemolytic anemias.

Extravascular hemolysis

Findings: macrophages in spleen clear RBCs. Spherocytes in peripheral smear, ↑ LDH, no hemoglobinuria/hemosiderinuria, ↑ unconjugated bilirubin, which can cause jaundice. Can present with urobilinogen in urine.

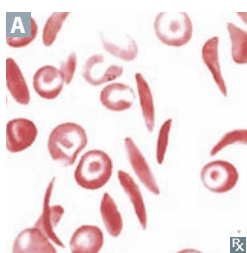
Nonhemolytic, normocytic anemia

	DESCRIPTION	FINDINGS
Anemia of chronic disease	Inflammation → ↑ 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 rheumatoid arthritis, SLE, neoplastic disorders, and chronic kidney disease.	↓ iron, ↓ TIBC, ↑ ferritin. Normocytic, but can become microcytic. Treatment: EPO (chronic kidney disease only).
Aplastic anemia	Caused by failure or destruction of myeloid stem cells due to: <ul style="list-style-type: none"> ▪ Radiation and drugs (benzene, chloramphenicol, alkylating agents, antimetabolites) ▪ Viral agents (parvovirus B19, EBV, HIV, hepatitis viruses) ▪ Fanconi anemia (DNA repair defect causing bone marrow failure); also short stature, ↑ incidence of tumors/leukemia, café-au-lait spots, thumb/radial defects ▪ Idiopathic (immune mediated, 1° stem cell defect); may follow acute hepatitis 	↓ reticulocyte count, ↑ EPO. Pancytopenia characterized by severe anemia, leukopenia, and thrombocytopenia. Normal cell morphology, but hypocellular bone marrow with fatty infiltration A (dry bone marrow tap). Symptoms: fatigue, malaise, pallor, purpura, mucosal bleeding, petechiae, infection. Treatment: withdrawal of offending agent, immunosuppressive regimens (eg, antithymocyte globulin, cyclosporine), bone marrow allograft, RBC/platelet transfusion, bone marrow stimulation (eg, GM-CSF).



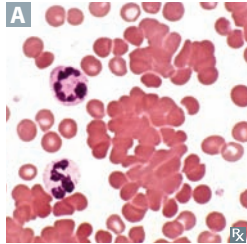
Intrinsic hemolytic anemia

	DESCRIPTION	FINDINGS
Hereditary spherocytosis	Extravascular hemolysis due to defect in proteins interacting with RBC membrane skeleton and plasma membrane (eg, ankyrin, band 3, protein 4.2, spectrin). Results in small, round RBCs with less surface area and no central pallor (↑ MCHC) → premature removal by spleen.	Splenomegaly, aplastic crisis (parvovirus B19 infection). Labs: osmotic fragility test ⊕. Normal to ↓ MCV with abundance of cells. Treatment: splenectomy.
G6PD deficiency	Most common enzymatic disorder of RBCs. Causes extravascular and intravascular hemolysis. X-linked recessive. Defect in G6PD → ↓ glutathione → ↑ RBC susceptibility to oxidant stress. Hemolytic anemia following oxidant stress (eg, sulfa drugs, antimalarials, infections, fava beans).	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. Defect in pyruvate kinase → ↓ ATP → rigid RBCs → extravascular hemolysis.	Hemolytic anemia in a newborn.
HbC disease	Glutamic acid-to-lysine mutation in β-globin. Causes extravascular hemolysis.	Patients with HbSC (1 of each mutant gene) have milder disease than HbSS patients. Labs (homozygotes): blood smear shows hemoglobin crystals inside RBCs and target cells.
Paroxysmal nocturnal hemoglobinuria	↑ complement-mediated intravascular RBC lysis (impaired synthesis of GPI anchor for decay-accelerating factor that protects RBC membrane from complement). Acquired mutation in a hematopoietic stem cell. ↑ incidence of acute leukemias.	Triad: Coombs ⊖ hemolytic anemia, pancytopenia, and venous thrombosis. Labs: CD55/59 ⊖ RBCs on flow cytometry. Treatment: eculizumab (terminal complement inhibitor).
Sickle cell anemia	HbS point mutation causes a single amino acid replacement in β chain (substitution of glutamic acid with valine). Causes extravascular and intravascular hemolysis. Pathogenesis: low O ₂ , high altitude, or acidosis precipitates sickling (deoxygenated HbS polymerizes) → anemia and vaso-occlusive disease. Newborns are initially asymptomatic because of ↑ HbF and ↓ HbS. Heterozygotes (sickle cell trait) also 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).	Complications in sickle cell disease: <ul style="list-style-type: none"> ▪ Aplastic crisis (due to parvovirus B19). ▪ Autosplenectomy (Howell-Jolly bodies) → ↑ risk of infection by encapsulated organisms (eg, <i>S pneumoniae</i>). ▪ Splenic infarct/sequestration crisis. ▪ <i>Salmonella</i> osteomyelitis. ▪ Painful crises (vaso-occlusive): dactylitis B (painful swelling of hands/feet), priapism, acute chest syndrome, avascular necrosis, stroke. ▪ Renal papillary necrosis (↓ Po₂ in papilla) and microhematuria (medullary infarcts). Diagnosis: hemoglobin electrophoresis. Treatment: hydroxyurea (↑ HbF), hydration.



Extrinsic hemolytic anemia

Autoimmune hemolytic anemia

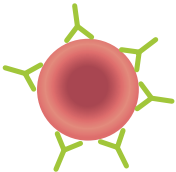

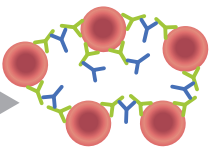
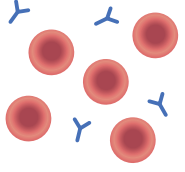

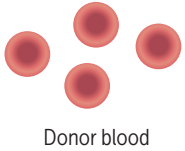



DESCRIPTION

Warm (IgG)—chronic anemia seen in SLE and CLL and with certain drugs (eg, α -methyl dopa) (“**w**arm **w**eather is **G**reat”).
Cold (IgM and complement)—acute anemia triggered by cold; seen in CLL, *Mycoplasma pneumonia* infections, and infectious Mononucleosis (“**c**old **w**eather is **M**MMiserable”). RBC agglutinates **A** may cause painful, blue fingers and toes with cold exposure.
 Many warm and cold AIHAs are idiopathic in etiology.

FINDINGS

Autoimmune hemolytic anemias are usually Coombs \oplus .
 Direct Coombs test—anti-Ig antibody (Coombs reagent) added to patient’s blood. RBCs agglutinate if RBCs are coated with Ig.
 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)	\oplus Result (agglutination)	\ominus Result (no agglutination)
Direct Coombs	 RBCs +/- anti-RBC Ab	 Anti-human globulin (Coombs reagent)	 \oplus Result Anti-RBC Ab present	 \ominus Result Anti-RBC Ab absent
			 Patient serum +/- anti-donor RBC Ab	 Donor blood
 Anti-human globulin (Coombs reagent)				

Microangiopathic anemia

Pathogenesis: RBCs are damaged when passing through obstructed or narrowed vessel lumina. Seen in DIC, TTP/HUS, SLE, and malignant hypertension.

Schistocytes (eg, “helmet cells”) are seen on peripheral blood smear due to mechanical destruction (*schisto* = to split) of RBCs.

Macroangiopathic anemia

Prosthetic heart valves and aortic stenosis may also cause hemolytic anemia 2° to mechanical destruction of RBCs.

Schistocytes on peripheral blood smear.

Infections

↑ destruction of RBCs (eg, malaria, *Babesia*).

Lab values in anemia

	Iron deficiency	Chronic disease	Hemo-chromatosis	Pregnancy/OCP use
Serum iron	↓ (1°)	↓	↑ (1°)	—
Transferrin or TIBC	↑	↓ ^a	↓	↑ (1°)
Ferritin	↓	↑ (1°)	↑	—
% transferrin saturation (serum iron/TIBC)	↓↓	—	↑↑	↓

Transferrin—transports iron in blood.

TIBC—indirectly measures transferrin.

Ferritin—1° iron storage protein of body.

^aEvolutionary 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.

Leukopenias

CELL TYPE	CELL COUNT	CAUSES
Neutropenia	Absolute neutrophil count < 1500 cells/mm ³ . Severe infections typical when < 500 cells/mm ³ .	Sepsis/postinfection, drugs (including chemotherapy), aplastic anemia, SLE, radiation
Lymphopenia	Absolute lymphocyte count < 1500 cells/mm ³ (< 3000 cells/mm ³ in children)	HIV, DiGeorge syndrome, SCID, SLE, corticosteroids, ^a radiation, sepsis, postoperative
Eosinopenia	Absolute eosinophil count < 30 cells/mm ³	Cushing syndrome, corticosteroids ^a

^aCorticosteroids 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.

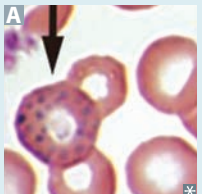

Left shift

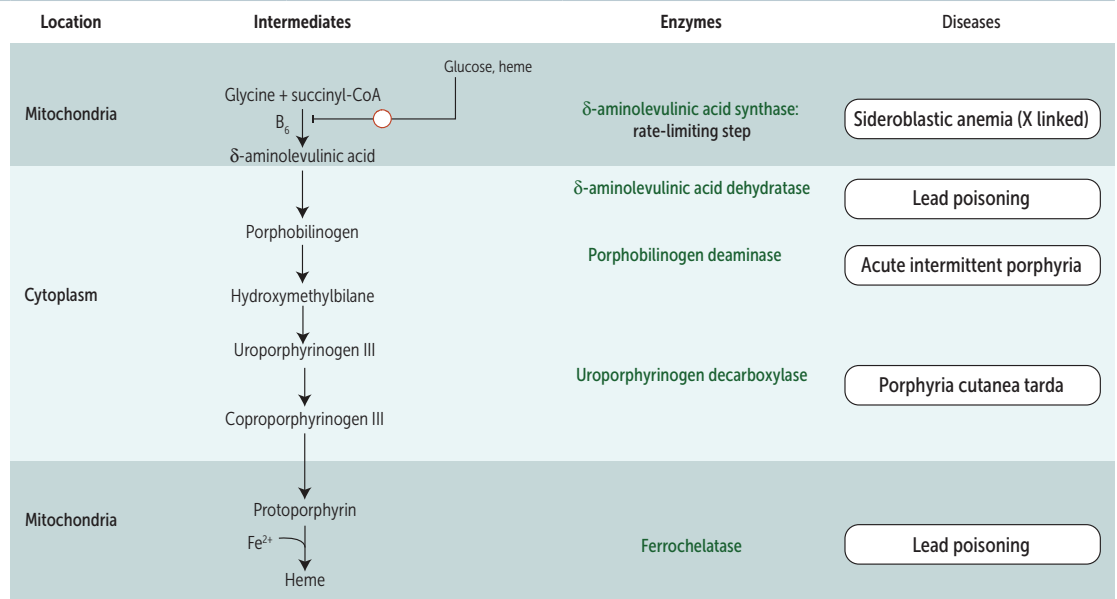
↑ neutrophil precursors, such as band cells and metamyelocytes, in peripheral blood. Usually seen with neutrophilia in the acute response to infection or inflammation. Called **leukoerythroblastic reaction** when left shift is seen with immature RBCs; occurs with severe anemia (physiologic response) 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.

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
<p>Lead poisoning</p> 	Ferrochelatase and ALA dehydratase	Protoporphyrin, δ -ALA (blood)	<p>Microcytic anemia (basophilic stippling A), GI and kidney disease.</p> <p>Children—exposure to lead paint → mental deterioration.</p> <p>Adults—environmental exposure (eg, batteries, ammunition) → headache, memory loss, demyelination.</p>
<p>Acute intermittent porphyria</p>	Porphobilinogen deaminase	Porphobilinogen, δ -ALA, coporphobilinogen (urine)	<p>Symptoms (5 P's):</p> <ul style="list-style-type: none"> ▪ Painful abdomen ▪ Port wine-colored urine ▪ Polyneuropathy ▪ Psychological disturbances ▪ Precipitated by drugs (eg, cytochrome P-450 inducers), alcohol, starvation <p>Treatment: glucose and heme, which inhibit ALA synthase.</p>
<p>Porphyria cutanea tarda</p> 	Uroporphyrinogen decarboxylase	Uroporphyrin (tea-colored urine)	<p>Blistering cutaneous photosensitivity B. Most common porphyria.</p>

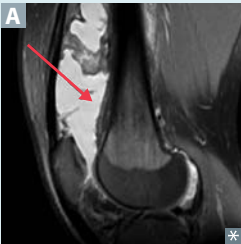


↓ heme → ↑ ALA synthase activity
 ↑ heme → ↓ ALA synthase activity

Iron poisoning	High mortality rate with accidental ingestion by children (adult iron tablets may look like candy).
MECHANISM	Cell death due to peroxidation of membrane lipids.
SYMPTOMS/SIGNS	Nausea, vomiting, gastric bleeding, lethargy, scarring leading to GI obstruction.
TREATMENT	Chelation (eg, IV deferoxamine, oral deferasirox) and dialysis.

Coagulation disorders PT—tests function of common and extrinsic pathway (factors I, II, V, VII, and X). Defect → ↑ PT. INR (international normalized ratio)—calculated from PT. 1 = normal, > 1 = prolonged. Most common test used to follow patients on warfarin.

PTT—tests function of common and intrinsic pathway (all factors except VII and XIII). Defect → ↑ PTT.

DISORDER	PT	PTT	MECHANISM AND COMMENTS
Hemophilia A, B, or C 	—	↑	Intrinsic pathway coagulation defect. <ul style="list-style-type: none"> ▪ A: deficiency of factor VIII → ↑ PTT; X-linked recessive. ▪ B: deficiency of factor IX → ↑ PTT; X-linked recessive. ▪ C: deficiency of factor XI → ↑ PTT; autosomal recessive. Macrohemorrhage in hemophilia—hemarthroses (bleeding into joints, such as knee A), easy bruising, bleeding after trauma or surgery (eg, dental procedures). Treatment: desmopressin + factor VIII concentrate (A); factor IX concentrate (B); factor XI concentrate (C).
Vitamin K deficiency	↑	↑	General coagulation defect. Bleeding time normal. ↓ activity of factors II, VII, IX, X, protein C, protein S.

Platelet disorders

Defects in platelet plug formation → ↑ bleeding time (BT).

Platelet abnormalities → microhemorrhage: mucous membrane bleeding, epistaxis, petechiae, purpura, ↑ bleeding time, possibly decreased platelet count (PC).

DISORDER	PC	BT	MECHANISM AND COMMENTS
Bernard-Soulier syndrome	–/↓	↑	Defect in platelet plug formation. Large platelets. ↓ GpIb → defect in platelet-to-vWF adhesion.
Glanzmann thrombasthenia	–	↑	Defect in platelet plug formation. ↓ GpIIb/IIIa → defect in platelet-to-platelet aggregation. Labs: blood smear shows no platelet clumping.
Hemolytic-uremic syndrome	↓	↑	Characterized by thrombocytopenia, microangiopathic hemolytic anemia, and acute renal failure. Typical HUS is seen in children, accompanied by diarrhea and commonly caused by Shiga toxin-producing <i>E coli</i> (STEC) (eg, O157:H7). HUS in adults does not present with diarrhea; STEC infection not required. Same spectrum as TTP, with a similar clinical presentation and same initial treatment of plasmapheresis.
Immune thrombocytopenia	↓	↑	Anti-GpIIb/IIIa antibodies → splenic macrophage consumption of platelet-antibody complex. Commonly due to viral illness. Labs: ↑ megakaryocytes on bone marrow biopsy. Treatment: steroids, IVIG, splenectomy (for refractory ITP).
Thrombotic thrombocytopenic purpura	↓	↑	Inhibition or deficiency of ADAMTS 13 (vWF metalloprotease) → ↓ degradation of vWF multimers. Pathogenesis: ↑ large vWF multimers → ↑ platelet adhesion → ↑ platelet aggregation and thrombosis. Labs: schistocytes, ↑ LDH. Symptoms: pentad of neurologic and renal symptoms, fever, thrombocytopenia, and microangiopathic hemolytic anemia. Treatment: plasmapheresis, steroids.

Mixed platelet and coagulation disorders

DISORDER	PC	BT	PT	PTT	MECHANISM AND COMMENTS
von Willebrand disease	—	↑	—	↑ ^a	<p>Intrinsic pathway coagulation defect: ↓ vWF → ↑ PTT (vWF acts to carry/protect factor VIII).</p> <p>Defect in platelet plug formation: ↓ vWF → defect in platelet-to-vWF adhesion.</p> <p>Autosomal dominant. Mild but most common inherited bleeding disorder. No platelet aggregation with ristocetin cofactor assay.</p> <p>Treatment: desmopressin, which releases vWF stored in endothelium.</p>
Disseminated intravascular coagulation	↓	↑	↑	↑	<p>Widespread activation of clotting → deficiency in clotting factors → bleeding state.</p> <p>Causes: Sepsis (gram ⊖), Trauma, Obstetric complications, acute Pancreatitis, Malignancy, Nephrotic syndrome, Transfusion (STOP Making New Thrombi).</p> <p>Labs: schistocytes, ↑ fibrin degradation products (D-dimers), ↓ fibrinogen, ↓ factors V and VIII.</p>

^aPTT may also be normal in von Willebrand disease.

Hereditary thrombosis syndromes leading to hypercoagulability

DISEASE	DESCRIPTION
Antithrombin deficiency	<p>Inherited deficiency of antithrombin: has no direct effect on the PT, PTT, or thrombin time but diminishes the increase in PTT following heparin administration.</p> <p>Can also be acquired: renal failure/nephrotic syndrome → antithrombin loss in urine → ↓ inhibition of factors IIa and Xa.</p>
Factor V Leiden	<p>Production of mutant factor V (G → A DNA point mutation → Arg506Gln mutation near the cleavage site) that is resistant to degradation by activated protein C. Most common cause of inherited hypercoagulability in Caucasians. Complications include DVT, cerebral vein thromboses, recurrent pregnancy loss.</p>
Protein C or S deficiency	<p>↓ 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.</p>
Prothrombin gene mutation	<p>Mutation in 3′ untranslated region → ↑ production of prothrombin → ↑ plasma levels and venous clots.</p>

Blood transfusion therapy

COMPONENT	DOSAGE EFFECT	CLINICAL USE
Packed RBCs	↑ Hb and O ₂ carrying capacity	Acute blood loss, severe anemia
Platelets	↑ platelet count (↑ ~ 5000/mm ³ /unit)	Stop significant bleeding (thrombocytopenia, qualitative platelet defects)
Fresh frozen plasma	↑ coagulation factor levels	DIC, cirrhosis, immediate warfarin reversal
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 Ca²⁺ 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**

Localized, single group of nodes; contiguous spread (stage is strongest predictor of prognosis). Many patients have a relatively good prognosis.

Characterized by Reed-Sternberg cells.

Bimodal distribution—young adulthood and > 55 years; more common in men except for nodular sclerosing type.

Associated with EBV.

Constitutional (“B”) signs/symptoms: low-grade fever, night sweats, weight loss.

Non-Hodgkin

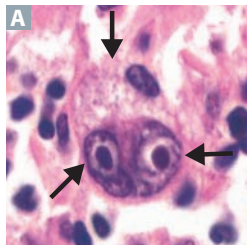
Multiple lymph nodes involved; extranodal involvement common; noncontiguous spread.

Majority involve B cells; a few are of T-cell lineage.

Can occur in children and adults.

May be associated with HIV and autoimmune diseases.

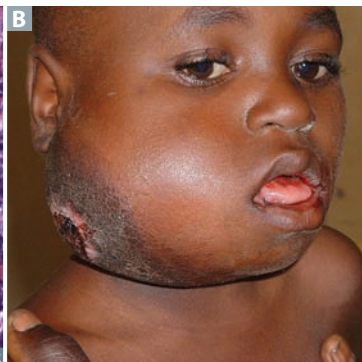
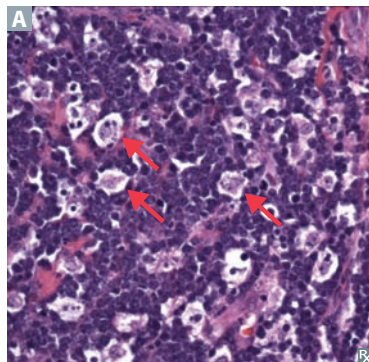
May present with constitutional signs/symptoms.

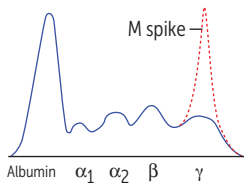
Reed-Sternberg cells

Distinctive tumor giant cell seen in Hodgkin lymphoma; binucleate or bilobed with the 2 halves as mirror images (“owl eyes” **A**). 2 owl eyes × 15 = 30. RS cells are CD15+ and CD30+ B-cell origin. Necessary but not sufficient for a diagnosis of Hodgkin lymphoma.

Non-Hodgkin lymphoma

TYPE	OCCURS IN	GENETICS	COMMENTS
Neoplasms of mature B cells			
Burkitt lymphoma	Adolescents or young adults	t(8;14)—translocation of <i>c-myc</i> (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		Most common type of non-Hodgkin lymphoma in adults.
Follicular lymphoma	Adults	t(14;18)—translocation of heavy-chain Ig (14) and <i>BCL-2</i> (18)	Indolent course; Bcl-2 inhibits apoptosis. Presents with painless “waxing and waning” lymphadenopathy. Follicular architecture: small cleaved cells (grade 1), large cells (grade 3), or mixture (grade 2).
Mantle cell lymphoma	Adult males	t(11;14)—translocation of cyclin D1 (11) and heavy-chain Ig (14)	Very aggressive, patients typically present with late-stage disease.
Primary central nervous system lymphoma	Adults	Most commonly associated with HIV/AIDS	Considered an AIDS-defining illness. Variable presentation: confusion, memory loss, seizures. Mass lesion(s) on MRI, needs to be distinguished from toxoplasmosis via CSF analysis or other lab tests.
Neoplasms of mature T cells			
Adult T-cell lymphoma	Adults	Caused by HTLV (associated with IV drug abuse)	Adults present with cutaneous lesions; especially affects populations in Japan, West Africa, and the Caribbean. Lytic bone lesions, hypercalcemia.
Mycosis fungoides/Sézary syndrome	Adults		Mycosis fungoides presents with skin patches C /plaques (cutaneous T-cell lymphoma), characterized by atypical CD4+ cells with “cerebriform” nuclei. May progress to Sézary syndrome (T-cell leukemia).



Multiple myeloma

Monoclonal plasma cell (“fried egg” appearance) cancer that arises in the marrow and produces large amounts of IgG (55%) or IgA (25%). Most common 1° tumor arising within bone in people > 40–50 years old.

Associated with:

- ↑ susceptibility to infection
- Primary amyloidosis (AL)
- Punched-out lytic bone lesions on x-ray **A**
- M spike on serum protein electrophoresis
- Ig light chains in urine (Bence Jones protein)
- Rouleaux formation **B** (RBCs stacked like poker chips in blood smear)

Numerous plasma cells **C** with “clock-face” chromatin and intracytoplasmic inclusions containing immunoglobulin.

Monoclonal gammopathy of undetermined significance (MGUS)—monoclonal expansion of plasma cells, asymptomatic, may lead to multiple myeloma. No “**CRAB**” findings. Patients with MGUS develop multiple myeloma at a rate of 1–2% per year.

Think **CRAB**:

Hyper**C**alcemia
Renal involvement
Anemia

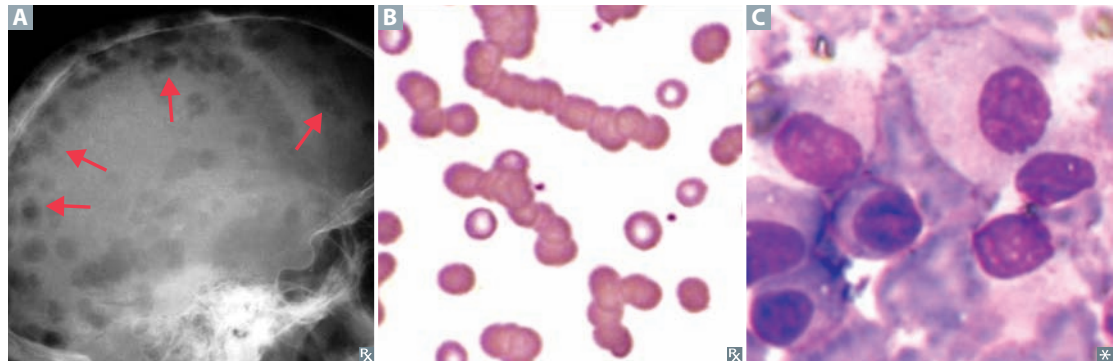
Bone lytic lesions/**B**ack pain

Multiple Myeloma: Monoclonal M protein spike

Distinguish from **Waldenström**

macroglobulinemia → M spike = IgM

→ hyperviscosity syndrome (eg, blurred vision, Raynaud phenomenon); no “**CRAB**” findings.

**Myelodysplastic syndromes**

Stem-cell disorders involving ineffective hematopoiesis → defects in cell maturation of all nonlymphoid lineages. Caused by de novo mutations or environmental exposure (eg, radiation, benzene, chemotherapy). Risk of transformation to AML.

Pseudo-Pelger-Huet anomaly—neutrophils with bilobed nuclei. Typically seen after chemotherapy.

Leukemias

Unregulated growth and differentiation of WBCs in bone marrow → marrow failure → anemia (↓ RBCs), infections (↓ mature WBCs), and hemorrhage (↓ platelets). Usually presents with ↑ circulating WBCs (malignant leukocytes in blood); rare cases present with normal/↓ 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) → better prognosis.

Chronic lymphocytic leukemia/small lymphocytic lymphoma

Age: > 60 years. Most common adult leukemia. CD20+, 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**—SLL/CLL transformation into an aggressive lymphoma, most commonly diffuse large B-cell lymphoma (DLBCL).

Hairy cell leukemia

Age: Adult males. Mature B-cell tumor. Cells have filamentous, hair-like projections (fuzzy appearing on LM **C**). Causes marrow fibrosis → dry tap on aspiration. Patients usually present with massive splenomegaly. Stains TRAP (tartrate-resistant acid phosphatase) ⊕. TRAP stain largely replaced with flow cytometry. Treatment: cladribine, pentostatin.

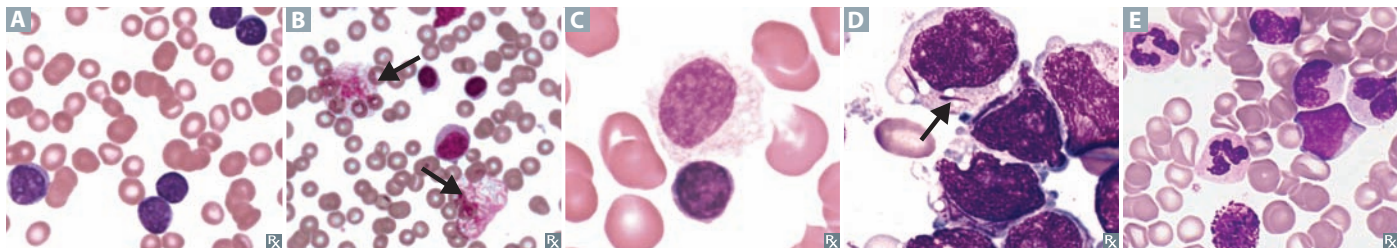
Myeloid neoplasms

Acute myelogenous leukemia

Median onset 65 years. Auer rods **D**; myeloperoxidase ⊕ cytoplasmic inclusions seen mostly in APL (formerly M3 AML); ↑↑↑ circulating myeloblasts on peripheral smear; adults. Risk factors: prior exposure to alkylating chemotherapy, radiation, myeloproliferative disorders, Down syndrome. t(15;17) → APL subtype responds to all-*trans* retinoic acid (vitamin A), inducing differentiation of promyelocytes; DIC is a common presentation.

Chronic myelogenous leukemia

Occurs across the age spectrum with peak incidence 45–85 years, median age at diagnosis 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 **E**) and splenomegaly. May accelerate and transform to AML or ALL (“blast crisis”). Very low LAP as a result of low activity in malignant neutrophils (vs benign neutrophilia [leukemoid reaction], in which LAP is ↑). Responds to *bcr-abl* tyrosine kinase inhibitors (eg, imatinib).

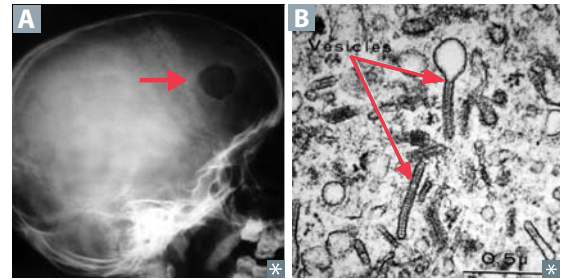


Chromosomal translocations

TRANSLOCATION	ASSOCIATED DISORDER	
t(8;14)	Burkitt lymphoma (<i>c-myc</i> activation)	
t(9;22) (Philadelphia chromosome)	CML (<i>BCR-ABL</i> hybrid), rarely ALL	Philadelphia CreaML cheese. The Ig heavy chain genes on chromosome 14 are constitutively expressed. When other genes (eg, <i>c-myc</i> and <i>BCL-2</i>) are translocated next to this heavy chain gene region, they are overexpressed.
t(11;14)	Mantle cell lymphoma (cyclin D1 activation)	
t(14;18)	Follicular lymphoma (<i>BCL-2</i> activation)	
t(15;17)	APL (M3 type of AML)	Responds to all- <i>trans</i> retinoic acid.

Langerhans cell histiocytosis

Collective group of proliferative disorders of dendritic (Langerhans) cells. Presents in a child as lytic bone lesions **A** 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 CD1a. Birbeck granules (“tennis rackets” or rod shaped on EM) are characteristic **B**.



Chronic myeloproliferative disorders

The myeloproliferative disorders (polycythemia vera, essential thrombocythemia, myelofibrosis, and CML) are malignant hematopoietic neoplasms with varying impacts on WBCs and myeloid cell lines. Associated with V617F *JAK2* mutation.

Polycythemia vera

A form of 1° polycythemia. Disorder of ↑ hematocrit. May present as intense itching after hot shower. Rare but classic symptom is erythromelalgia (severe, burning pain and red-blue coloration) due to episodic blood clots in vessels of the extremities **A**. Responds to aspirin. ↓ EPO (vs 2° polycythemia, which presents with endogenous or artificially ↑ EPO).

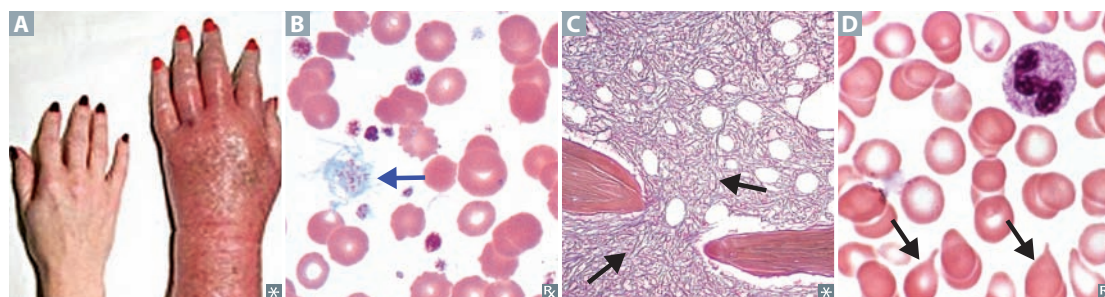
Essential thrombocythemia

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 **C** due to ↑ fibroblast activity. Often associated with massive splenomegaly and “teardrop” RBCs **D**. “Bone marrow is **crying** because it’s fibrosed and is a dry tap.”

	RBCs	WBCs	PLATELETS	PHILADELPHIA CHROMOSOME	<i>JAK2</i> MUTATIONS
Polycythemia vera	↑	↑	↑	⊖	⊕
Essential thrombocythemia	–	–	↑	⊖	⊕ (30–50%)
Myelofibrosis	↓	Variable	Variable	⊖	⊕ (30–50%)
CML	↓	↑	↑	⊕	⊖

**Polycythemia**

	PLASMA VOLUME	RBC MASS	O ₂ SATURATION	EPO LEVELS	ASSOCIATIONS
Relative	↓	–	–	–	Dehydration, burns.
Appropriate absolute	–	↑	↓	↑	Lung disease, congenital heart disease, high altitude.
Inappropriate absolute	–	↑	–	↑	Malignancy (eg, renal cell carcinoma, hepatocellular carcinoma), hydronephrosis. Due to ectopic EPO secretion.
Polycythemia vera	↑	↑↑	–	↓	EPO ↓ in PCV due to negative feedback suppressing renal EPO production.

▶ HEMATOLOGY AND ONCOLOGY—PHARMACOLOGY

Heparin

MECHANISM	Lowers the activity of thrombin and factor Xa. Short half-life.
CLINICAL USE	Immediate anticoagulation for pulmonary embolism (PE), acute coronary syndrome, MI, deep venous thrombosis (DVT). Used during pregnancy (does not cross placenta). Follow PTT.
ADVERSE EFFECTS	Bleeding, thrombocytopenia (HIT), osteoporosis, drug-drug interactions. For rapid reversal (antidote), use protamine sulfate (positively charged molecule that binds negatively charged heparin).
NOTES	Low-molecular-weight heparins (eg, enoxaparin, dalteparin) and fondaparinux act more on factor Xa, have better bioavailability, and 2–4 times longer half-life; can be administered subcutaneously and without laboratory monitoring. Not easily reversible. Heparin-induced thrombocytopenia (HIT) —development of IgG antibodies against heparin-bound platelet factor 4 (PF4). Antibody-heparin-PF4 complex activates platelets → thrombosis and thrombocytopenia.

Direct thrombin inhibitors

Bivalirudin (related to hirudin, the anticoagulant used by leeches).

MECHANISM	Directly inhibits activity of free and clot-associated thrombin.
CLINICAL USE	Venous thromboembolism, atrial fibrillation. Can be used in HIT. Does not require lab monitoring.
ADVERSE EFFECTS	Bleeding; no specific reversal agent. Can attempt to use activated prothrombin complex concentrates (PCC) and/or fibrinolytics (eg, tranexamic acid).

Warfarin**MECHANISM**

Interferes with γ -carboxylation of vitamin K–dependent clotting factors II, VII, IX, and X, and proteins C and S. Metabolism affected by polymorphisms in the gene for vitamin K epoxide reductase complex (*VKORC1*). In laboratory assay, has effect on **EX**trinsic pathway and \uparrow **PT**. Long half-life.

The **EX-Pr**esident**T** 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. Proteins C and S have shorter half-lives than clotting factors II, VII, IX, and X, resulting in early transient hypercoagulability with warfarin use. Skin/tissue necrosis within first few days of large doses believed to be due to small vessel microthromboses.

For reversal of warfarin, give vitamin K. For rapid reversal, give fresh frozen plasma. 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.

Heparin vs warfarin

	Heparin	Warfarin
STRUCTURE	Large, anionic, acidic polymer	Small, amphipathic molecule
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 \downarrow the action of IIa (thrombin) and factor Xa	Impairs synthesis of vitamin K–dependent clotting factors II, VII, IX, and X, and anti-clotting proteins C and S
DURATION OF ACTION	Acute (hours)	Chronic (days)
INHIBITS COAGULATION IN VITRO	Yes	No
AGENTS FOR REVERSAL	Protamine sulfate	Vitamin K, fresh frozen plasma
MONITORING	PTT (intrinsic pathway)	PT/INR (extrinsic pathway)
CROSSES PLACENTA	No	Yes (teratogenic)

Direct factor Xa inhibitorsApi**X**aban, rivaro**X**aban.

MECHANISM	Bind to and directly inhibit factor Xa .
CLINICAL USE	Treatment and prophylaxis for DVT and PE (rivaroxaban); stroke prophylaxis in patients with atrial fibrillation. Oral agents do not usually require coagulation monitoring.
ADVERSE EFFECTS	Bleeding (no reversal agent available).

Thrombolytics

Alteplase (tPA), reteplase (rPA), streptokinase, tenecteplase (TNK-tPA).

MECHANISM	Directly or indirectly aid conversion of plasminogen to plasmin, which cleaves thrombin and fibrin clots. ↑ PT, ↑ PTT, no change in platelet count.
CLINICAL USE	Early MI, early ischemic stroke, direct thrombolysis of severe PE.
ADVERSE EFFECTS	Bleeding. Contraindicated in patients with active bleeding, history of intracranial bleeding, recent surgery, known bleeding diatheses, or severe hypertension. Treat toxicity with aminocaproic acid, an inhibitor of fibrinolysis. Fresh frozen plasma and cryoprecipitate can also be used to correct factor deficiencies.

ADP receptor inhibitors

Clopidogrel, prasugrel, ticagrelor (reversible), ticlopidine.

MECHANISM	Inhibit platelet aggregation by irreversibly blocking ADP receptors. Prevent expression of glycoproteins IIb/IIIa on platelet surface.
CLINICAL USE	Acute coronary syndrome; coronary stenting. ↓ incidence or recurrence of thrombotic stroke.
ADVERSE EFFECTS	Neutropenia (ticlopidine). TTP may be seen.

Cilostazol, dipyridamole

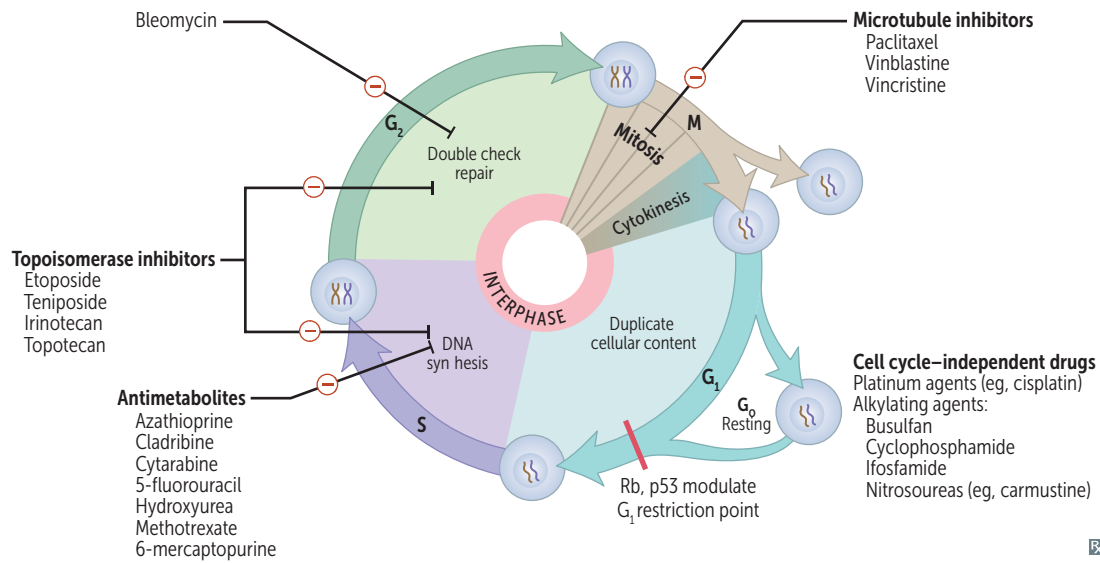
MECHANISM	Phosphodiesterase III inhibitor; ↑ cAMP in platelets, resulting in inhibition of platelet aggregation; vasodilators.
CLINICAL USE	Intermittent claudication, coronary vasodilation, prevention of stroke or TIAs (combined with aspirin), angina prophylaxis.
ADVERSE EFFECTS	Nausea, headache, facial flushing, hypotension, abdominal pain.

Glycoprotein IIb/IIIa inhibitors

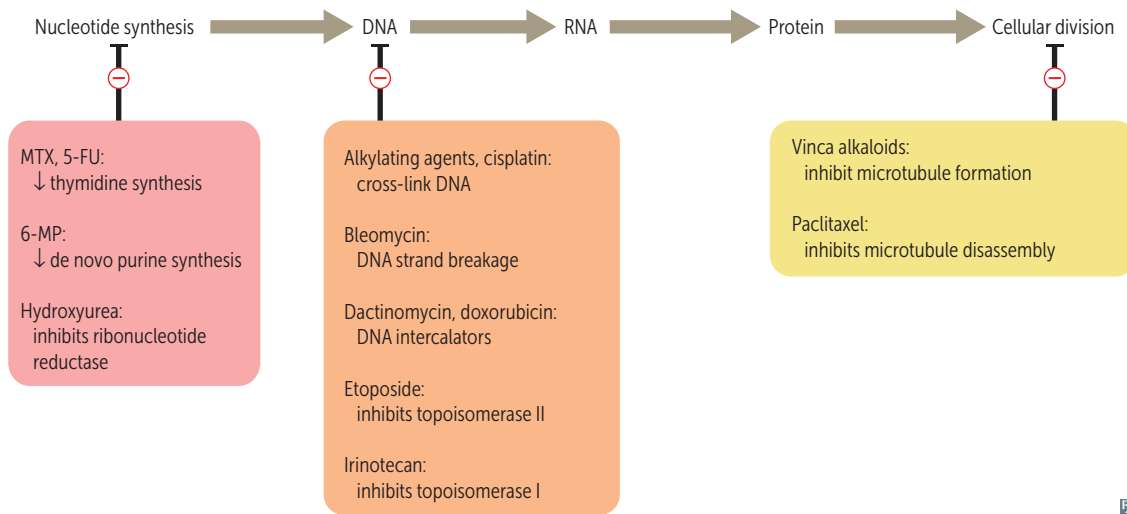
Abciximab, eptifibatide, tirofiban.

MECHANISM	Bind to the glycoprotein receptor IIb/IIIa on activated platelets, preventing aggregation. Abciximab is made from monoclonal antibody Fab fragments.
CLINICAL USE	Unstable angina, percutaneous transluminal coronary angioplasty.
ADVERSE EFFECTS	Bleeding, thrombocytopenia.

Cancer drugs—cell cycle



Cancer drugs—targets



Antimetabolites

DRUG	MECHANISM ^a	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. Azathioprine and 6-MP are metabolized by xanthine oxidase; thus both have ↑ 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 → inhibition of DNA polymerase.	Leukemias (AML), lymphomas.	Myelosuppression with megaloblastic anemia. CYT arabine causes pan CYT openia.
5-fluorouracil	Pyrimidine analog bioactivated to 5-FdUMP, which covalently complexes folic acid. This complex inhibits thymidylate synthase → ↓ dTMP → ↓ DNA synthesis.	Colon cancer, pancreatic cancer, basal cell carcinoma (topical). Effects enhanced with the addition of leucovorin.	Myelosuppression—worsened with the addition of leucovorin (folinic acid).
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 “rescue.” Hepatotoxicity. Mucositis (eg, mouth ulcers). Pulmonary fibrosis.

^aAll are S-phase specific.

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 in DNA.	Wilms tumor, Ewing sarcoma, rhabdomyosarcoma. Used for childhood tumors (“children act out”).	Myelosuppression.
Doxorubicin, daunorubicin	Generate free radicals. Intercalate in DNA → breaks in DNA → ↓ replication.	Solid tumors, leukemias, lymphomas.	Cardiotoxicity (dilated cardiomyopathy), myelosuppression, alopecia. Dexrazoxane (iron chelating agent), used to prevent cardiotoxicity.

Alkylating agents

DRUG	MECHANISM	CLINICAL USE	ADVERSE EFFECTS
Busulfan	Cross-links DNA.	CML. Also 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 N-7. Require bioactivation by liver.	Solid tumors, leukemia, lymphomas.	Myelosuppression; hemorrhagic cystitis, prevented with mesna (thiol group of mesna binds toxic metabolites) or N-acetylcysteine.
Nitrosoureas Carmustine, lomustine, semustine, streptozocin)	Require bioactivation. Cross blood-brain barrier → CNS. Cross-link DNA.	Brain tumors (including glioblastoma multiforme).	CNS toxicity (convulsions, dizziness, ataxia).

Microtubule inhibitors

DRUG	MECHANISM	CLINICAL USE	ADVERSE EFFECTS
Paclitaxel, other taxols	Hyperstabilize polymerized microtubules in M phase so that mitotic spindle cannot break down (anaphase cannot occur).	Ovarian and breast carcinomas.	Myelosuppression, neuropathy, hypersensitivity.
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 (vinblastine) and non-Hodgkin (vincristine) lymphomas.	Vincristine: neurotoxicity (areflexia, peripheral neuritis), constipation (including paralytic ileus).

Cisplatin, carboplatin

MECHANISM	Cross-link DNA.
CLINICAL USE	Testicular, bladder, ovary, and lung carcinomas.
ADVERSE EFFECTS	Nephrotoxicity, peripheral neuropathy, ototoxicity. Prevent nephrotoxicity with amifostine (free radical scavenger) and chloride (saline) diuresis.

Etoposide, teniposide

MECHANISM	E toposide inhibits t opoiso m erase II → ↑ DNA degradation.
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 S ynthesis (S -phase specific).
CLINICAL USE	Melanoma, CML, sickle cell disease (↑ HbF).
ADVERSE EFFECTS	Severe myelosuppression.

Prednisone, prednisolone

MECHANISM	Various; bind intracytoplasmic steroid receptor; alter gene transcription.
CLINICAL USE	Most commonly used glucocorticoids in cancer chemotherapy. Used in CLL, non-Hodgkin lymphoma (part of combination chemotherapy regimen). Also used as immunosuppressants (eg, in autoimmune diseases).
ADVERSE EFFECTS	Cushing-like symptoms; weight gain, central obesity, muscle breakdown, cataracts, acne, osteoporosis, hypertension, peptic ulcers, hyperglycemia, psychosis.

Bevacizumab

MECHANISM	Monoclonal antibody against VEGF. Inhibits angiogenesis.
CLINICAL USE	Solid tumors (colorectal cancer, renal cell carcinoma).
ADVERSE EFFECTS	Hemorrhage, blood clots, and impaired wound healing.

Erlotinib

MECHANISM	EGFR tyrosine kinase inhibitor.
CLINICAL USE	Non-small cell lung carcinoma.
ADVERSE EFFECTS	Rash.

Cetuximab

MECHANISM	Monoclonal antibody against EGFR.
CLINICAL USE	Stage IV colorectal cancer (wild-type <i>KRAS</i>), head and neck cancer.
ADVERSE EFFECTS	Rash, elevated LFTs, diarrhea.

Imatinib

MECHANISM	Tyrosine kinase inhibitor of <i>BCR-ABL</i> (Philadelphia chromosome fusion gene in CML) and <i>c-kit</i> (common in GI stromal tumors).
CLINICAL USE	CML, GI stromal tumors.
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.
ADVERSE EFFECTS	↑ risk of progressive multifocal leukoencephalopathy.

Tamoxifen, raloxifene

MECHANISM	Selective estrogen receptor modulators (SERMs)—receptor antagonists in breast and agonists in bone. Block the binding of estrogen to ER ⊕ cells.
CLINICAL USE	Breast cancer treatment (tamoxifen only) and prevention. Raloxifene also useful to prevent osteoporosis.
ADVERSE EFFECTS	Tamoxifen—partial agonist in endometrium, which ↑ the risk of endometrial cancer; “hot flashes.” Raloxifene—no ↑ in endometrial carcinoma because it is an estrogen receptor antagonist in endometrial tissue. Both ↑ risk of thromboembolic events (eg, DVT, PE).

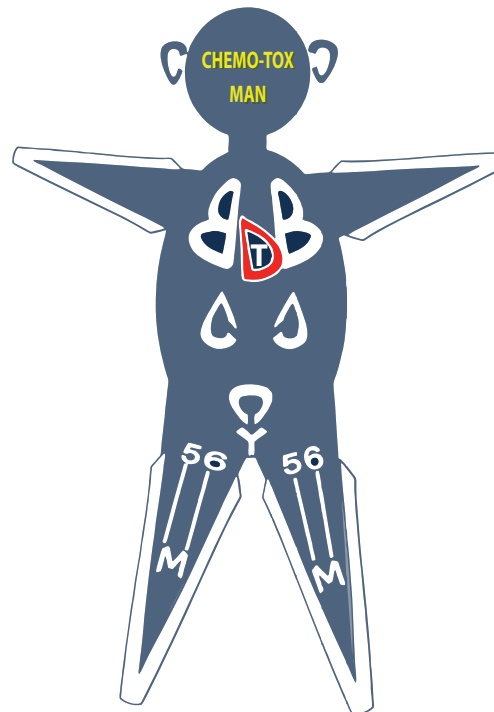
Trastuzumab (Herceptin)

MECHANISM	Monoclonal antibody against HER-2 (<i>c-erbB2</i>), a tyrosine kinase receptor. Helps kill cancer cells that overexpress HER-2, through inhibition of HER2-initiated cellular signaling and antibody-dependent cytotoxicity.
CLINICAL USE	HER-2 ⊕ breast cancer and gastric cancer (tras2zumab).
ADVERSE EFFECTS	Cardiotoxicity. “ Heart ceptin” damages the heart .

Vemurafenib

MECHANISM	Small molecule inhibitor of <i>BRAF</i> oncogene ⊕ melanoma. VE mu RAF -enib is for V600E -mutated BRAF inhibition.
CLINICAL USE	Metastatic melanoma.

Common chemotoxicities



Cisplatin/Carboplatin → ototoxicity (and nephrotoxicity)

Vincristine → peripheral neuropathy

Bleomycin, Busulfan → pulmonary fibrosis

Doxorubicin → cardiotoxicity

Trastuzumab → cardiotoxicity

Cisplatin/Carboplatin → nephrotoxic (and acoustic nerve damage)

CYclophosphamide → hemorrhagic cystitis

5-FU → myelosuppression

6-MP → myelosuppression

Methotrexate → myelosuppression

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.”

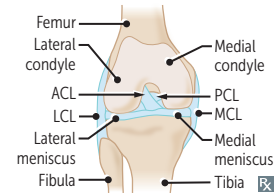
—Leonardo da Vinci

▶ Anatomy and Physiology	416
▶ Pathology	426
▶ Dermatology	437
▶ Pharmacology	446

▶ MUSCULOSKELETAL, SKIN, AND CONNECTIVE TISSUE—ANATOMY AND PHYSIOLOGY

Knee exam

ACL: extends from lateral femoral condyle to anterior tibia.
 PCL: extends from medial femoral condyle to posterior tibia.
 Perform knee exam with patient supine.



TEST

PROCEDURE

Anterior drawer sign

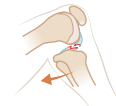
Bending knee at 90° angle, ↑ anterior gliding of tibia due to ACL injury. Lachman test is similar, but at 30° angle.



ACL tear
Anterior drawer sign

Posterior drawer sign

Bending knee at 90° angle, ↑ posterior gliding of tibia due to PCL injury.



PCL tear
Posterior drawer sign

Abnormal passive abduction

Knee either extended or at ~ 30° angle, lateral (valgus) force → medial space widening of tibia → MCL injury.

External rotation



MCL tear

Abnormal passive adduction

Knee either extended or at ~ 30° angle, medial (varus) force → lateral space widening of tibia → LCL injury.

Internal rotation



LCL tear

McMurray test

During flexion and extension of knee with rotation of tibia/foot:

- Pain, “popping” on external rotation → medial meniscal tear
- Pain, “popping” on internal rotation → lateral meniscal tear

External rotation



Medial tear

Internal rotation

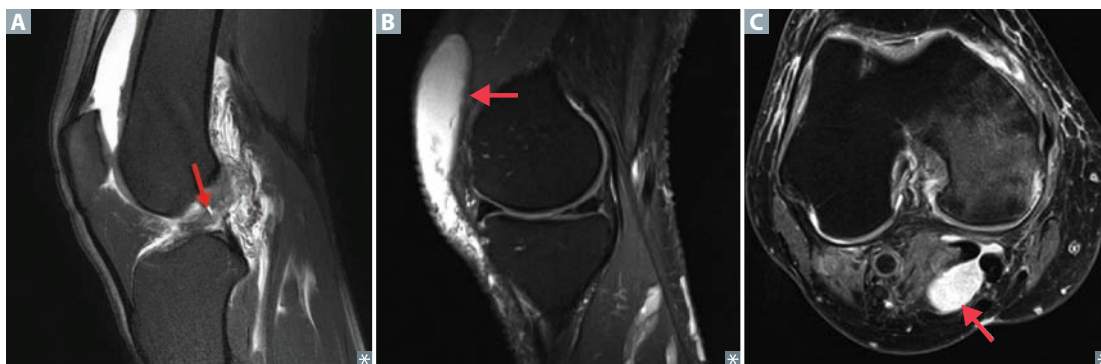
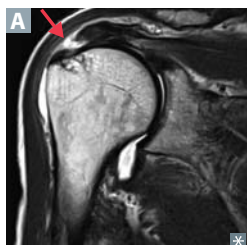


Lateral tear

Rx

Common knee conditions

“Unhappy triad”	Common injury in contact sports due to lateral force applied to a planted leg. Classically, consists of damage to the ACL A , MCL, and medial meniscus (attached to MCL); however, lateral meniscus injury is more common. Presents with acute knee pain and signs of joint injury/instability.
Prepatellar bursitis	Inflammation of knee’s largest sac of synovial fluid B . Can be caused by repeated trauma or pressure from excessive kneeling.
Baker cyst	Popliteal fluid collection in gastrocnemius-semimembranous bursa C commonly communicating with synovial space and related to chronic joint disease.

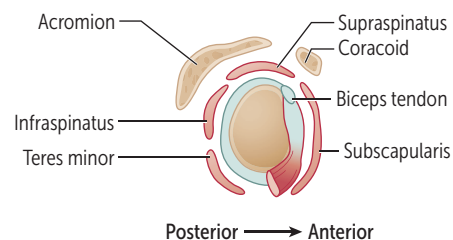
**Rotator cuff muscles**

Shoulder muscles that form the rotator cuff:

- **S**upraspinatus (suprascapular nerve)—abducts arm initially (before the action of the deltoid); most common rotator cuff injury **A** (trauma or degeneration and impingement → tendinopathy or tear), assessed by “empty/full can” test.
- **I**nfraspinatus (suprascapular nerve)—laterally rotates arm; pitching injury.
- **t**eres minor (axillary nerve)—adducts and laterally rotates arm.
- **S**ubscapularis (upper and lower subscapular nerves)—medially rotates and adducts arm.

Innervated primarily by C5-C6.

SItS (small t is for teres **minor**).

**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.

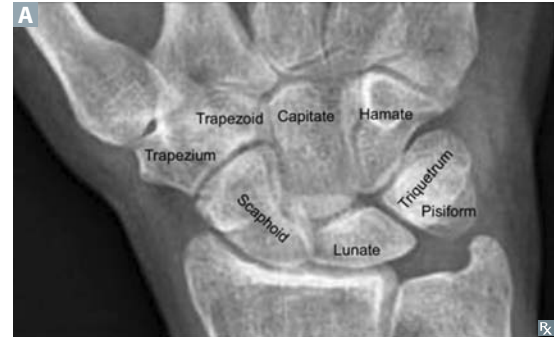
Wrist bones

Scaphoid, Lunate, Triquetrum, Pisiform, Hamate, Capitate, Trapezoid, Trapezium **A**. (So Long To Pinky, Here Comes The Thumb).

Scaphoid (palpated in anatomic snuff box) is the most commonly fractured carpal bone (typically from a fall on an outstretched hand) and is prone to avascular necrosis owing to retrograde blood supply.

Dislocation of lunate may cause acute carpal tunnel syndrome.

A fall on an outstretched hand that damages the hook of the hamate can cause ulnar nerve injury.

**Carpal tunnel syndrome**

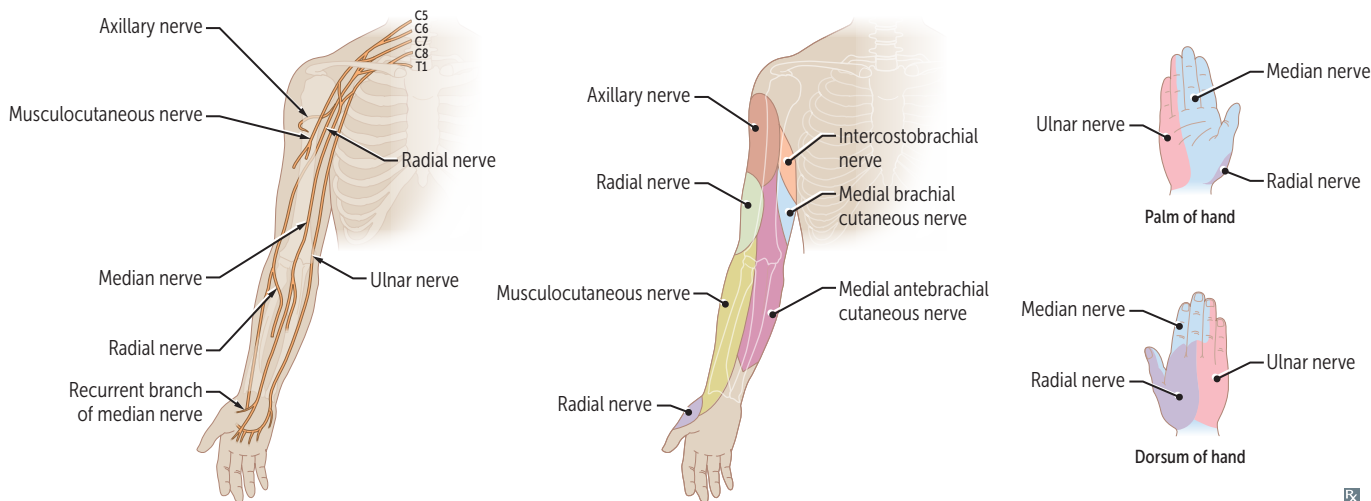
Entrapment of median nerve in carpal tunnel; nerve compression → paresthesia, pain, and numbness in distribution of median nerve (thenar eminence atrophies but sensation spared, because palmar cutaneous branch enters the hand external to carpal tunnel). Associated with pregnancy, rheumatoid arthritis, hypothyroidism, diabetes, dialysis-related amyloidosis; may be associated with repetitive use.

Guyon canal syndrome

Compression of ulnar nerve at wrist or hand. Classically seen in cyclists due to pressure from handlebars.

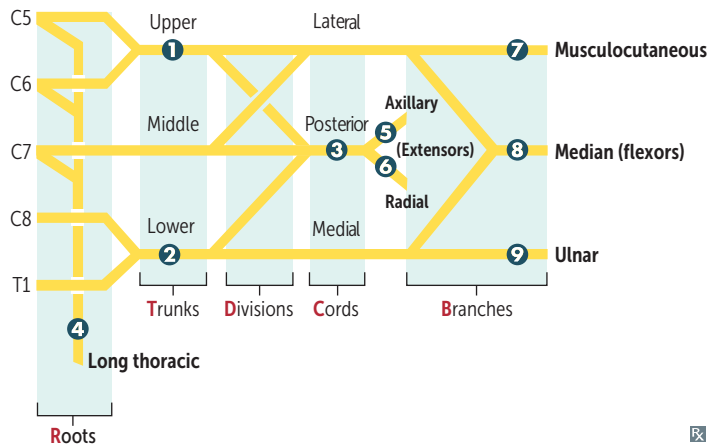
Upper extremity nerves

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 degrees) Loss of sensation over deltoid muscle and lateral arm
Musculocutaneous (C5-C7)	Upper trunk compression	Loss of forearm flexion and supination Loss of sensation over lateral forearm
Radial (C5-T1)	Midshaft fracture of humerus; compression of axilla, eg, due to crutches or sleeping with arm over chair (“Saturday night palsy”)	Wrist drop: loss of elbow, wrist, and finger extension ↓ 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); carpal tunnel syndrome and wrist laceration (distal lesion)	“Ape hand” and “Pope’s blessing” Loss of wrist flexion, flexion of lateral fingers, thumb opposition, lumbricals of 2nd and 3rd digits Loss of sensation over thenar eminence and dorsal and palmar aspects of lateral 3½ fingers with proximal lesion Tinel sign (tingling on percussion) in carpal tunnel syndrome
Ulnar (C8-T1)	Fracture of medial epicondyle of humerus “funny bone” (proximal lesion); fractured hook of hamate (distal lesion)	“Ulnar claw” on digit extension Radial deviation of wrist upon flexion (proximal lesion) Loss of wrist flexion, flexion of medial fingers, abduction and adduction of fingers (interossei), 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

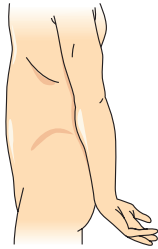




Brachial plexus lesions

- 1 Erb palsy ("waiter's tip")
- 2 Claw hand (Klumpke palsy)
- 3 Wrist drop
- 4 Winged scapula
- 5 Deltoid paralysis
- 6 "Saturday night palsy" (wrist drop)
- 7 Difficulty flexing elbow, variable sensory loss
- 8 Decreased thumb function, "Pope's blessing"
- 9 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 upper ("Erb-er") trunk: C5-C6 roots	Infants—lateral traction on neck during delivery Adults—trauma	Deltoid, supraspinatus Infraspinatus Biceps brachii	Abduction (arm hangs by side) Lateral rotation (arm medially rotated) Flexion, supination (arm extended and pronated)	
Klumpke palsy	Traction or tear of lower trunk : C8-T1 root	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	
Thoracic outlet syndrome	Compression of lower trunk and subclavian vessels	Cervical rib, Pancoast tumor	Same as Klumpke palsy	Atrophy of intrinsic hand muscles; ischemia, pain, and edema due to vascular compression	
Winged scapula	Lesion of long thoracic nerve	Axillary node dissection after mastectomy, stab wounds	Serratus anterior	Inability to anchor scapula to thoracic cage → cannot abduct arm above horizontal position	

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).

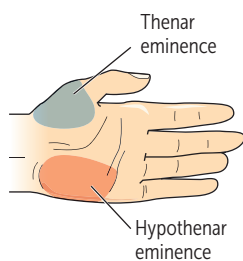
“Clawing”—seen best with **distal** lesions of median or ulnar nerves. Remaining extrinsic flexors of the digits exaggerate the loss of the lumbricals → fingers extend at MCP, flex at DIP and PIP joints.

Deficits less pronounced in **proximal** lesions; deficits present during voluntary flexion of the digits.

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
SIGN	“Ulnar claw”	“Pope’s blessing”	“Median claw”	“OK gesture” (with digits 1–3 flexed)

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.

Hand muscles



Thenar (median)—**O**pponens pollicis, **A**bductor pollicis brevis, **F**lexor pollicis brevis, superficial head (deep head by ulnar nerve).

Hypothenar (ulnar)—**O**pponens digiti minimi, **A**bductor digiti minimi, **F**lexor digiti minimi brevis.

Dorsal interossei—abduct the fingers.

Palmar interossei—adduct the fingers.

Lumbricals—flex at the MCP joint, extend PIP and DIP joints.

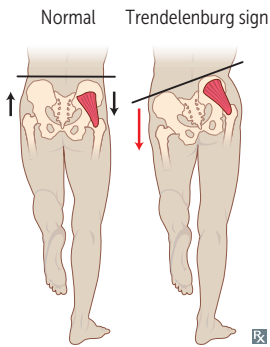
Both groups perform the same functions: **O**ppose, **A**bduct, and **F**lex (**OAF**).

DAB = **D**orsals **AB**duct.

PAD = **P**almars **AD**duct.

Lower extremity nerves

NERVE	CAUSE OF INJURY	PRESENTATION
Obturator (L2–L4)	Pelvic surgery	↓ thigh sensation (medial) and ↓ adduction.
Femoral (L2–L4)	Pelvic fracture	↓ thigh flexion and leg extension.
Common peroneal (L4–S2)	Trauma or compression of lateral aspect of leg, fibular neck fracture	Foot drop—inverted and plantarflexed at rest, loss of eversion and dorsiflexion. “Steppage gait.” Loss of sensation on dorsum of foot.
Tibial (L4–S3)	Knee trauma, Baker cyst (proximal lesion); tarsal tunnel syndrome (distal lesion)	Inability to curl toes and loss of sensation on sole of foot. In proximal lesions, foot everted at rest with loss of inversion and plantarflexion.
Superior gluteal (L4–S1)	Iatrogenic injury during intramuscular injection to upper medial gluteal 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)	Posterior hip dislocation	Difficulty climbing stairs, rising from seated position. Loss of hip extension.



Superior gluteal nerve innervates gluteus medius, gluteus minimus, and tensor fascia latae. Inferior gluteal nerve innervates gluteus maximus.

PED = **P**eroneal **E**verts and **D**orsiflexes; if injured, foot drop **PED**.

TIP = **T**ibial **I**nverts and **P**lantarflexes; if injured, can't stand on **TIP**toes.

Sciatic nerve (L4–S3) innervates posterior thigh, splits into common peroneal and tibial nerves.

Pudendal nerve (S2–S4) innervates perineum. Can be blocked with local anesthetic during childbirth using the ischial spine as a landmark for injection.

Choose superolateral gluteal quadrant as intramuscular injection site to avoid nerve injury.

Signs of lumbosacral radiculopathy

Paresthesias and weakness in distribution of specific lumbar or sacral spinal nerves. Often due to intervertebral disc herniation in which the nerve associated with the inferior vertebral body is impinged (eg, herniation of L3–L4 disc affects the L4 spinal nerve).

Intervertebral discs generally herniate posterolaterally, due to the thin posterior longitudinal ligament and thicker anterior longitudinal ligament along the midline of the vertebral bodies.

DISC LEVEL

L3–L4

L4–L5

L5–S1

FINDINGS

Weakness of knee extension, ↓ patellar reflex

Weakness of dorsiflexion, difficulty in heel-walking

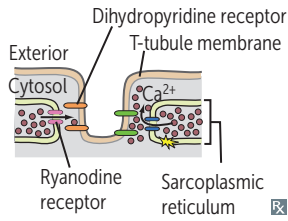
Weakness of plantarflexion, difficulty in toe-walking, ↓ Achilles reflex

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

Muscle conduction to contraction

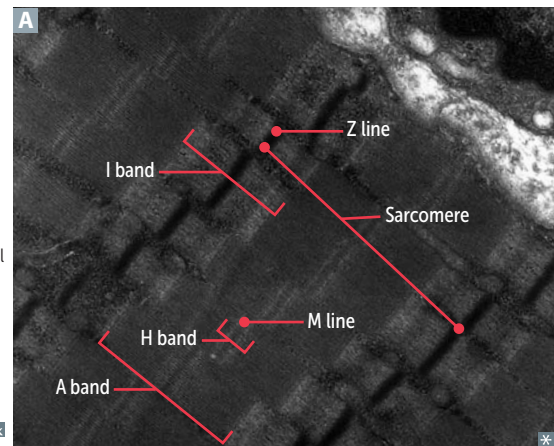
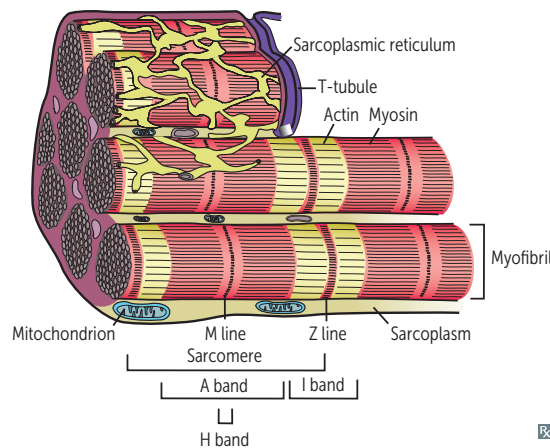


T-tubules are extensions of plasma membrane juxtaposed with terminal cisternae of the sarcoplasmic reticulum.

In skeletal muscle, 1 T-tubule + 2 terminal cisternae = triad.

In cardiac muscle, 1 T-tubule + 1 terminal cisterna = dyad.

1. Action potential depolarization opens presynaptic voltage-gated Ca²⁺ channels, inducing neurotransmitter release.
2. Postsynaptic ligand binding leads to muscle cell depolarization in the motor end plate.
3. Depolarization travels along muscle cell and down the T-tubule.
4. Depolarization of the voltage-sensitive dihydropyridine receptor, mechanically coupled to the ryanodine receptor on the sarcoplasmic reticulum, induces a conformational change in both receptors, causing Ca²⁺ release from sarcoplasmic reticulum.
5. Released Ca²⁺ binds to troponin C, causing a conformational change that moves tropomyosin out of the myosin-binding groove on actin filaments.
6. Myosin releases bound ADP and P_i → displacement of myosin on the actin filament (power stroke). Contraction results in shortening of **H** and **I** bands and between **Z** lines (**HIZ** shrinkage), but the **A** band remains the same length (**A** band is **A**lways the same length) **A**.
7. Binding of a new ATP molecule causes detachment of myosin head from actin filament. Hydrolysis of bound ATP → ADP, myosin head adopts high-energy position (“cocked”) for the next contraction cycle.



Types of muscle fibers

Type 1 muscle

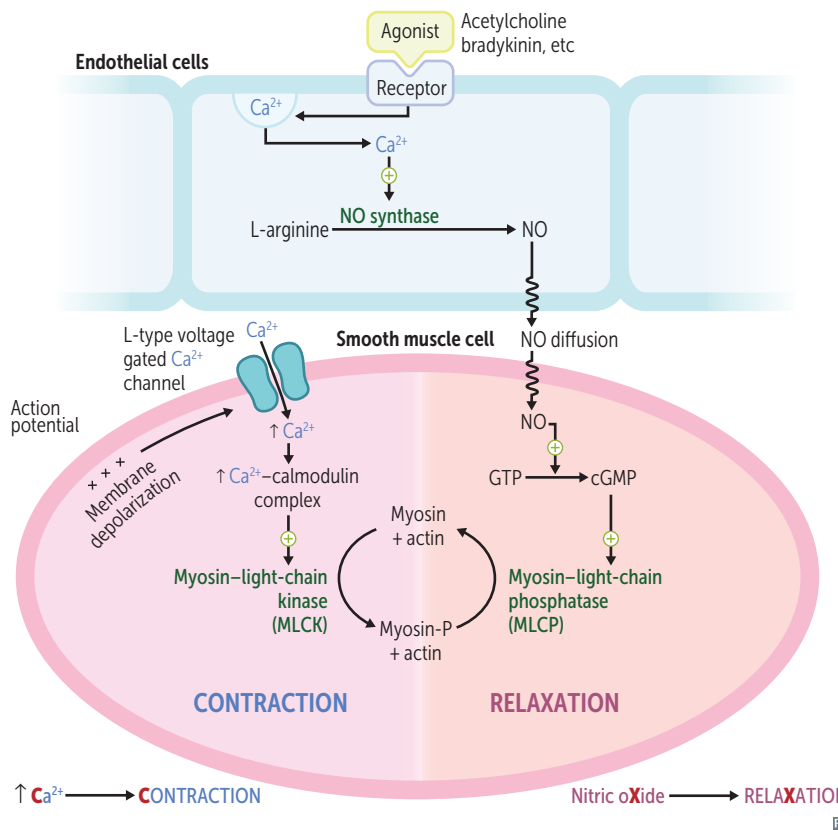
Slow twitch; **red** fibers resulting from ↑ mitochondria and myoglobin concentration (↑ **o**xidative phosphorylation) → sustained contraction. Proportion ↑ after endurance training.

Think “**1** **s**low **r**ed **o**x.”

Type 2 muscle

Fast twitch; **white** fibers resulting from ↓ mitochondria and myoglobin concentration (↑ **a**naerobic glycolysis). Proportion ↑ after weight/resistance training.

Smooth muscle contraction



Bone formation

Endochondral ossification

Bones of axial skeleton, appendicular skeleton, and base of skull. Cartilaginous model of bone is 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.

Membranous ossification

Bones of calvarium and facial bones. Woven bone formed directly without cartilage. Later remodeled to lamellar bone.

Cell biology of bone

Osteoblast

Builds **b**one by secreting collagen and catalyzing mineralization in alkaline environment via ALP. Differentiates from mesenchymal stem cells in periosteum.

Osteoclast

Dissolves bone by secreting H⁺ and collagenases. Differentiates from a fusion of monocyte/macrophage lineage precursors.

Parathyroid hormone

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).

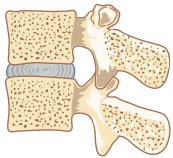
Estrogen

Inhibits apoptosis in bone-forming osteoblasts and induces apoptosis in bone-resorbing osteoclasts. Estrogen deficiency (surgical or postmenopausal), excess cycles of remodeling, and bone resorption lead to osteoporosis.

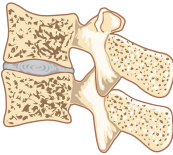
► MUSCULOSKELETAL, SKIN, AND CONNECTIVE TISSUE—PATHOLOGY

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). Most common cause of dwarfism.

Osteoporosis

Normal vertebrae



Mild compression fracture

Trabecular (spongy) and cortical bone lose mass and interconnections despite normal bone mineralization and lab values (serum Ca^{2+} and PO_4^{3-}).

Most commonly due to ↑ bone resorption related to ↓ estrogen levels and old age.

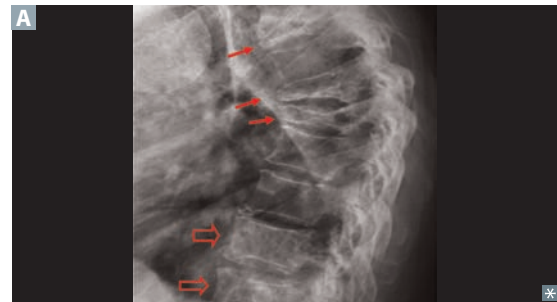
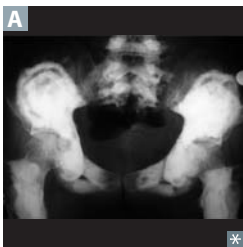
Can be secondary to drugs (eg, steroids, alcohol, anticonvulsants, anticoagulants, thyroid replacement therapy) or other medical conditions (eg, hyperparathyroidism, hyperthyroidism, multiple myeloma, malabsorption syndromes).

Diagnosed by a bone mineral density scan (dual-energy x-ray absorptiometry) with a T-score of ≤ -2.5 or by a fragility fracture of hip or vertebra.

Prophylaxis: regular weight-bearing exercise and adequate Ca^{2+} and vitamin D intake throughout adulthood.

Treatment: bisphosphonates, teriparatide, SERMs, rarely calcitonin; denosumab (monoclonal antibody against RANKL).

Can lead to **vertebral compression fractures** (A), small arrows; large arrows show normal-for-age vertebral body height for comparison—acute back pain, loss of height, kyphosis. Also can present with fractures of femoral neck, distal radius (Colles fracture).

**Osteopetrosis (marble bone disease)**

Failure of normal bone resorption due to defective osteoclasts → thickened, dense bones that are prone to fracture. Bone fills marrow space → pancytopenia, extramedullary hematopoiesis. Mutations (eg, carbonic anhydrase II) impair ability of osteoclast to generate acidic environment necessary for bone resorption. X-rays show bone-in-bone (“stone” bone) appearance (A). Can result in cranial nerve impingement and palsies as a result of narrowed foramina. Bone marrow transplant is potentially curative as osteoclasts are derived from monocytes.

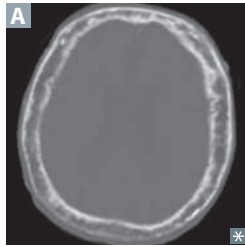
Osteomalacia/rickets

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 bow legs **A**, bead-like costochondral junctions (rachitic rosary), craniotabes (soft skull).

↓ vitamin D → ↓ serum Ca^{2+} → ↑ PTH secretion → ↓ serum PO_4^{3-} .

Hyperactivity of osteoblasts → ↑ ALP.

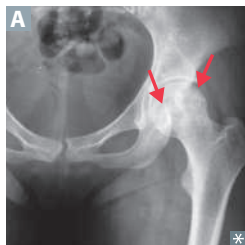
**Paget disease of bone (osteitis deformans)**

Common, localized disorder of bone remodeling caused by ↑ osteoclastic activity followed by ↑ osteoblastic activity that forms poor-quality bone. Serum Ca^{2+} , phosphorus, and PTH levels are normal. ↑ ALP. Mosaic pattern of woven and lamellar bone (osteocytes with lacunae in chaotic juxtapositions); long bone chalk-stick fractures. ↑ blood flow from ↑ arteriovenous shunts may cause high-output heart failure. ↑ risk of osteogenic sarcoma.

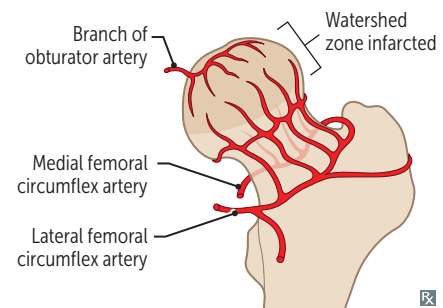
Hat size can be increased due to skull thickening **A**; hearing loss is common due to auditory foramen narrowing.

Stages of Paget disease:

- Lytic—osteoclasts
- Mixed—osteoclasts + osteoblasts
- Sclerotic—osteoblasts
- Quiescent—minimal osteoclast/osteoblast activity

Osteonecrosis (avascular necrosis)

Infarction of bone and marrow, usually very painful. Most common site is femoral head **A** (due to insufficiency of medial circumflex femoral artery). Causes include **C**orticosteroids, **A**lcoholism, **S**ickle cell disease, **T**rauma, “the **B**ends” (caisson/decompression disease), **L**Egg-Calvé-Perthes disease (idiopathic), **G**aucher disease, **S**lipped capital femoral epiphysis—**C**AST **B**ent **L**EGS.

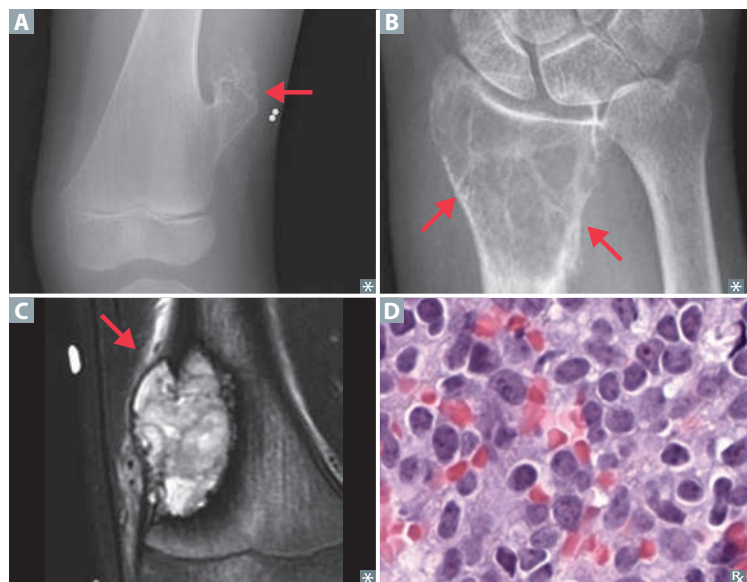
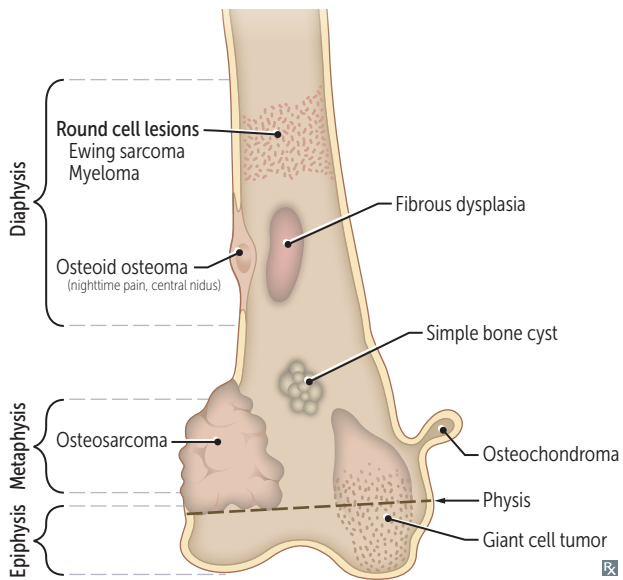


Lab values in bone disorders

DISORDER	SERUM Ca ²⁺	PO ₄ ³⁻	ALP	PTH	COMMENTS
Osteoporosis	—	—	—	—	↓ bone mass
Osteopetrosis	—/↓	—	—	—	Dense, brittle bones. Ca ²⁺ ↓ in severe, malignant disease
Paget disease of bone	—	—	↑	—	Abnormal “mosaic” bone architecture
Osteitis fibrosa cystica					“Brown tumors” due to fibrous replacement of bone, subperiosteal thinning
Primary hyperparathyroidism	↑	↓	↑	↑	Idiopathic or parathyroid hyperplasia, adenoma, carcinoma
Secondary hyperparathyroidism	↓	↑	↑	↑	Often as compensation for CKD (↓ PO ₄ ³⁻ excretion and production of activated vitamin D)
Osteomalacia/rickets	↓	↓	↑	↑	Soft bones; vitamin D deficiency also causes 2° hyperparathyroidism
Hypervitaminosis D	↑	↑	—	↓	Caused by oversupplementation or granulomatous disease (eg, sarcoidosis)

Primary bone tumors

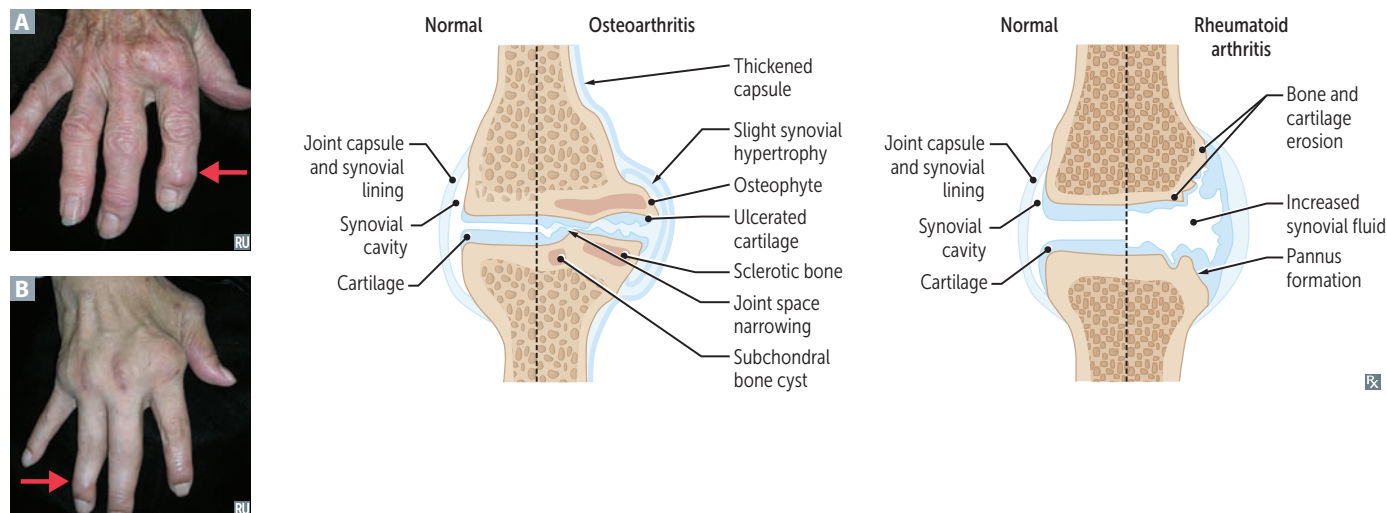
TUMOR TYPE	EPIDEMIOLOGY/LOCATION	CHARACTERISTICS
Benign tumors		
Osteochondroma	Most common benign bone tumor. Males < 25 years old.	Bony exostosis with cartilaginous (chondroid) cap A . Rarely transforms to chondrosarcoma.
Giant cell tumor	20–40 years old. Epiphyseal end of long bones. Often around knee. “Osteoclastoma.”	Locally aggressive benign tumor. “Soap bubble” appearance on x-ray B . Multinucleated giant cells.
Malignant tumors		
Osteosarcoma (osteogenic sarcoma)	2nd most common 1° malignant bone tumor (after multiple myeloma). Bimodal distribution: 10–20 years old (1°), > 65 (2°). Predisposing factors: Paget disease of bone, bone infarcts, radiation, familial retinoblastoma, Li-Fraumeni syndrome (germline <i>p53</i> mutation). Metaphysis of long bones, often around knee C .	Codman triangle (from elevation of periosteum) or sunburst pattern on x-ray. Aggressive. Treat with surgical en bloc resection (with limb salvage) and chemotherapy.
Ewing sarcoma	Boys < 15 years old. Commonly appears in diaphysis of long bones, pelvis, scapula, ribs.	Anaplastic small blue cell malignant tumor D . Extremely aggressive with early metastases, but responsive to chemotherapy. “Onion skin” periosteal reaction in bone. Associated with t(11;22) translocation causing fusion protein EWS-FLI 1. 11 + 22 = 33 (Patrick Ewing’s jersey number).



Osteoarthritis and rheumatoid arthritis

	Osteoarthritis	Rheumatoid arthritis
PATHOGENESIS	Mechanical—wear and tear destroys articular cartilage (“degenerative joint disease”). Chondrocytes mediate degradation and inadequate repair.	Autoimmune—inflammatory cytokines and cells induce pannus (proliferative granulation tissue) formation, which erodes articular cartilage and bone.
PREDISPOSING FACTORS	Age, female, obesity, joint trauma.	Female, HLA-DR4, smoking, silica exposure. ⊕ rheumatoid factor (anti-IgG antibody; 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 non-inflammatory (WBC < 2000/mm ³). Involves DIP (Heberden nodes A) and PIP (Bouchard nodes), and 1st CMC; not MCP.	Erosions, juxtaarticular osteopenia, joint space narrowing, soft tissue swelling, subchondral cysts. Deformities include subluxation, fingers with ulnar deviation, swan neck B , and boutonniere. Synovial fluid inflammatory (WBC > 2000/mm ³). Involves MCP, PIP, wrist; not DIP or 1st CMC.
TREATMENT	Acetaminophen, NSAIDs, intra-articular glucocorticoids.	NSAIDs, glucocorticoids, disease-modifying agents (methotrexate, sulfasalazine, hydroxychloroquine, leflunomide), biologic agents (eg, TNF- α inhibitors).

*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.



Gout**FINDINGS**

Acute inflammatory monoarthritis caused by precipitation of monosodium urate crystals in joints **A**. More common in males. Associated with hyperuricemia, which can be caused by:

- Underexcretion of uric acid (90% of patients)—largely idiopathic; 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.

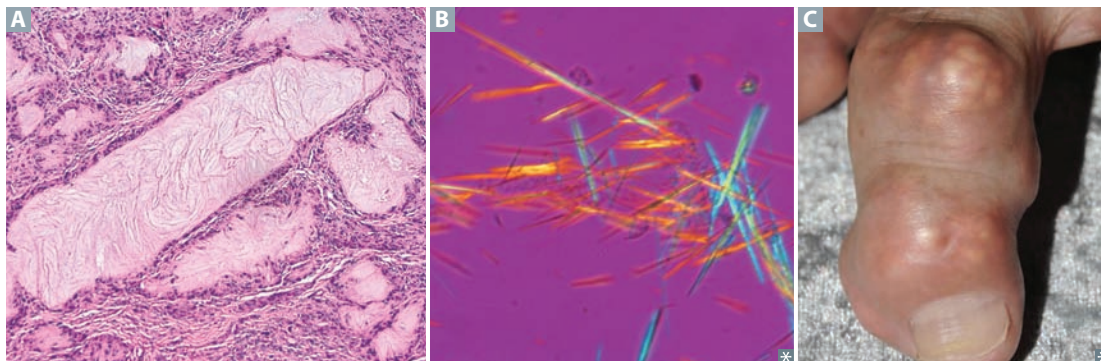
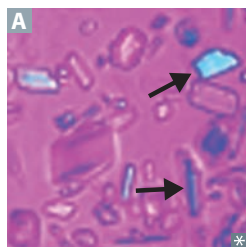
Crystals are needle shaped and ⊖ birefringent under polarized light (yellow under parallel light, blue under perpendicular light **B**).

SYMPTOMS

Asymmetric joint distribution. Joint is swollen, red, and painful. Classic manifestation is painful MTP joint of big toe (podagra). Tophus formation **C** (often on external ear, olecranon bursa, or Achilles tendon). Acute attack tends to occur after a large meal 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**


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.

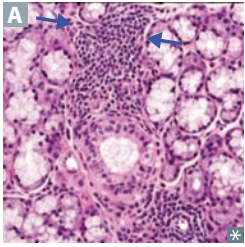
Pain and swelling with acute inflammation (pseudogout) and/or chronic degeneration (pseudo-osteoarthritis). Knee most commonly affected joint.

Chondrocalcinosis (cartilage calcification) on x-ray.

Crystals are rhomboid and weakly ⊕ birefringent under polarized light (blue when parallel to light) **A**.

Acute treatment: NSAIDs, colchicine, glucocorticoids.

Prophylaxis: colchicine.

Sjögren syndrome

Autoimmune disorder characterized by destruction of exocrine glands (especially lacrimal and salivary) by lymphocytic infiltrates **A**. Predominantly affects females 40–60 years old.

Findings:

- Inflammatory joint pain
- Keratoconjunctivitis sicca (↓ tear production and subsequent corneal damage)
- Xerostomia (↓ saliva production)
- Presence of antinuclear antibodies: SS-A (anti-Ro) and/or SS-B (anti-La)
- Bilateral parotid enlargement

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).

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/mm³).

Gonococcal arthritis—STI that presents as either purulent arthritis (eg, knee) or triad of polyarthralgias, tenosynovitis (eg, hand), dermatitis (eg, pustules).

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 1/3 of patients with psoriasis.

Ankylosing spondylitis

Symmetric involvement of spine and sacroiliac joints → ankylosis (joint fusion), uveitis, aortic regurgitation.

Bamboo spine (vertebral fusion) **C**. More common in males.

Inflammatory bowel disease

Crohn disease and ulcerative colitis are often associated with spondyloarthritis.

Reactive arthritis

Formerly known as Reiter syndrome.

Classic triad:

- **Conjunctivitis**
- **Urethritis**
- **Arthritis**

“Can’t see, can’t pee, can’t bend my knee.”

Post-GI (*Shigella*, *Salmonella*, *Yersinia*, *Campylobacter*) or *Chlamydia* infections.



Systemic lupus erythematosus

SYMPTOMS



Classic presentation: rash, joint pain, and fever, most commonly in a female of reproductive age and African-American descent.

Libman-Sacks Endocarditis—nonbacterial, verrucous thrombi usually on mitral or aortic valve (**LSE** in **SLE**).

Lupus nephritis (glomerular deposition of anti-DNA immune complexes) can be nephritic or nephrotic (hematuria or proteinuria).

Most common and severe type is diffuse proliferative.

Common causes of death in SLE:

- Cardiovascular disease
- Infections
- Renal disease

RASH OR PAIN:

Rash (malar **A** or discoid)

Arthritis (nonerosive)

Serositis

Hematologic disorders (eg, cytopenias)

Oral/nasopharyngeal ulcers

Renal disease

Photosensitivity

Antinuclear antibodies

Immunologic disorder (anti-dsDNA, anti-Sm, antiphospholipid)

Neurologic disorders (eg, seizures, psychosis)

FINDINGS

Antinuclear antibodies (ANA)

Sensitive, not specific

Anti-dsDNA antibodies

Specific, poor prognosis (renal disease)

Anti-Smith antibodies

Specific, not prognostic (directed against snRNPs)

Antihistone antibodies

Sensitive for drug-induced lupus (eg, hydralazine, procainamide)

↓ C3, C4, and CH₅₀ due to immune complex formation.

TREATMENT

NSAIDs, steroids, immunosuppressants, hydroxychloroquine.

Antiphospholipid syndrome

1° or 2° autoimmune disorder (most commonly in SLE).

Diagnose based on clinical criteria including history of thrombosis (arterial or venous) or spontaneous abortion along with laboratory findings of lupus anticoagulant, anticardiolipin, anti-β₂ glycoprotein antibodies.

Treat with systemic anticoagulation.

Anticardiolipin antibodies and lupus anticoagulant can cause false-positive VDRL/RPR and prolonged PTT.

Mixed connective tissue disease

Features of SLE, systemic sclerosis, and/or polymyositis. Associated with anti-U1 RNP antibodies (speckled ANA).

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. Findings on CXR of bilateral adenopathy and coarse reticular opacities **B**; CT of the chest better demonstrates the extensive hilar and mediastinal adenopathy **C**.

Associated with restrictive lung disease (interstitial fibrosis), erythema nodosum, lupus pernio (skin lesions on face resembling lupus), Bell palsy, epithelioid granulomas containing microscopic Schaumann and asteroid bodies, uveitis, hypercalcemia (due to ↑ 1 α -hydroxylase–mediated vitamin D activation in macrophages).

Treatment: steroids (if symptomatic).

**Polymyalgia rheumatica**

SYMPTOMS

Pain and stiffness in shoulders and 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.

Fibromyalgia

Most commonly seen in females 20–50 years old. Chronic, widespread musculoskeletal pain associated with stiffness, paresthesias, poor sleep, fatigue, cognitive disturbance (“fibro fog”).

Treatment: regular exercise, antidepressants (TCAs, SNRIs), anticonvulsants.

**Polymyositis/
dermatomyositis**

↑ CK, ⊕ ANA, ⊕ anti-Jo-1, ⊕ anti-SRP, ⊕ anti-Mi-2 antibodies. Treatment: steroids followed by long-term immunosuppressant therapy (eg, methotrexate).

Polymyositis

Progressive symmetric proximal muscle weakness, characterized by endomysial inflammation with CD8+ T cells. Most often involves shoulders.

Dermatomyositis

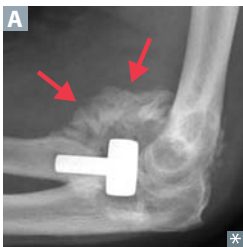
Similar to polymyositis, but also involves malar rash (similar to SLE), Gottron papules **A**, heliotrope (erythematous periorbital) rash **B**, “shawl and face” rash **C**, “mechanic’s hands.” ↑ risk of occult malignancy. Perimysial inflammation and atrophy with CD4+ T cells.

**Neuromuscular junction diseases**

	Myasthenia gravis	Lambert-Eaton myasthenic syndrome
FREQUENCY	Most common NMJ disorder	Uncommon
PATHOPHYSIOLOGY	Autoantibodies to postsynaptic ACh receptor	Autoantibodies to presynaptic Ca ²⁺ channel → ↓ ACh release
CLINICAL	Ptosis, diplopia, weakness Worsens with muscle use	Proximal muscle weakness, autonomic symptoms (dry mouth, impotence) Improves with muscle use
ASSOCIATED WITH	Thymoma, thymic hyperplasia	Small cell lung cancer
AChE INHIBITOR ADMINISTRATION	Reverses symptoms (edrophonium to diagnose, pyridostigmine to treat)	Minimal effect

Myositis ossificans

Heterotopic ossification of skeletal muscle following muscular trauma **A**. Most often seen in upper or lower extremity. May present as suspicious “mass” at site of known trauma or as incidental finding on radiography.



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**. Also sclerosis of renal, pulmonary (most common cause of death), cardiovascular, GI systems. 75% female. 2 major types:

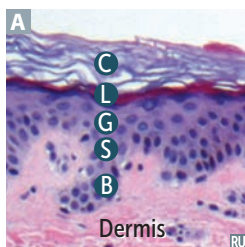
- **Diffuse scleroderma**—widespread skin involvement, rapid progression, early visceral involvement. Associated with anti-Scl-70 antibody (anti-DNA topoisomerase I antibody).
- **Limited scleroderma**—limited skin involvement confined to fingers and face. Also with **CREST** syndrome: **C**alcinosis **C**, **R**aynaud phenomenon, **E**sophageal dysmotility, **S**clerodactyly, and **T**elangiectasia. More benign clinical course. Associated with anti-centromere antibody.

**Raynaud phenomenon**

↓ blood flow to the 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 **A** 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 (limited form of systemic sclerosis) syndrome. Digital ulceration (critical ischemia) seen in 2° Raynaud syndrome. Treat with Ca²⁺ channel blockers.



▶ MUSCULOSKELETAL, SKIN, AND CONNECTIVE TISSUE—DERMATOLOGY

Skin layers

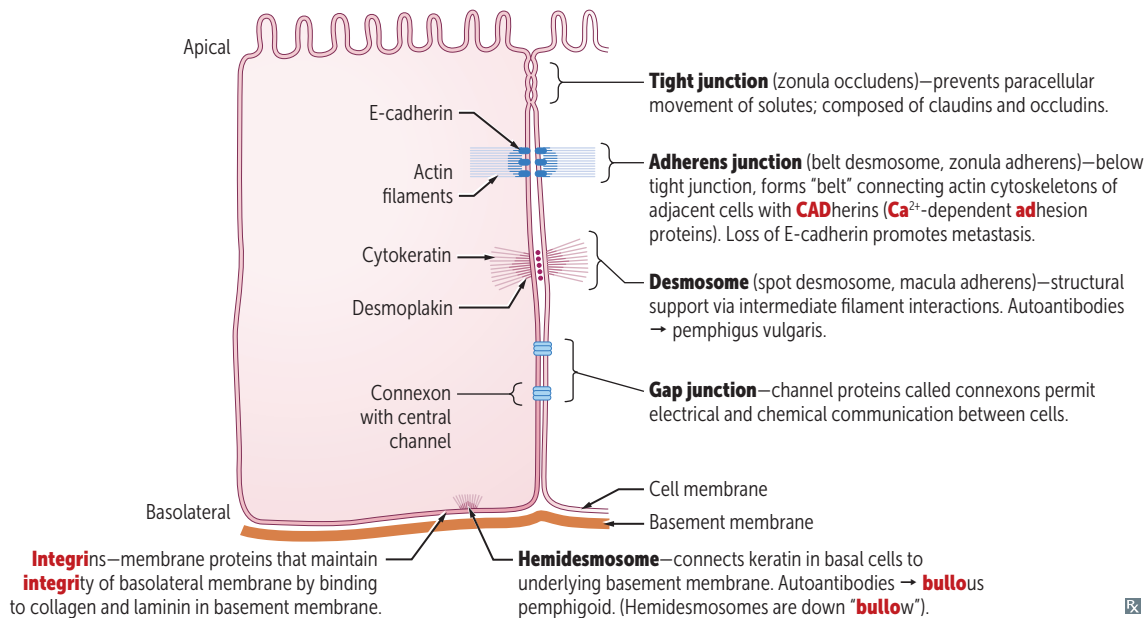
Skin has 3 layers: epidermis, dermis, subcutaneous fat (hypodermis, subcutis).

Epidermis layers from surface to base **A**:

- Stratum **C**orneum (keratin)
- Stratum **L**ucidum
- Stratum **G**ranulosum
- Stratum **S**pinosum (desmosomes)
- Stratum **B**asale (stem cell site)

Californians **L**ike **G**irls in **S**tring **B**ikinis.

Epithelial cell junctions



Dermatologic macroscopic terms (morphology)

LESION	CHARACTERISTICS	EXAMPLES
Macule	Flat lesion with well-circumscribed change in skin color < 1 cm	Freckle, labial macule A
Patch	Macule > 1 cm	Large birthmark (congenital nevus) B
Papule	Elevated solid skin lesion < 1 cm	Mole (nevus) C , acne
Plaque	Papule > 1 cm	Psoriasis D
Vesicle	Small fluid-containing blister < 1 cm	Chickenpox (varicella), shingles (zoster) E
Bulla	Large fluid-containing blister > 1 cm	Bullous pemphigoid F
Pustule	Vesicle containing pus	Pustular psoriasis G
Wheal	Transient smooth papule or plaque	Hives (urticaria) H
Scale	Flaking off of stratum corneum	Eczema, psoriasis, SCC I
Crust	Dry exudate	Impetigo J



Dermatologic microscopic terms

LESION	CHARACTERISTICS	EXAMPLES
Hyperkeratosis	↑ thickness of stratum corneum	Psoriasis, calluses
Parakeratosis	Hyperkeratosis with retention of nuclei in stratum corneum	Psoriasis
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

Pigmented skin disorders

Albinism	Normal melanocyte number with ↓ melanin production A due to ↓ tyrosinase activity or defective tyrosine transport. ↑ risk of skin cancer.
Melasma (chloasma)	Hyperpigmentation associated with pregnancy (“mask of pregnancy” B) or OCP use.
Vitiligo	Irregular areas of complete depigmentation C . Caused by autoimmune destruction of melanocytes.



Common skin disorders

Acne	Pilosebaceous follicles with ↑ sebum, keratin, <i>Propionibacterium acnes</i> → obstruction (comedones) and inflammation (papules/pustules A , nodules, cysts). Treatment includes retinoids, benzoyl peroxide, antibiotics.
Atopic dermatitis (eczema)	Pruritic eruption, commonly on skin flexures. Often associated with other atopic diseases (asthma, allergic rhinitis, food allergies); ↑ serum IgE. Usually appears on face in infancy B and then antecubital fossae C .
Allergic contact dermatitis	Type IV hypersensitivity reaction that follows exposure to allergen. Lesions occur at site of contact (eg, nickel D , poison ivy, neomycin E).
Melanocytic nevus	Common mole. Benign, but melanoma can arise in congenital or atypical moles. Intradermal nevi are papular F . Junctional nevi are flat macules G .
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 (arrow in I)—pinpoint bleeding spots from exposure of dermal papillae when scales are scraped off. Can be associated with nail pitting and psoriatic arthritis.
Rosacea	Inflammatory facial skin disorder characterized by erythematous papules and pustules J , 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 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 L —sudden appearance of multiple seborrheic keratoses, indicating an underlying malignancy (eg, GI, lymphoid).
Verrucae	Warts; caused by HPV. Soft, tan-colored, cauliflower-like papules M . Epidermal hyperplasia, hyperkeratosis, koilocytosis. Condyloma acuminatum on genitals N .
Urticaria	Hives. Pruritic wheals that form after mast cell degranulation O . Characterized by superficial dermal edema and lymphatic channel dilation.



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 henselae</i> infections. Frequently mistaken for Kaposi sarcoma, but has neutrophilic infiltrate.
Cherry hemangioma	Benign capillary hemangioma of the elderly B . Does not regress. Frequency ↑ with age.
Cystic hygroma	Cavernous lymphangioma of the neck C . Associated with Turner syndrome.
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 of the skin, but also mouth, GI tract, and respiratory tract. Associated with HHV-8 and HIV. Frequently 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 E . Appears in first few weeks of life (1/200 births); grows rapidly and regresses spontaneously by 5–8 years old.



Skin infections

Bacterial infections

Impetigo	Very superficial skin infection. Usually from <i>S aureus</i> or <i>S pyogenes</i> . Highly contagious. Honey-colored 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 with well-defined demarcation between infected and normal skin C .
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 D .
Abscess	Collection of pus from a walled-off infection within deeper layers of skin E . Offending organism is almost always <i>S aureus</i> .
Necrotizing fasciitis	Deeper tissue injury, usually from anaerobic bacteria or <i>S pyogenes</i> . Results in crepitus from methane and CO ₂ production. “Flesh-eating bacteria.” Causes bullae and a purple color to the skin F .
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 G that heals completely. ⊕ Nikolsky sign. Seen in newborns and children, adults with renal insufficiency.

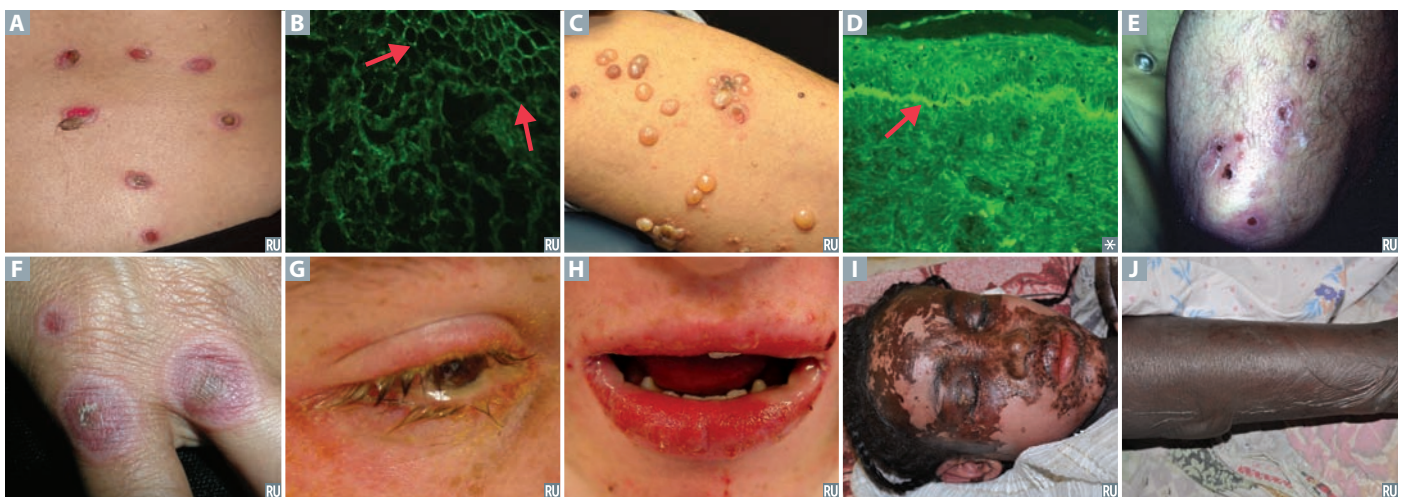
Viral infections

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 I 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 J . EBV mediated. Occurs in HIV-positive patients, organ transplant recipients. Contrast with thrush (scrapable) and leukoplakia (precancerous).



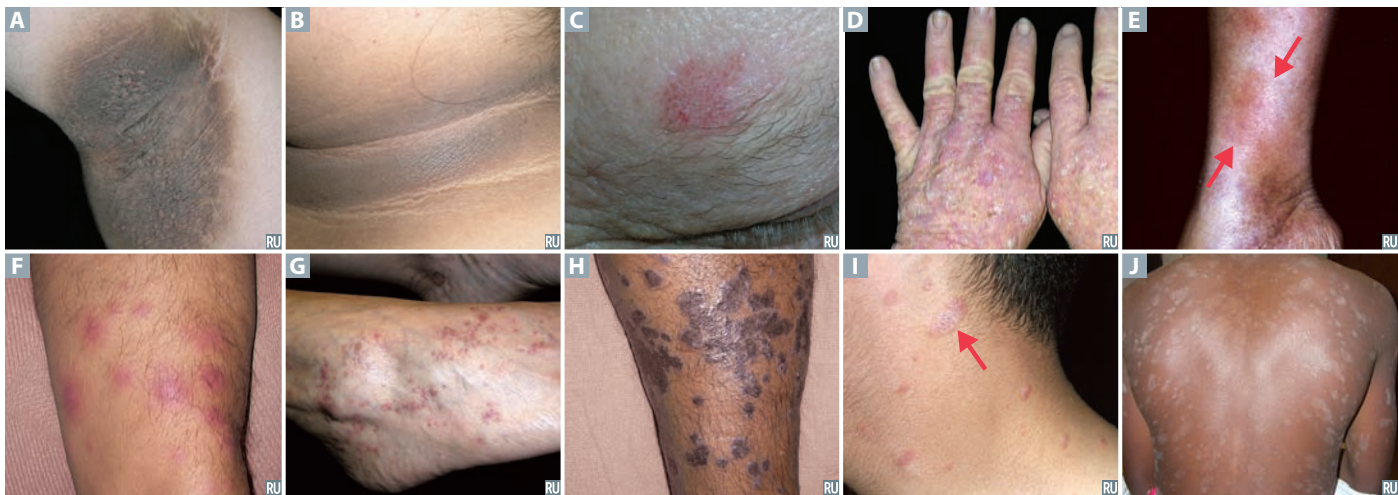
Blistering skin disorders

Pemphigus vulgaris	<p>Potentially fatal autoimmune skin disorder with IgG antibody against desmoglein (component of desmosomes).</p> <p>Flaccid intraepidermal bullae A caused by acantholysis (keratinocytes in stratum spinosum are connected by desmosomes); oral mucosa also involved.</p> <p>Immunofluorescence reveals antibodies around epidermal cells in a reticular (net-like) pattern B. Nikolsky sign \oplus (separation of epidermis upon manual stroking of skin).</p>
Bullous pemphigoid	<p>Less severe than pemphigus vulgaris. Involves IgG antibody against hemidesmosomes (epidermal basement membrane; antibodies are “bullo” the epidermis).</p> <p>Tense blisters C containing eosinophils affect skin but spare oral mucosa.</p> <p>Immunofluorescence reveals linear pattern at epidermal-dermal junction D. Nikolsky sign \ominus.</p>
Dermatitis herpetiformis	<p>Pruritic papules, vesicles, and bullae (often found on elbows) E. Deposits of IgA at tips of dermal papillae. Associated with celiac disease. Treatment: dapsone, gluten-free diet.</p>
Erythema multiforme	<p>Associated with infections (eg, <i>Mycoplasma pneumoniae</i>, HSV), drugs (eg, sulfa drugs, β-lactams, phenytoin), cancers, autoimmune disease. Presents with multiple types of lesions—macules, papules, vesicles, target lesions (look like targets with multiple rings and dusky center showing epithelial disruption) F.</p>
Stevens-Johnson syndrome	<p>Characterized by fever, bullae formation and necrosis, sloughing of skin at dermal-epidermal junction, high mortality rate. Typically 2 mucous membranes are involved G H, and targetoid skin lesions may appear, as seen in erythema multiforme. Usually associated with adverse drug reaction. A more severe form of Stevens-Johnson syndrome (SJS) with > 30% of the body surface area involved is toxic epidermal necrolysis I J (TEN). 10–30% involvement denotes SJS-TEN.</p>



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), visceral malignancy (eg, gastric adenocarcinoma).
- Actinic keratosis** Premalignant lesions caused by sun exposure. Small, rough, erythematous or brownish papules or plaques **C D**. Risk of squamous cell carcinoma is proportional to degree of epithelial dysplasia.
- Erythema nodosum** Painful inflammatory lesions of subcutaneous fat, usually on anterior shins. Often idiopathic, but can be associated with sarcoidosis, coccidioidomycosis, histoplasmosis, TB, streptococcal infections **E**, leprosy **F**, inflammatory bowel disease.
- Lichen Planus** Pruritic, **P**urple, **P**olygonal **P**lanar **P**apules and **P**laques are the **6 P's** of lichen **P**lanus **G H**. Mucosal involvement manifests as Wickham striae (reticular white lines). Sawtooth infiltrate of lymphocytes at dermal-epidermal junction. Associated with hepatitis C.
- Pityriasis rosea** “Herald patch” **I** followed days later by other scaly erythematous plaques, often in a “Christmas tree” distribution on trunk **J**. Multiple 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 sun**B**urn, **UVA** in t**A**nning and photo**A**ging. Can lead to impetigo, skin cancers (basal cell carcinoma, squamous cell carcinoma, melanoma).



Skin cancer

Basal cell carcinoma

Most common skin cancer. Found in sun-exposed areas of body (eg, face). Locally invasive, but rarely metastasizes. Pink, pearly nodules, commonly with telangiectasias, rolled borders, central crusting or ulceration **A**. BCCs also appear as nonhealing ulcers with infiltrating growth **B** or as a scaling plaque (superficial BCC) **C**. Basal cell tumors have “palisading” nuclei **D**.

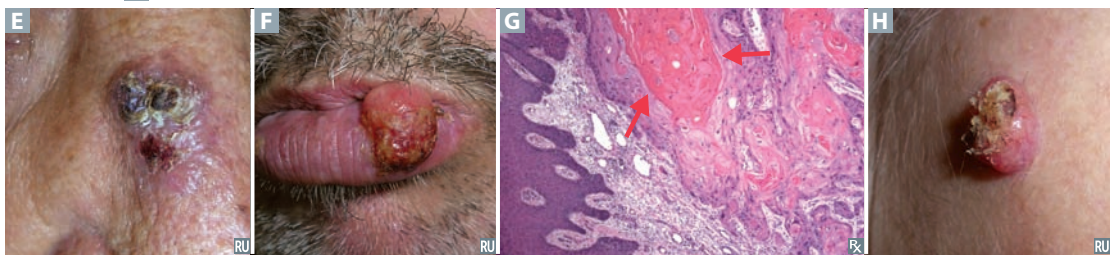


Squamous cell carcinoma

Second most common skin cancer. Associated with excessive exposure to sunlight, immunosuppression, and occasionally arsenic exposure. Commonly appears on face **E**, lower lip **F**, ears, hands. Locally invasive, may spread to lymph nodes, and will rarely metastasize. Ulcerative red lesions with frequent scale. Associated with chronic draining sinuses. Histopathology: keratin “pearls” **G**.

Actinic keratosis, a scaly plaque, is a precursor to squamous cell carcinoma.

Keratoacanthoma is a variant that grows rapidly (4–6 weeks) and may regress spontaneously over months **H**.



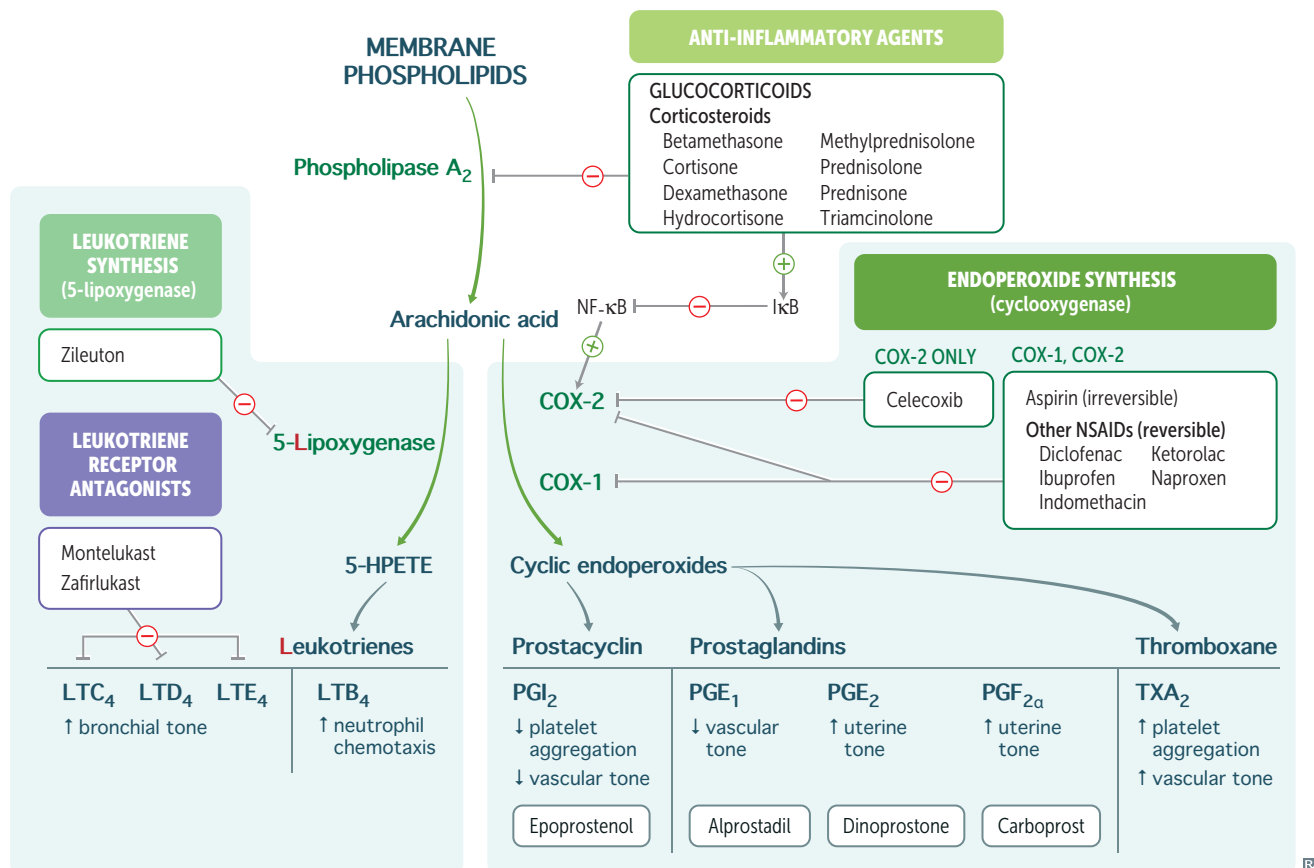
Melanoma

Common tumor with significant risk of metastasis. S-100 tumor marker. Associated with sunlight exposure; fair-skinned persons are at ↑ risk. Depth of tumor correlates with risk of metastasis. Look for the **ABCDEs**: **A**symmetry, **B**order irregularity, **C**olor variation, **D**iameter > 6 mm, and **E**volution over time. At least 4 different types of melanoma, including superficial spreading **I**, nodular **J**, lentigo maligna **K**, and acral lentiginous **L**. 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.



► MUSCULOSKELETAL, SKIN, AND CONNECTIVE TISSUE—PHARMACOLOGY

Arachidonic acid pathway



LTB₄ is a **neutrophil** chemotactic agent.

PGI₂ 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. <i>N</i> -acetylcysteine is antidote—regenerates glutathione.

Aspirin

MECHANISM	NSAID that irreversibly inhibits cyclooxygenase (both COX-1 and COX-2) by covalent acetylation → ↓ synthesis of TXA ₂ and prostaglandins. ↑ bleeding time. No effect on PT, PTT. Effect lasts until new platelets are produced.
CLINICAL USE	Low dose (< 300 mg/day): ↓ platelet aggregation. Intermediate dose (300–2400 mg/day): antipyretic and analgesic. High dose (2400–4000 mg/day): anti-inflammatory.
ADVERSE EFFECTS	Gastric ulceration, tinnitus (CN VIII). Chronic use can lead to acute renal failure, interstitial nephritis, GI bleeding. Risk of Reye syndrome in children treated with aspirin for viral infection. Causes respiratory alkalosis early, but transitions to mixed metabolic acidosis-respiratory alkalosis.

Celecoxib

MECHANISM	Reversibly inhibits specifically the cyclooxygenase (COX) isoform 2, 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 ₂ production is dependent on COX-1.
CLINICAL USE	Rheumatoid arthritis, osteoarthritis.
ADVERSE EFFECTS	↑ risk of thrombosis. Sulfa allergy.

NSAIDs

	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).

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 stress fractures.

Teriparatide

MECHANISM	Recombinant PTH analog given subcutaneously daily. ↑ osteoblastic activity.
CLINICAL USE	Osteoporosis. Causes ↑ bone growth compared to antiresorptive therapies (eg, bisphosphonates).
ADVERSE EFFECTS	Transient hypercalcemia.

Gout drugs**Chronic gout drugs (preventive)**

Allopurinol Competitive inhibitor of xanthine oxidase. ↓ conversion of hypoxanthine and xanthine to urate. Also used in lymphoma and leukemia to prevent tumor lysis–associated urate nephropathy. ↑ concentrations of azathioprine and 6-MP (both normally metabolized by xanthine oxidase).

Febuxostat Inhibits xanthine oxidase.

Pegloticase Recombinant uricase that catalyzes metabolism of uric acid to allantoin (a more water-soluble product).

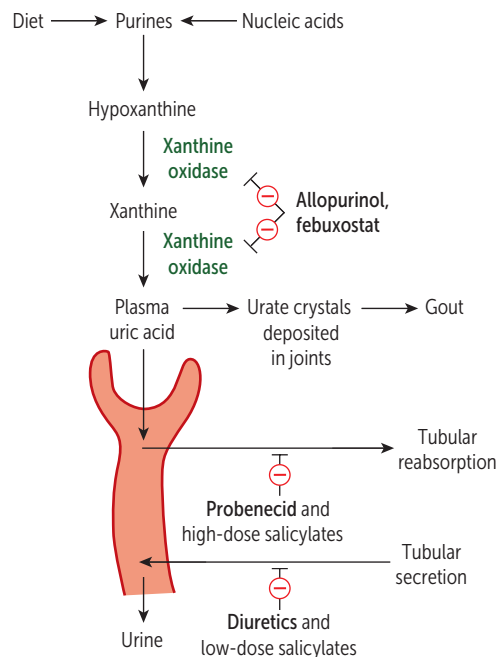
Probenecid Inhibits reabsorption of uric acid in proximal convoluted tubule (also inhibits secretion of penicillin). Can precipitate uric acid calculi.

Acute gout drugs

NSAIDs Naproxen, indomethacin. Do not give salicylates; all but the highest doses depress uric acid clearance. Even high doses (5–6 g/day) have only minor uricosuric activity.

Glucocorticoids Oral, intra-articular, or parenteral.

Colchicine Binds and stabilizes tubulin to inhibit microtubule polymerization, impairing neutrophil chemotaxis and degranulation. Acute and prophylactic value. GI side effects.



TNF- α inhibitors All TNF- α inhibitors predispose to infection, including reactivation of latent TB, since TNF is important in granuloma formation and stabilization.

DRUG	MECHANISM	CLINICAL USE
Etanercept	Fusion protein (receptor for TNF- α + IgG ₁ Fc), produced by recombinant DNA. Etanercept is a TNF decoy receptor.	Rheumatoid arthritis, psoriasis, ankylosing spondylitis
Infliximab, adalimumab	Anti-TNF- α monoclonal antibody.	Inflammatory bowel disease, rheumatoid arthritis, ankylosing spondylitis, psoriasis

Rasburicase

MECHANISM Recombinant uricase that catalyzes metabolism of uric acid to allantoin.

CLINICAL USE Prevention and treatment of tumor lysis syndrome.

Neurology

“Estimated amount of glucose used by an adult human brain each day, expressed in M&Ms: 250.”

—Harper’s Index

“He has two neurons held together by a spirochete.”

—Anonymous

“Anything’s possible if you’ve got enough nerve.”

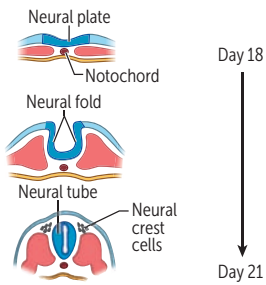
—J.K. Rowling, *Harry Potter and the Order of the Phoenix*

“I like nonsense; it wakes up the brain cells.”

—Dr. Seuss

▶ Embryology	450
▶ Anatomy and Physiology	453
▶ Ophthalmology	482
▶ Pathology	491
▶ Pharmacology	498

► NEUROLOGY—EMBRYOLOGY

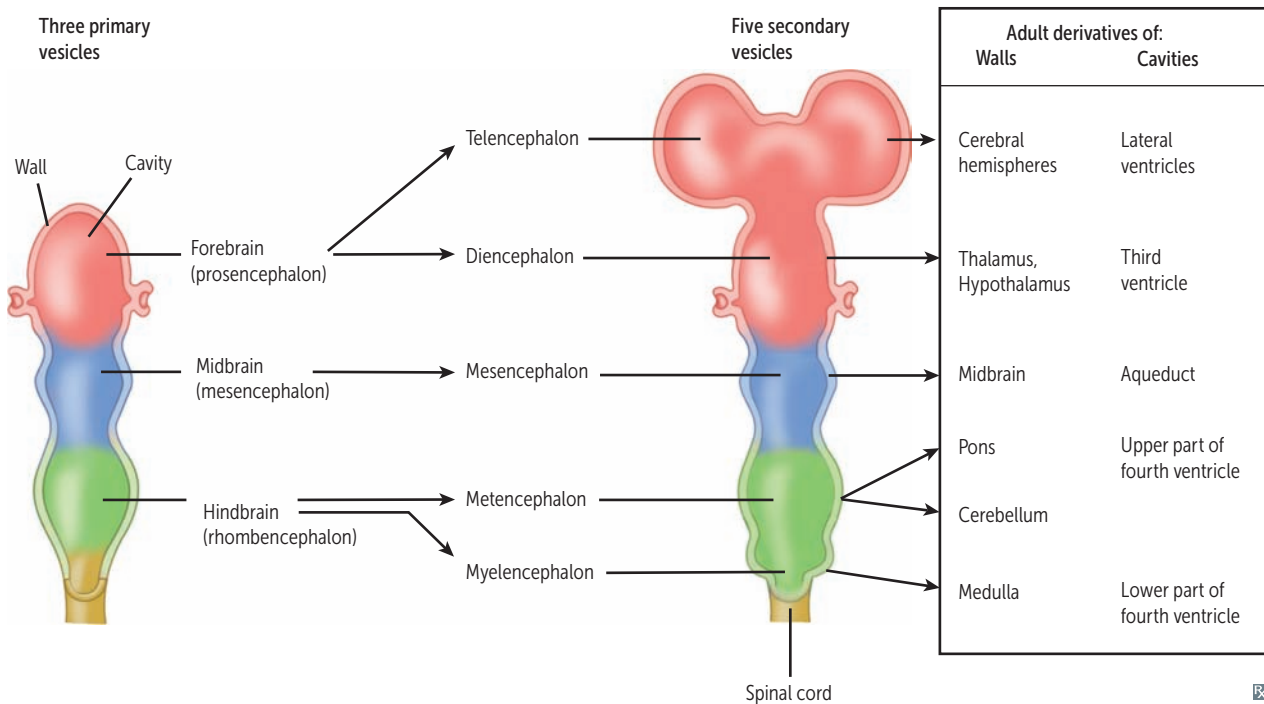
Neural development

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
Basal plate (ventral): motor } Same orientation as spinal cord.

Regional specification of developing brain**CNS/PNS origins**

Neuroectoderm—CNS neurons, ependymal cells (inner lining of ventricles, make CSF), oligodendroglia, astrocytes.

Neural crest—PNS neurons, Schwann cells.

Mesoderm—Microglia (like Macrophages).

Neural tube defects

Neuropores fail to fuse (4th week) → persistent connection between amniotic cavity and spinal canal. Associated with low folic acid intake before conception and during pregnancy.
 ↑ α -fetoprotein (AFP) in amniotic fluid and maternal serum (except spina bifida occulta).
 ↑ acetylcholinesterase (AChE) in amniotic fluid is a helpful confirmatory test (fetal AChE in CSF flows through defect into amniotic fluid).

Spina bifida occulta

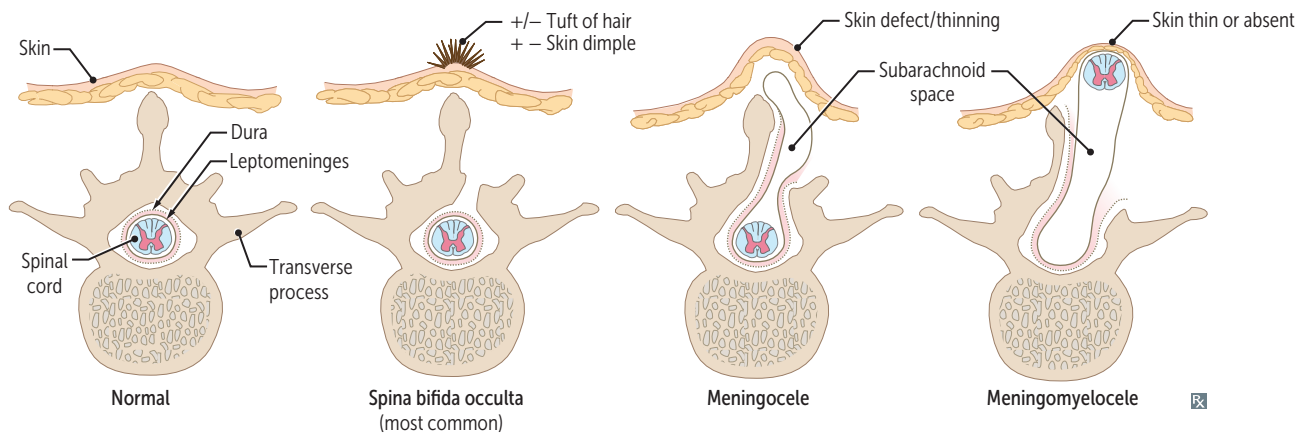
Failure of bony spinal canal to close, but no herniation. Usually seen at lower vertebral levels. Dura is intact. Associated with tuft of hair or skin dimple at level of bony defect. Normal AFP.

Meningocele

Meninges (but no neural tissue) herniate through bony defect.

Meningomyelocele

Meninges and neural tissue (eg, cauda equina) herniate through bony defect.

**Forebrain anomalies****Anencephaly**

Malformation of anterior neural tube → no forebrain, open calvarium. Clinical findings: ↑ AFP, polyhydramnios (no swallowing center in brain). Associated with maternal type 1 diabetes. Maternal folate supplementation ↓ risk.

Holoprosencephaly

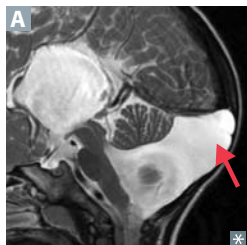
Failure of left and right hemispheres to separate; usually occurs during weeks 5–6. May be related to mutations in sonic hedgehog signaling pathway. Moderate form has cleft lip/palate, most severe form results in cyclopia. Seen in Patau syndrome and fetal alcohol syndrome.

Posterior fossa malformations**Chiari II malformation**

Herniation of low-lying cerebellar vermis through foramen magnum with aqueductal stenosis → hydrocephalus. Usually associated with lumbosacral meningocele (paralysis/sensory loss at and below the level of the lesion).

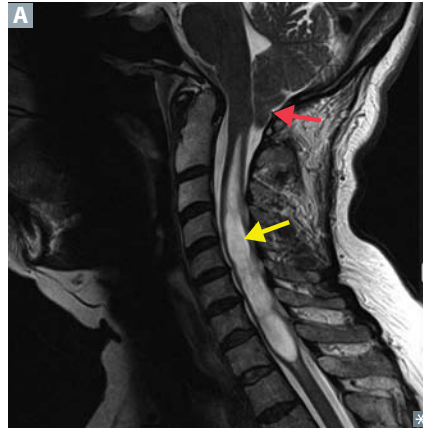
Dandy-Walker syndrome

Agenesis of cerebellar vermis with cystic enlargement of 4th ventricle (fills the enlarged posterior fossa **A**). Associated with noncommunicating hydrocephalus, spina bifida.



Syringomyelia

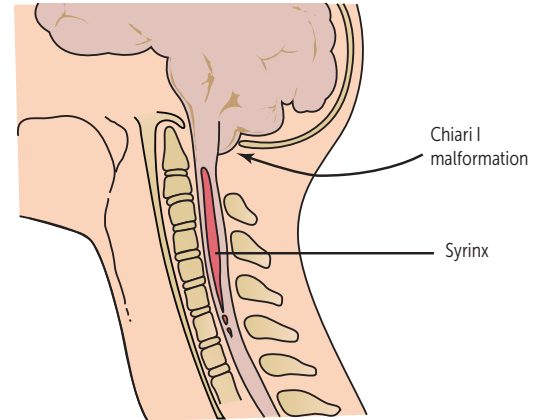
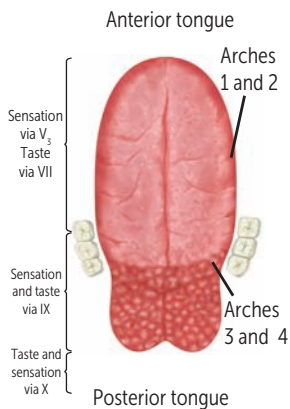
Cystic cavity (syrinx) within central canal of spinal cord (yellow arrow in **A**). Fibers crossing in anterior white commissure (spinothalamic tract) are typically damaged first. Results in a “cape-like,” bilateral loss of pain and temperature sensation in upper extremities (fine touch sensation is preserved). Associated with Chiari malformations (red arrow in **A**), trauma, and tumors.



Syrinx = tube, as in syringe.

Most common at C8–T1.

Chiari I malformation—cerebellar tonsillar ectopia > 3–5 mm; congenital, usually asymptomatic in childhood, manifests with headaches and cerebellar symptoms.

**Tongue development**

1st and 2nd branchial arches form anterior $\frac{2}{3}$ (thus sensation via CN V₃, taste via CN VII).
3rd and 4th branchial arches form posterior $\frac{1}{3}$ (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), genioglossus (protrudes tongue), and styloglossus (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 V₃, IX, X.

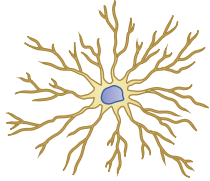
Motor—CN X, XII.

▶ NEUROLOGY—ANATOMY AND PHYSIOLOGY

Neurons

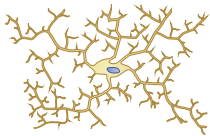
Signal-transmitting cells of the nervous system. Permanent cells—do not divide in adulthood. Signal-relaying cells with dendrites (receive input), cell bodies, and axons (send output). Cell bodies and dendrites can be seen on Nissl staining (stains RER). RER is not present in the axon. Injury to axon → Wallerian degeneration—degeneration distal to injury and axonal retraction proximally; allows for potential regeneration of axon (if in PNS).

Astrocytes



Physical support, repair, K^+ metabolism, removal of excess neurotransmitter, component of blood-brain barrier, glycogen fuel reserve buffer. Reactive gliosis in response to neural injury. Astrocyte marker: GFAP. Derived from neuroectoderm.

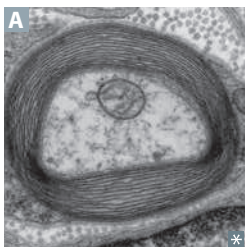
Microglia



Phagocytic scavenger cells of CNS (mesodermal, mononuclear origin). Activated in response to tissue damage. Not readily discernible by Nissl stain.

HIV-infected microglia fuse to form multinucleated giant cells in CNS.

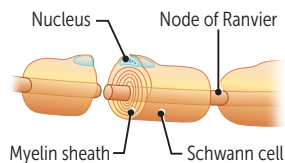
Myelin



↑ conduction velocity of signals transmitted down axons → saltatory conduction of action potential at the nodes of Ranvier, where there are high concentrations of Na^+ channels. CNS—oligodendrocytes; PNS—Schwann cells.

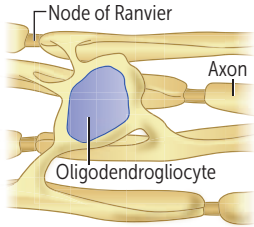
Wraps and insulates axons **A**: ↑ space constant and ↑ conduction velocity.

Schwann cells



Each Schwann cell myelinates only 1 PNS axon. Also promote axonal regeneration. Derived from neural crest. ↑ conduction velocity via saltatory conduction at the nodes of Ranvier, where there is a high concentration of Na^+ channels.

May be injured in Guillain-Barré syndrome. **Vestibular schwannoma**—typically located on CN VIII in internal acoustic meatus, may extend to cerebellopontine angle.

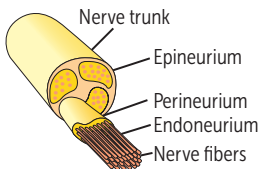
Oligodendroglia

Myelinates 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	C—slow, unmyelinated fibers A δ —fast, myelinated fibers	All skin, epidermis, some viscera	Pain, temperature
Meissner corpuscles	Large, myelinated fibers; adapt quickly	Glabrous (hairless) skin	Dynamic, fine/light touch, position sense
Pacinian corpuscles	Large, myelinated fibers; adapt quickly	Deep skin layers, ligaments, joints	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

Peripheral nerve

Endoneurium—invests single nerve fiber layers (inflammatory infiltrate in Guillain-Barré syndrome).

Perineurium (**P**ermeability barrier)—surrounds a fascicle of nerve fibers. Must be rejoined in microsurgery for limb reattachment.

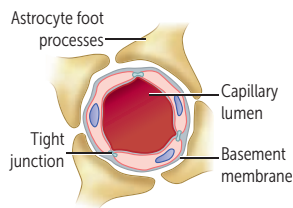
Epineurium—dense connective tissue that surrounds entire nerve (fascicles and blood vessels).

Endo = inner.
Peri = around.
Epi = outer.

Neurotransmitters

	LOCATION OF SYNTHESIS	ANXIETY	DEPRESSION	SCHIZOPHRENIA	ALZHEIMER DISEASE	HUNTINGTON DISEASE	PARKINSON DISEASE
Acetylcholine	Basal nucleus of Meynert				↓	↓	↑
Dopamine	Ventral tegmentum, SNpc		↓	↑		↑	↓
GABA	Nucleus accumbens	↓				↓	
Norepinephrine	Locus ceruleus	↑	↓				
Serotonin	Raphe nucleus	↓	↓				↑

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.

A few specialized brain regions with fenestrated capillaries and no blood-brain barrier allow molecules in blood to affect brain function (eg, area postrema—vomiting after chemo; OVLT—osmotic sensing) or neurosecretory products to enter circulation (eg, neurohypophysis—ADH release).

Infarction and/or neoplasm destroys endothelial cell tight junctions → vasogenic edema.

Other notable barriers include:

- Blood-testis barrier
- Maternal-fetal blood barrier of placenta

Hypothalamus

The hypothalamus wears **TAN HATS**—**T**hirst and water balance, **A**denohypophysis control (regulates anterior pituitary), **N**eurohypophysis releases hormones produced in the hypothalamus, **H**unger, **A**utonomic regulation, **T**emperature regulation, **S**exual urges.

Inputs (areas not protected by blood-brain barrier): OVLT (organum vasculosum of the lamina terminalis; senses change in osmolarity), area postrema (found in medulla, responds to emetics).

Supraoptic nucleus primarily makes ADH.

Paraventricular nucleus primarily makes oxytocin.

Hypothalamus makes ADH and oxytocin. They are carried by neurophysins down axons to posterior pituitary, where they are stored and released.

Lateral area	Hunger. Destruction → anorexia, failure to thrive (infants). Stimulated by ghrelin, inhibited by leptin.	If you zap your lateral area, you shrink laterally .
Ventromedial area	Satiety. Destruction (eg, craniopharyngioma) → hyperphagia. Stimulated by leptin.	If you zap your ventromedial area, you grow ventrally and medially .
Anterior hypothalamus	Cooling, parasympathetic.	Anterior nucleus = cool off (cooling , pArasympathetic). A/C = anterior cooling .
Posterior hypothalamus	Heating, sympathetic.	Posterior nucleus = get fired up (heating, sympathetic). If you zap your posterior hypothalamus, you become a poikilotherm (cold-blooded, like a snake).
Suprachiasmatic nucleus	Circadian rhythm.	You need sleep to be charismatic (chiasmatic).

Sleep physiology

Sleep cycle is regulated by the circadian rhythm, which is driven by suprachiasmatic nucleus (SCN) of 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. Extraocular movements during REM sleep due to activity of PPRF (paramedian pontine reticular formation/conjugate gaze center). REM sleep occurs every 90 minutes, and duration ↑ through the night. ↑ ACh in REM.

Alcohol, benzodiazepines, and barbiturates are associated with ↓ REM sleep and delta wave sleep; norepinephrine also ↓ REM sleep.

Treat bedwetting (sleep enuresis) with oral desmopressin (ADH analog); preferred over imipramine because of the latter’s adverse effects.

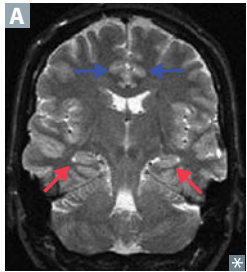
Benzodiazepines are useful for night terrors and sleepwalking.

SLEEP STAGE (% OF TOTAL SLEEP TIME IN YOUNG ADULTS)	DESCRIPTION	EEG WAVEFORM
Awake (eyes open)	Alert, active mental concentration	B eta (highest frequency, lowest amplitude)
Awake (eyes closed)		A lpha
Non-REM sleep		
Stage N1 (5%)	Light sleep	T heta
Stage N2 (45%)	Deeper sleep; when bruxism occurs	S leep spindles and K complexes
Stage N3 (25%)	Deepest non-REM sleep (slow-wave sleep); when sleepwalking, night terrors, and bedwetting occur	D elta (lowest frequency, highest amplitude)
REM sleep (25%)	Loss of motor tone, ↑ brain O ₂ use, ↑ and variable pulse and blood pressure; when dreaming, nightmares, and penile/clitoral tumescence occur; may serve memory processing function	B eta At night, BATS Drink B lood

Thalamus

Major relay for all ascending sensory information except olfaction.

NUCLEUS	INPUT	SENSES	DESTINATION	MNEMONIC
Ventral postero-lateral nucleus	Spinothalamic and dorsal columns/medial lemniscus	Pain, temperature; pressure, touch, vibration, proprioception	1° somatosensory cortex	
Ventral postero-Medial nucleus	Trigeminal and gustatory pathway	F ace sensation, taste	1° somatosensory cortex	M akeup goes on the f ace (VPM)
Lateral geniculate nucleus	CN II	Vision	Calcarine sulcus	L ateral = L ight
Medial geniculate nucleus	Superior olive and inferior colliculus of tectum	Hearing	Auditory cortex of temporal lobe	M edial = M usic
Ventral lateral nucleus	Basal ganglia, cerebellum	Motor	Motor cortex	

Limbic system

Collection of neural structures involved in emotion, long-term memory, olfaction, behavior modulation, ANS function. Structures include hippocampus (red arrows in **A**), amygdala, fornix, mammillary bodies, cingulate gyrus (blue arrows in **A**). Responsible for **F**eeding, **F**leeing, **F**ighting, **F**eeling, and **S**ex.

The famous **5 F**'s.**Dopaminergic pathways**

Commonly altered by drugs (eg, antipsychotics) and movement disorders (eg, Parkinson disease).

PATHWAY	SYMPTOMS OF ALTERED ACTIVITY	NOTES
Mesocortical	↓ activity → “negative” symptoms (eg, flat affect, limited speech).	Antipsychotic drugs have limited effect.
Mesolimbic	↑ activity → “positive” symptoms (eg, delusions, hallucinations).	Primary therapeutic target of antipsychotic drugs → ↓ positive symptoms (eg, in schizophrenia).
Nigrostriatal	↓ activity → extrapyramidal symptoms (eg, dystonia, akathisia, parkinsonism, tardive dyskinesia).	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.

Input:

- Contralateral cortex via middle cerebellar peduncle.
- Ipsilateral proprioceptive information via inferior cerebellar peduncle from spinal cord.

Output:

- Sends information to contralateral cortex to modulate movement. Output nerves = Purkinje cells → deep nuclei of cerebellum → contralateral cortex via superior cerebellar peduncle.
- Deep nuclei (lateral → medial)—**D**entate, **E**mboliform, **G**lobose, **F**astigial (“**D**on’t **E**at **G**reasy **F**oods”).

Lateral lesions—affect voluntary movement of extremities; when injured, propensity to fall toward injured (ipsilateral) side.

Medial lesions—involvement of midline structures (vermal cortex, fastigial nuclei) and/or flocculonodular lobe → truncal ataxia (wide-based cerebellar gait), nystagmus, head tilting. Generally result in bilateral motor deficits affecting axial and proximal limb musculature.

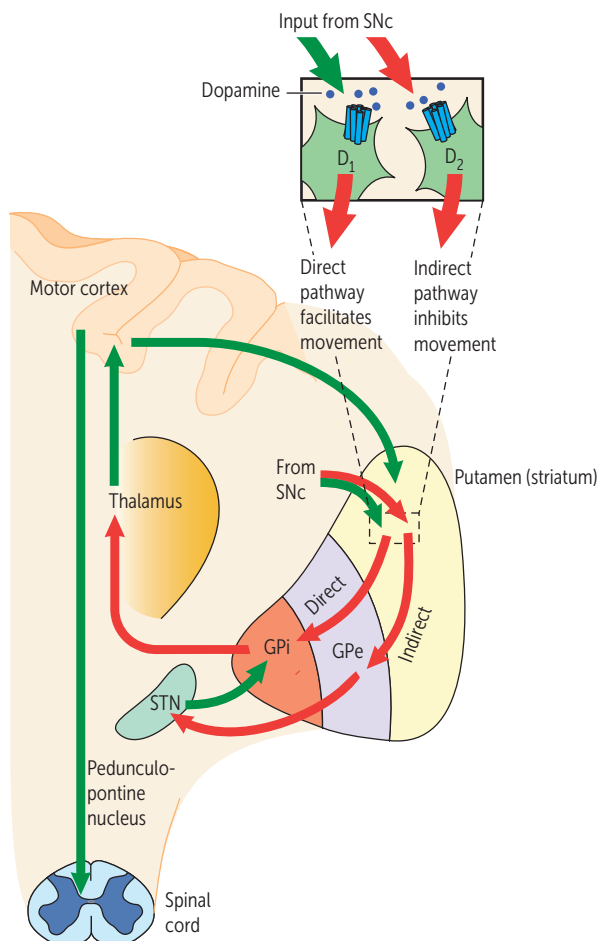
Basal ganglia

Important in voluntary movements and making postural adjustments.

Receives cortical input, provides negative feedback to cortex to modulate movement.

Striatum = putamen (motor) + caudate (cognitive).

Lentiform = putamen + globus pallidus.



D₁-Receptor = DIRECT pathway.

Indirect = Inhibitory.

■ Stimulatory

■ Inhibitory

SNc Substantia nigra pars compacta

GPe Globus pallidus externus

GPi Globus pallidus internus

STN Subthalamic nucleus

D₁ Dopamine D₁ receptor

D₂ Dopamine D₂ receptor

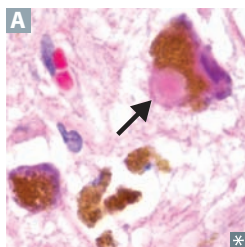
Excitatory pathway—cortical inputs stimulate the striatum, stimulating the release of GABA, which inhibits GABA release from the GPi, disinhibiting the thalamus via the GPi (↑ motion).

Inhibitory pathway—cortical inputs stimulate the striatum, releasing GABA that disinhibits STN via GPe inhibition, and STN stimulates GPi to inhibit the thalamus (↓ motion).

Dopamine binds to D₁, stimulating the excitatory pathway, and to D₂, inhibiting the inhibitory pathway → ↑ motion.

Movement disorders

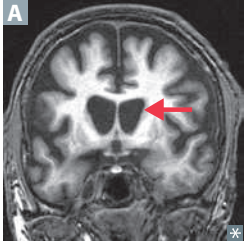
DISORDER	PRESENTATION	CHARACTERISTIC LESION	NOTES
Athetosis	Slow, writhing movements; especially seen in fingers	Basal ganglia (eg, Huntington)	Writhing, snake-like movement.
Chorea	Sudden, jerky, purposeless movements	Basal ganglia (eg, Huntington)	<i>Chorea</i> = dancing.
Dystonia	Sustained, involuntary muscle contractions		Writer's cramp; blepharospasm (sustained eyelid twitch).
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.
Hemiballismus	Sudden, wild flailing of 1 arm +/- ipsilateral leg	Contralateral subthalamic nucleus (eg, lacunar stroke)	Pronounce " Half -of-body ballistic ." Contralateral lesion.
Intention tremor	Slow, zigzag motion when pointing/extending toward a target	Cerebellar dysfunction	
Myoclonus	Sudden, brief, uncontrolled muscle contraction		Jerks; hiccups; common in metabolic abnormalities such as renal and liver failure.
Resting tremor	Uncontrolled movement of distal appendages (most noticeable in hands); tremor alleviated by intentional movement	Parkinson disease	Occurs at rest; "pill-rolling tremor" of Parkinson disease.

Parkinson disease

Degenerative disorder of CNS associated with Lewy bodies (composed of α-synuclein—intracellular eosinophilic inclusions **A**) and loss of dopaminergic neurons (ie, depigmentation) of substantia nigra pars compacta.

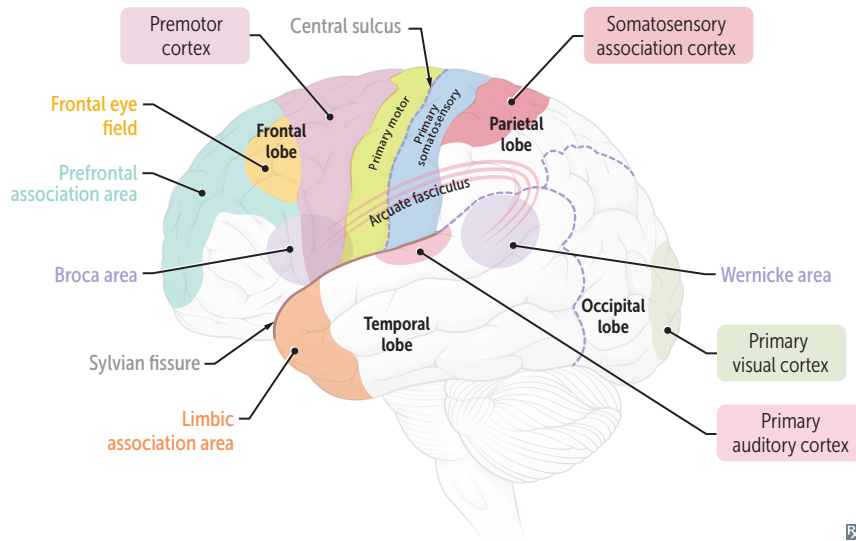
Parkinson **TRAPS** your body:

- T**remor (pill-rolling tremor at rest)
- R**igidity (cogwheel)
- A**kinesia (or bradykinesia)
- P**ostural instability
- S**huffling gait

Huntington disease

Autosomal dominant trinucleotide repeat disorder on chromosome 4. Symptoms manifest between ages 20 and 50; characterized by choreiform movements, aggression, depression, dementia (sometimes initially mistaken for substance abuse). ↑ dopamine, ↓ GABA, ↓ ACh in brain. Neuronal death via NMDA-R binding and glutamate excitotoxicity. Atrophy of caudate and putamen with hydrocephalus ex vacuo **A**.

Expansion of **CAG** repeats (anticipation).
Caudate loses **ACh** and **GABA**.

Cerebral cortex functions

Aphasia

Aphasia—higher-order language deficit (inability to understand/speak/read/write).

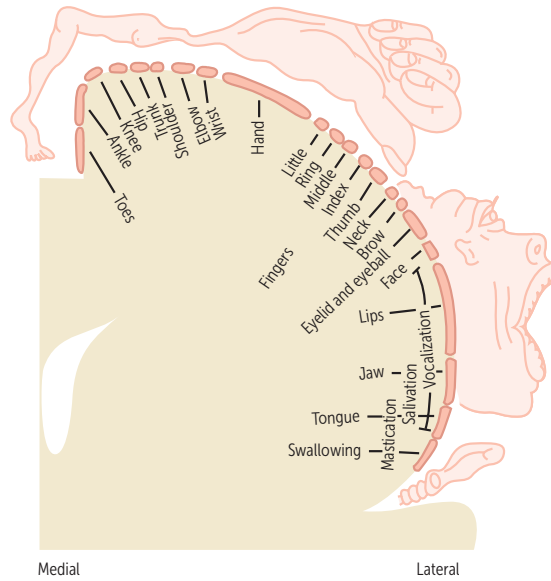
Dysarthria—motor inability to speak (movement deficit).

TYPE	SPEECH FLUIDITY	COMPREHENSION	REPETITION	COMMENTS
Broca	Nonfluent	Intact	Impaired	Broca = Broken Boca (<i>boca</i> = mouth in Spanish). Broca area in inferior frontal gyrus of frontal lobe.
Wernicke	Fluent	Impaired	Impaired	Wernicke is Wordy but makes no sense. Wernicke area in superior temporal gyrus of temporal lobe.
Conduction	Fluent	Intact	Impaired	Can be caused by damage to arcuate fasciculus.
Global	Nonfluent	Impaired	Impaired	Arcuate fasciculus; Broca and Wernicke areas affected.
Transcortical motor	Nonfluent	Intact	Intact	Affects frontal lobe around Broca area, but Broca area is spared.
Transcortical sensory	Fluent	Impaired	Intact	Affects temporal lobe around Wernicke area, but Wernicke area is spared.
Transcortical, mixed	Nonfluent	Impaired	Intact	Broca and Wernicke areas and arcuate fasciculus remain intact; surrounding watershed areas affected.

Common brain lesions

AREA OF LESION	CONSEQUENCE	NOTES
Amygdala (bilateral)	Klüver-Bucy syndrome—disinhibited behavior (eg, hyperphagia, hypersexuality, hyperorality).	Associated with HSV-1 encephalitis.
Frontal lobe	Disinhibition and deficits in concentration, orientation, judgment; may have reemergence of primitive reflexes.	
Nondominant parietal cortex	Hemispatial neglect syndrome (agnosia of the contralateral side of the world).	
Dominant parietal cortex	Agraphia, acalculia, finger agnosia, left-right disorientation.	Gerstmann syndrome.
Reticular activating system (midbrain)	Reduced levels of arousal and wakefulness (eg, coma).	
Mammillary bodies (bilateral)	Wernicke-Korsakoff syndrome—confusion, ophthalmoplegia, ataxia; memory loss (anterograde and retrograde amnesia), confabulation, personality changes.	Associated with thiamine (B ₁) deficiency and excessive alcohol use; can be precipitated by giving glucose without B ₁ to a B ₁ -deficient patient. Wernicke problems come in a CAN of beer: C onfusion, A taxia, N ystagmus.
Basal ganglia	May result in tremor at rest, chorea, athetosis.	Parkinson disease, Huntington disease.
Cerebellar hemisphere	Intention tremor, limb ataxia, loss of balance; damage to cerebellum → ipsilateral deficits; fall toward side of lesion.	Degeneration associated with chronic alcohol use. Cerebellar hemispheres are laterally located—affect lateral limbs.
Cerebellar vermis	Truncal ataxia, dysarthria.	Vermis is centrally located—affects central body.
Subthalamic nucleus	Contralateral hemiballismus.	
Hippocampus (bilateral)	Anterograde amnesia—inability to make new memories.	
Paramedian pontine reticular formation	Eyes look away from side of lesion.	
Frontal eye fields	Eyes look toward lesion.	

Homunculus

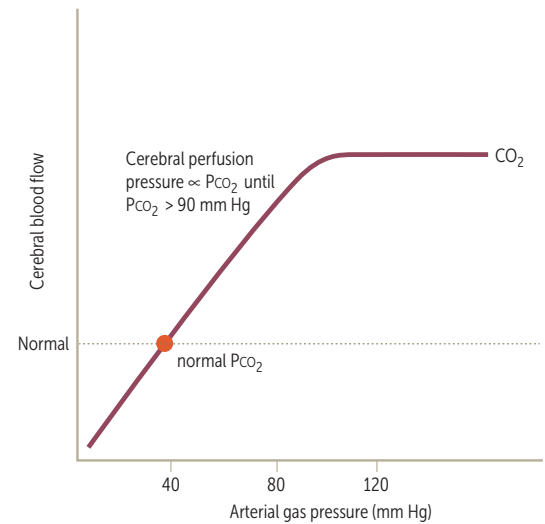
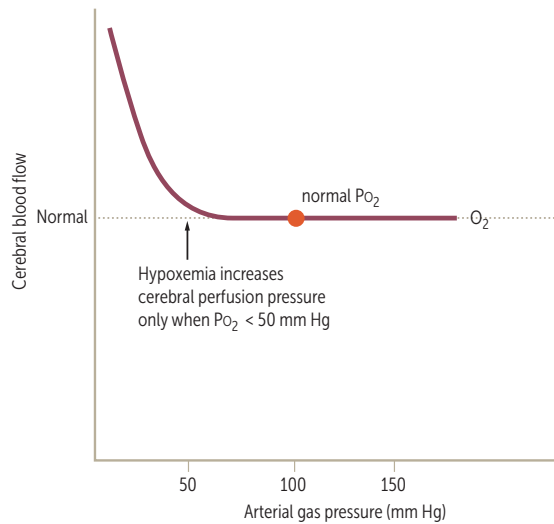


Topographic representation of motor (shown) and sensory areas in the cerebral cortex. Distorted appearance is due to certain body regions being more richly innervated and thus having ↑ cortical representation.

Cerebral perfusion

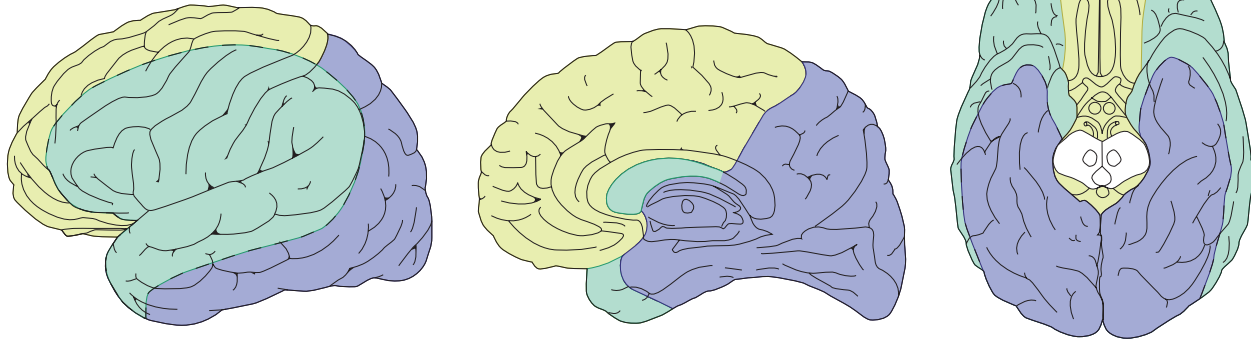
Brain perfusion relies on tight autoregulation. Cerebral perfusion is primarily driven by PCO_2 (PO_2 also modulates perfusion in severe hypoxia). Cerebral perfusion relies on a pressure gradient between mean arterial pressure (MAP) and ICP. ↓ blood pressure or ↑ ICP → ↓ cerebral perfusion pressure (CPP).

Therapeutic hyperventilation → ↓ PCO_2 → vasoconstriction → ↓ cerebral blood flow → ↓ intracranial pressure (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 → brain death.



Cerebral arteries—cortical distribution

- Anterior cerebral artery (supplies anteromedial surface)
- Middle cerebral artery (supplies lateral surface)
- Posterior cerebral artery (supplies posterior and inferior surfaces)

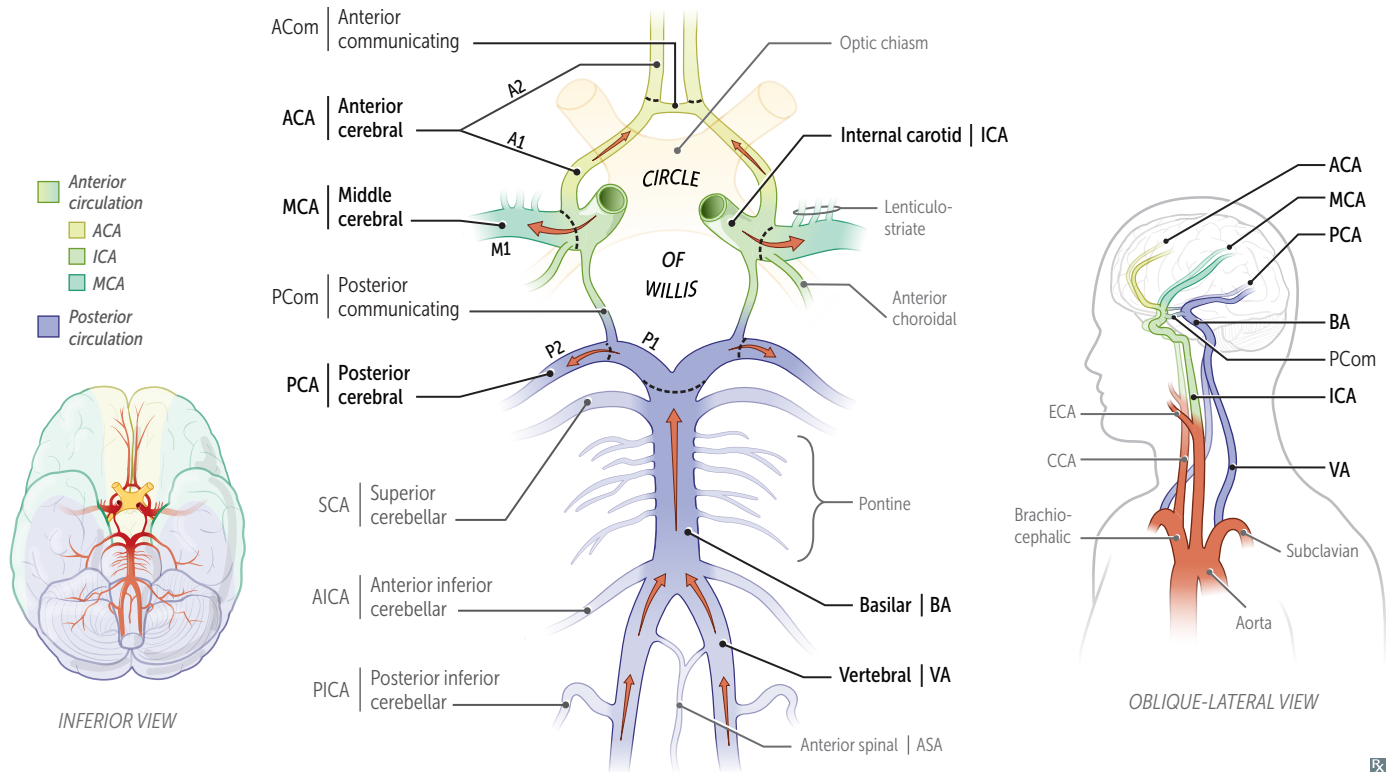


Watershed zones

Between anterior cerebral/middle cerebral, posterior cerebral/middle cerebral arteries. Damage by severe hypotension → upper leg/upper arm weakness, defects in higher-order visual processing.

Circle of Willis

System of anastomoses between anterior and posterior blood supplies to brain.



Effects of strokes

ARTERY	AREA OF LESION	SYMPTOMS	NOTES
Anterior circulation			
Middle cerebral artery	Motor and sensory cortices—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) side.	
Anterior cerebral artery	Motor and sensory cortices—lower limb.	Contralateral paralysis and sensory loss—lower limb.	
Lenticulo-striate artery	Striatum, internal capsule.	Contralateral paralysis and/or sensory loss—face and body. Absence of cortical signs (eg, neglect, aphasia, visual field loss).	Common location of lacunar infarcts, 2° to unmanaged hypertension.
Posterior circulation			
Anterior spinal artery	Lateral 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—vestibular nuclei, lateral spinothalamic tract, spinal trigeminal nucleus, nucleus ambiguus, sympathetic fibers, inferior cerebellar peduncle.	Vomiting, vertigo, nystagmus; ↓ pain and temperature sensation from ipsilateral face and contralateral body; dysphagia, hoarseness , ↓ gag reflex; ipsilateral Horner syndrome; ataxia, dysmetria.	Lateral medullary (Wallenberg) syndrome. Nucleus ambiguus effects are specific to PICA lesions. “Don’t pick a (PICA) horse (hoarseness) that can’t eat (dysphagia).”
Anterior inferior cerebellar artery	Lateral pons—cranial nerve nuclei (vestibular nuclei, facial nucleus, spinal trigeminal nucleus, cochlear nuclei), spinothalamic tract, corticospinal tract, sympathetic fibers. Middle and inferior cerebellar peduncles.	Vomiting, vertigo, nystagmus. Paralysis of face , ↓ lacrimation, salivation, ↓ taste from anterior 2/3 of tongue. Ipsilateral ↓ pain and temperature of the face, contralateral ↓ pain and temperature of the body. Ataxia, dysmetria.	Lateral pontine syndrome. Facial nucleus effects are specific to AICA lesions. “ Facial droop means AICA’s pooped. ”
Basilar artery	Pons, medulla, lower midbrain, corticospinal and corticobulbar tracts, ocular cranial nerve nuclei, paramedian pontine reticular formation.	Preserved consciousness, vertical eye movement, blinking; quadriplegia, loss of voluntary facial, mouth, and tongue movements.	“Locked-in syndrome.”
Posterior cerebral artery	Occipital cortex, visual cortex.	Contralateral hemianopia with macular sparing.	

Aneurysms	Abnormal dilation of an artery due to weakening of vessel wall.
Saccular (berry) aneurysm	Occurs at bifurcations in the circle of Willis. Most common site is junction of anterior communicating artery and anterior cerebral artery. Rupture (most common complication) → subarachnoid hemorrhage (“worst headache of my life”) or hemorrhagic stroke. Associated with ADPKD, Ehlers-Danlos syndrome. Other risk factors: advanced age, hypertension, smoking, race (↑ risk in blacks).
Charcot-Bouchard microaneurysm	Common, associated with chronic hypertension; affects small vessels (eg, in basal ganglia, thalamus); not seen on angiogram.
Effects of saccular aneurysms	Usually clinically silent until rupture → subarachnoid hemorrhage (eg, thunderclap headache). Can also cause symptoms via direct compression on surrounding structures by growing aneurysm.
ARTERY	ASSOCIATED SYMPTOMS
Anterior communicating artery	Compression may cause bitemporal hemianopia (compression of optic chiasm); visual acuity deficits. Rupture may cause ischemia in ACA distribution → contralateral lower extremity hemiparesis, sensory deficits.
Posterior communicating artery	Compression may cause ipsilateral CN III palsy → mydriasis (“blown pupil”); may also see ptosis, “down and out” eye.
Middle cerebral artery	Rupture may cause ischemia in MCA distribution → contralateral upper extremity and facial hemiparesis, sensory deficits.
Central post-stroke pain syndrome	Neuropathic pain due to thalamic lesions. Initial paresthesias followed in weeks to months by allodynia (ordinarily painless stimuli cause pain) and dysesthesia. Occurs in 10% of stroke patients.

Intracranial hemorrhage**Epidural hematoma**

Rupture of middle meningeal artery (branch of maxillary artery), often 2° to skull fracture **A**.
 Lucid interval. Rapid expansion under systemic arterial pressure → transtentorial herniation, CN III palsy.
 CT shows biconvex (lenticiform), hyperdense blood collection **B** **not crossing suture lines**.

Subdural hematoma

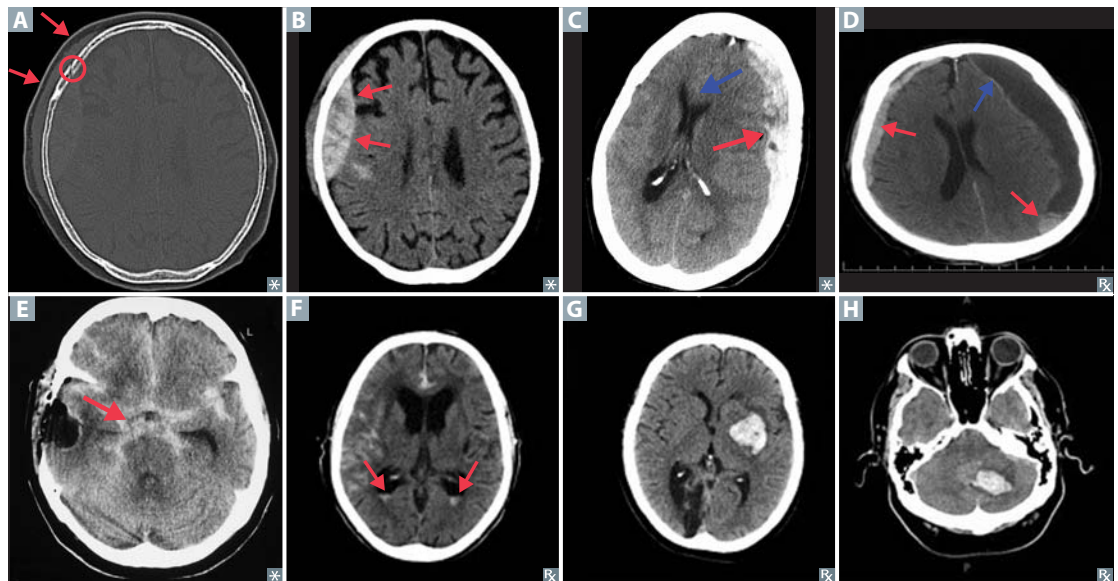
Rupture of bridging veins. Can be acute (traumatic, high-energy impact → hyperdense on CT) or chronic (associated with mild trauma, cerebral atrophy, elderly, alcoholism → hypodense on CT).
 Also seen in shaken babies. Predisposing factors: brain atrophy, trauma.
 Crescent-shaped hemorrhage that **crosses suture lines** (red arrows in **C** and **D**). Can cause midline shift (blue arrow in **C**), findings of “acute on chronic” hemorrhage (blue arrow in **D**).

Subarachnoid hemorrhage

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) spinal tap. 4–10 days after hemorrhage, vasospasm (narrowing of blood vessels) can occur → ischemic infarct; nimodipine used for prevention **F**. ↑ 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. Typically occurs in basal ganglia **G** and internal capsule (Charcot-Bouchard aneurysm of lenticulostriate vessels), but can be lobar **H**.

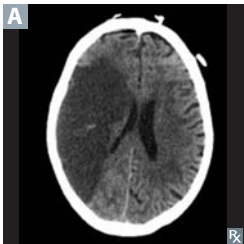


Ischemic brain disease/stroke

Irreversible damage begins after 5 minutes of hypoxia. Most vulnerable: hippocampus, neocortex, cerebellum, watershed areas. Irreversible neuronal injury. Ischemic **hypoxia**—“**hypocampus**” is most vulnerable.

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	12–48 HOURS	24–72 HOURS	3–5 DAYS	1–2 WEEKS	> 2 WEEKS
Histologic features	Red neurons	Necrosis + neutrophils	Macrophages (microglia)	Reactive gliosis + vascular proliferation	Glial scar

Ischemic stroke

Acute blockage of vessels → disruption of blood flow and subsequent ischemia → liquefactive necrosis.

3 types:

- Thrombotic—due to a clot forming directly at site of infarction (commonly the MCA **A**), usually over an atherosclerotic plaque.
- Embolic—embolus from another part of the body obstructs vessel. Can affect multiple vascular territories. Examples: atrial fibrillation; DVT with patent foramen ovale.
- 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). Reduce risk with medical therapy (eg, aspirin, clopidogrel); optimum control of blood pressure, blood sugars, lipids; and treat conditions that ↑ risk (eg, atrial fibrillation).

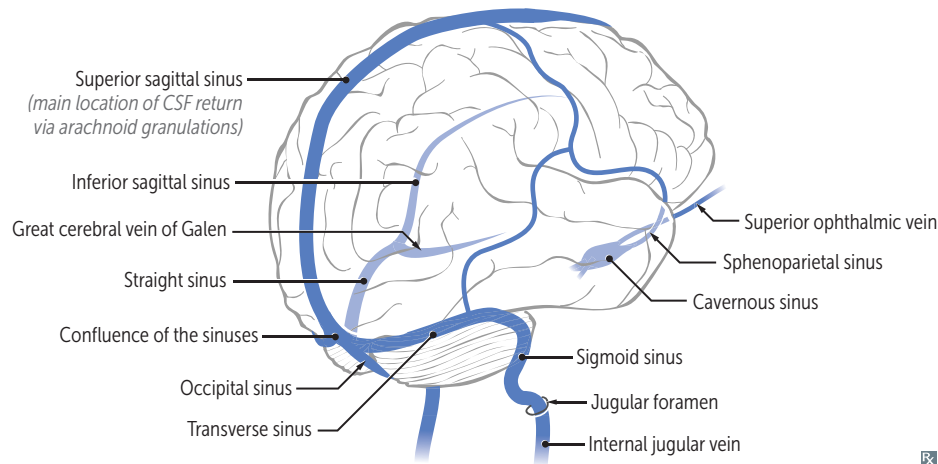
Transient ischemic attack

Brief, reversible episode of focal neurologic dysfunction without acute infarction (⊖ MRI), with the majority resolving in < 15 minutes; deficits due to focal ischemia.

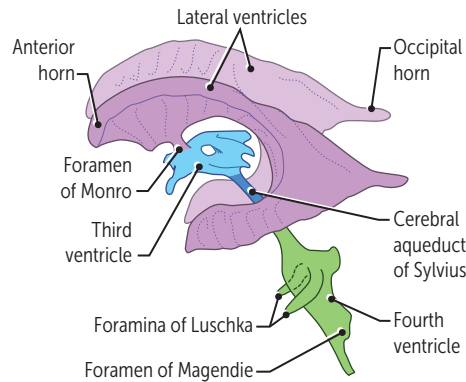
Dural venous sinuses

Large venous channels that run through the dura. Drain blood from cerebral veins and receive CSF from arachnoid granulations. Empty into internal jugular vein.

Venous sinus thrombosis—presents with signs/symptoms of ↑ ICP (eg, headache, seizures, focal neurologic deficits). May lead to venous hemorrhage. Associated with hypercoagulable states (eg, pregnancy, OCP use, factor V Leiden).



Ventricular system



Lateral ventricle → 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 **L**uschka = **L**ateral.
 ■ Foramen of **M**agendie = **M**edial.
 CSF is made by ependymal cells of choroid plexus; it is reabsorbed by arachnoid granulations and then drains into dural venous sinuses.

Idiopathic intracranial hypertension (pseudotumor cerebri)

↑ ICP with no apparent cause on imaging (eg, hydrocephalus, obstruction of CSF outflow). Risk factors include being a woman of childbearing age, vitamin A excess, danazol, tetracycline. Findings: headache, diplopia (usually from CN VI palsy), without change in mental status. Papilledema seen on fundoscopy. Lumbar puncture reveals ↑ opening pressure and provides headache relief. Treatment: weight loss, acetazolamide, topiramate, invasive procedures for refractory cases (eg, repeat lumbar puncture, CSF shunt placement, optic nerve fenestration surgery).

Hydrocephalus

↑ CSF volume → ventricular dilation +/- ↑ ICP.

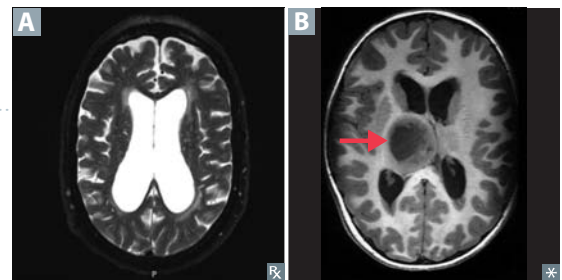
Communicating

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 **A** distorts the fibers of the corona radiata → triad of **u**rinary **i**ncontinence, **a**taxia, and **c**ognitive **d**ysfunction (sometimes reversible). “**W**et, **w**obbly, and **w**acky.” Characteristic magnetic gait (feet appear stuck to floor).



Noncommunicating (obstructive)

Noncommunicating hydrocephalus

Caused by structural blockage of CSF circulation within ventricular system (eg, stenosis of aqueduct of Sylvius; colloid cyst blocking foramen of Monro; tumors **B**).

Hydrocephalus mimics

Ex vacuo ventriculomegaly

Appearance of ↑ CSF on imaging, but is actually due to decreased brain tissue (neuronal atrophy) (eg, Alzheimer disease, advanced HIV, Pick disease). ICP is normal; triad is not seen.

Spinal nerves

There are 31 pairs of spinal nerves in total:
8 cervical, 12 thoracic, 5 lumbar, 5 sacral,
1 coccygeal.

Nerves C1–C7 exit above the corresponding vertebra. C8 spinal nerve exits below C7 and above T1. All other nerves exit below (eg, C3 exits above the 3rd cervical vertebra; L2 exits below the 2nd lumbar vertebra).

Vertebral disc herniation—nucleus pulposus (soft central disc) herniates through annulus fibrosus (outer ring); usually occurs posterolaterally at L4–L5 or L5–S1. Compression of S1 nerve root → absent ankle reflex.

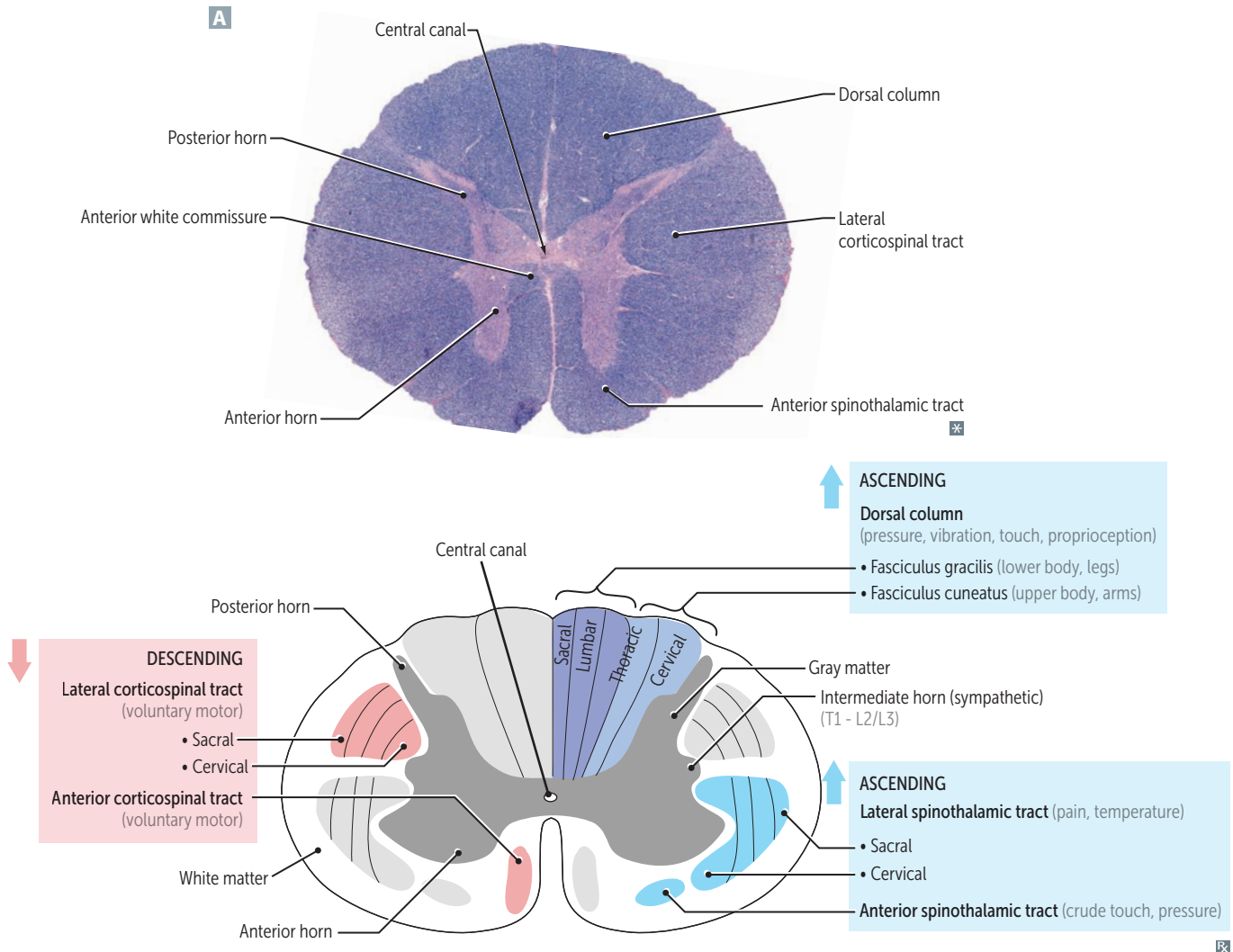
Spinal cord—lower extent

In adults, spinal cord ends at lower border of L1–L2 vertebrae. Subarachnoid space (which contains the CSF) extends to lower border of S2 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**.

Spinal cord and associated tracts

Legs (Lumbosacral) are **L**ateral in **L**ateral corticospinal, spinothalamic tracts **A**.
Dorsal columns are organized as you are, with hands at sides. Arms outside, legs inside.



Spinal tract anatomy and functions

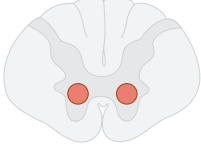
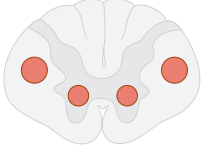
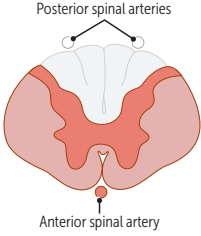



Remember, ascending tracts synapse and then cross.

TRACT AND FUNCTION	1ST-ORDER NEURON	SYNAPSE 1	2ND-ORDER NEURON	SYNAPSE 2	3RD-ORDER NEURON
Dorsal column Ascending: pressure, vibration, fine touch, and proprioception	Sensory nerve ending → cell body in dorsal root ganglion → enters spinal cord, ascends ipsilaterally in dorsal column	Ipsilateral nucleus cuneatus or gracilis (medulla)	Decussates in medulla → ascends contralaterally in medial lemniscus	VPL (thalamus)	Sensory cortex
Spinothalamic tract Ascending Lateral: pain, temperature Anterior: crude touch, pressure	Sensory nerve ending (Aδ and C fibers) → cell body in dorsal root ganglion → enters spinal cord	Ipsilateral gray matter (spinal cord)	Decussates at anterior white commissure → ascends contralaterally	VPL (thalamus)	Sensory cortex
Lateral corticospinal tract Descending: voluntary movement of contralateral limbs	UMN: cell body in 1° motor cortex → descends ipsilaterally (through internal capsule), most fibers decussate at caudal medulla (pyramidal decussation) → descends contralaterally	Cell body of anterior horn (spinal cord)	LMN: leaves spinal cord	NMJ	

Motor neuron signs

SIGN	UMN LESION	LMN LESION	COMMENTS
Weakness	+	+	Lower motor neuron = everything lowered (less muscle mass, ↓ muscle tone, ↓ reflexes, downgoing toes).
Atrophy	–	+	
Fasciculations	–	+	Upper motor neuron = everything up (tone, DTRs, toes).
Reflexes	↑	↓	
Tone	↑	↓	Fasciculations = muscle twitching. Positive Babinski is normal in infants.
Babinski	+	–	
Spastic paralysis	+	–	
Flaccid paralysis	–	+	
Clasp knife spasticity	+	–	

Spinal cord lesions

AREA AFFECTED	DISEASE	CHARACTERISTICS
	Poliomyelitis and Werdnig-Hoffmann disease	<p>Congenital degeneration of anterior horns of spinal cord. LMN lesions only. “Floppy baby” with marked hypotonia and tongue fasciculations. Infantile type has median age of death of 7 months. Autosomal recessive inheritance.</p> <p>Poliomyelitis → asymmetric weakness. Werdnig-Hoffmann disease → symmetric weakness.</p>
	Amyotrophic lateral sclerosis	<p>Combined UMN and LMN deficits with no sensory or bowel/bladder deficits (due to loss of cortical and spinal cord motor neurons, respectively). Can be caused by defect in superoxide dismutase 1. Commonly presents with asymmetric limb weakness (hands/feet), fasciculations, eventual atrophy. Fatal. Commonly known as Lou Gehrig disease. Treatment: riluzole.</p>
	Complete occlusion of anterior spinal artery	<p>Sparses dorsal columns and Lissauer tract; upper thoracic ASA territory is watershed area, as artery of Adamkiewicz supplies ASA below ~ T8.</p>
	Tabes dorsalis	<p>Caused by 3° syphilis. Results from degeneration (demyelination) of dorsal columns and roots → progressive sensory ataxia (impaired proprioception → poor coordination). Associated with Charcot joints, shooting pain, Argyll Robertson pupils. Exam will demonstrate absence of DTRs and ⊕ Romberg sign.</p>
	Syringomyelia	<p>Syrinx expands and damages anterior white commissure of spinothalamic tract (2nd-order neurons) → bilateral loss of pain and temperature sensation in cape-like distribution; seen with Chiari I malformation; can expand and affect other tracts.</p>
	Vitamin B ₁₂ deficiency	<p>Subacute combined degeneration (SCD)—demyelination of Spinocerebellar tracts, lateral Corticospinal tracts, and Dorsal columns. Ataxic gait, paresthesia, impaired position/vibration sense.</p>

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).

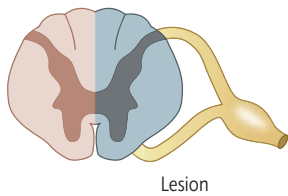
Signs of LMN lesion: weakness, hypotonia, flaccid paralysis, fasciculations, hyporeflexia, muscle atrophy. Signs of infection: malaise, headache, fever, nausea, etc.

CSF shows ↑ WBCs and slight ↑ of protein (with no change in CSF glucose). Virus recovered from stool or throat.

Friedreich ataxia

Autosomal recessive trinucleotide repeat disorder $(GAA)_n$ on chromosome 9 in gene that encodes frataxin (iron binding protein). Leads to impairment in mitochondrial functioning. Degeneration of multiple spinal cord tracts → muscle weakness and loss of DTRs, vibratory sense, proprioception. **Staggering** gait, frequent **falling**, nystagmus, dysarthria, pes cavus, hammer toes, **diabetes mellitus**, **hypertrophic cardiomyopathy** (cause of death). Presents in childhood with kyphoscoliosis **A**.

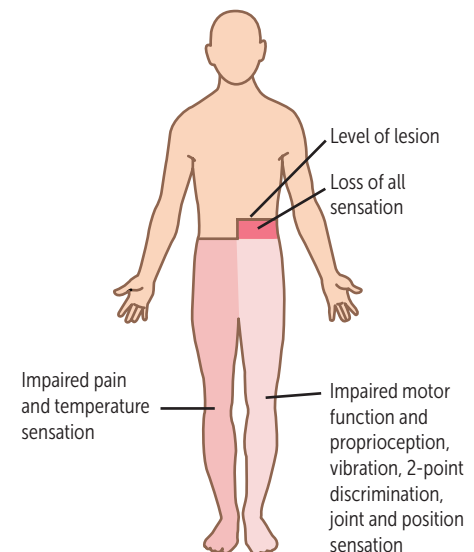
Friedreich is **Frataxic (frataxin)**: he's your favorite **frat** brother, always **staggering** and **falling** but has a **sweet, big heart**. Ataxic **GAA**it.

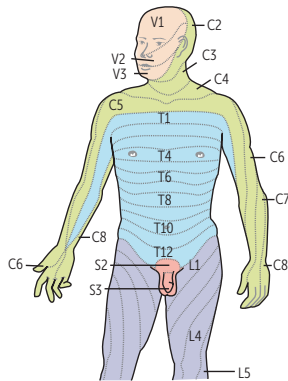
Brown-Séquard syndrome

Hemisection of spinal cord. Findings:

- Ipsilateral UMN signs below level of lesion (due to corticospinal tract damage)
- Ipsilateral loss of tactile, vibration, proprioception sense below level of lesion (due to dorsal column damage)
- Contralateral pain and temperature loss below level of lesion (due to spinothalamic tract damage)
- Ipsilateral loss of all sensation at level of lesion
- Ipsilateral LMN signs (eg, flaccid paralysis) at level of lesion

If lesion occurs above T1, patient may present with ipsilateral Horner syndrome due to damage of oculosympathetic pathway.



Landmark dermatomes

C2—posterior half of a skull “cap.”
 C3—high turtleneck shirt.
 C4—low-collar shirt.
 C6—includes thumbs.
 T4—at the nipple.
 T7—at the xiphoid process.
 T10—at the umbilicus (important for early appendicitis pain referral).
 L1—at the inguinal ligament.
 L4—includes the kneecaps.
 S2, S3, S4—erection and sensation of penile and anal zones.

Diaphragm and gallbladder pain referred to the right shoulder via phrenic nerve.

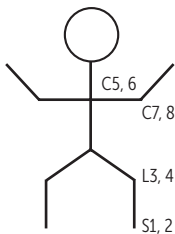
Thumbs up sign on left hand looks like a **six** for C6.
T4 at the **teat pore**.

T10 at the belly **butten**.

L1 is **IL** (Inguinal **L**igament).

Down on **ALL 4's (L4)**.

“**S2, 3, 4** keep the penis off the **floor**.”

Clinical reflexes

Biceps = C5 nerve root.

Triceps = C7 nerve root.

Patella = L4 nerve root.

Achilles = S1 nerve root.

Reflexes count up in order:

S1, 2—“buckle my shoe” (Achilles reflex)

L3, 4—“kick the door” (patellar reflex)

C5, 6—“pick up sticks” (biceps reflex)

C7, 8—“lay them straight” (triceps reflex)

Additional reflexes:

L1, L2—“testicles move” (cremaster reflex)

S3, S4—“winks galore” (anal wink reflex)

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

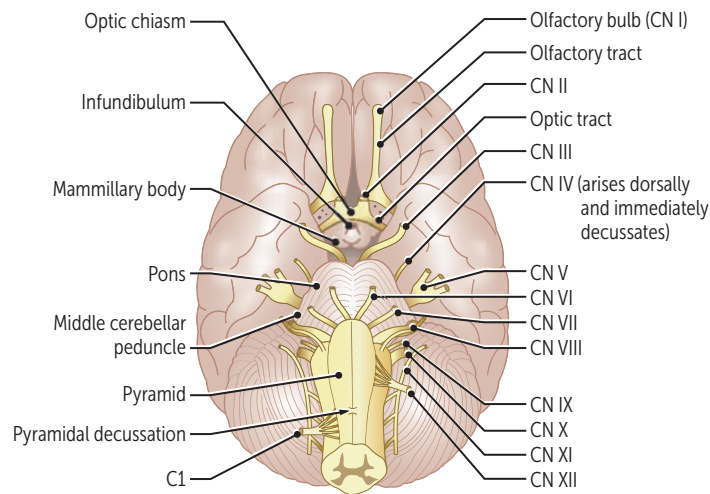
Plantar reflex

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

Brain stem—ventral view

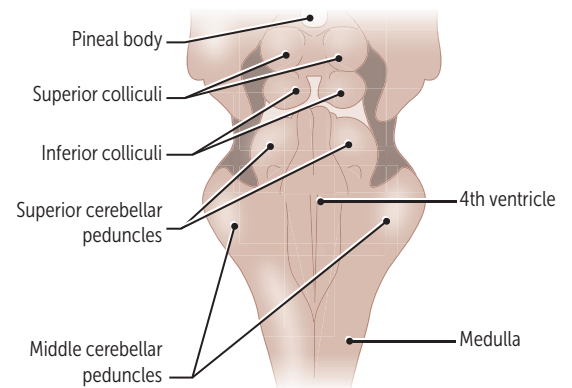


- 4 CN are in above pons (I, II, III, IV).
- 4 CN are in pons (V, VI, VII, VIII).
- 4 CN are in medulla (IX, X, XI, XII).
- 4 CN nuclei are medial (III, IV, VI, XII). “Factors of 12, except 1 and 2.”

Brain stem—dorsal view (cerebellum removed)

Pineal gland—melatonin secretion, circadian rhythms.
 Superior colliculi—conjugate vertical gaze center.
 Inferior colliculi—auditory.
Parinaud syndrome—paralysis of conjugate vertical gaze due to lesion in superior colliculi (eg, stroke, hydrocephalus, pinealoma).

Your eyes are **above** your ears, and the superior colliculus (visual) is **above** the inferior colliculus (auditory).



Cranial nerve nuclei

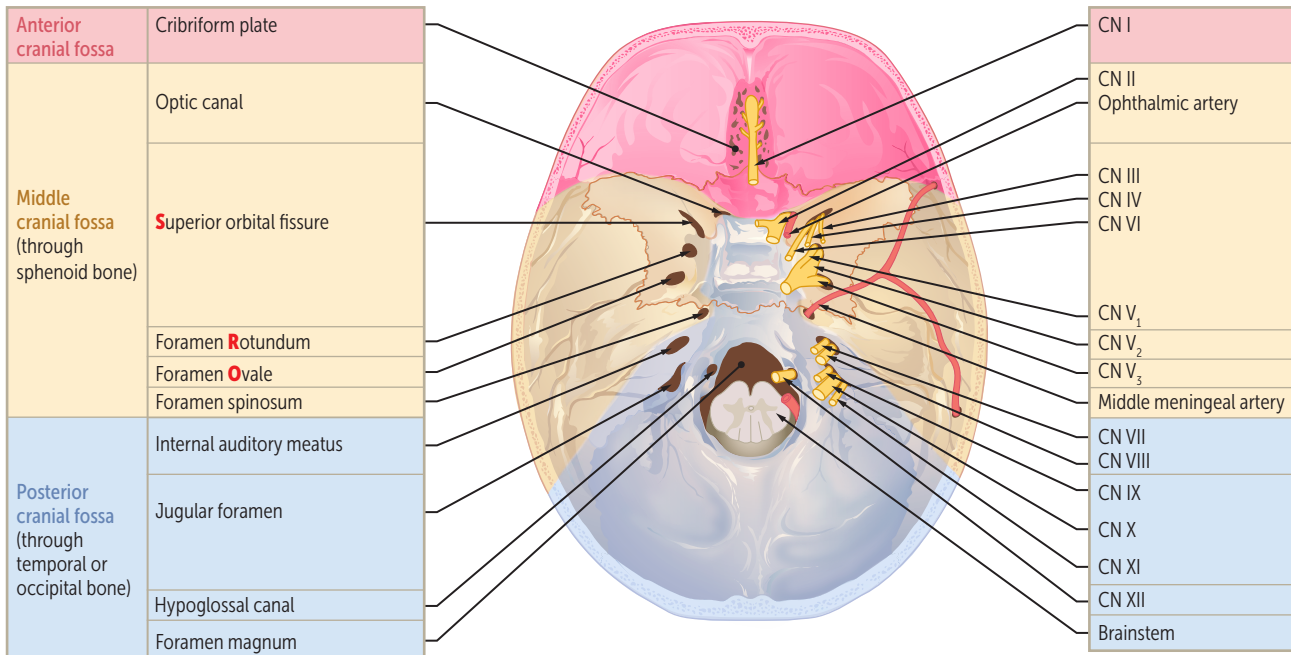
Located in tegmentum portion of brain stem
(between dorsal and ventral portions):

- 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 (a**L**ar plate).

—Sulcus limitans—

Medial nuclei = **M**otor (basal plate).

Cranial nerve and vessel pathways

Divisions of CN V exit owing to **S**tanding **R**oom **O**nly



Cranial nerves

NERVE	CN	FUNCTION	TYPE	MNEMONIC
Olfactory	I	Smell (only CN without thalamic relay to cortex)	Sensory	Some
Optic	II	Sight	Sensory	Say
Oculomotor	III	Eye movement (SR, IR, MR, IO), pupillary constriction (sphincter pupillae: Edinger-Westphal nucleus, muscarinic receptors), accommodation, eyelid opening (levator palpebrae)	Motor	Marry
Trochlear	IV	Eye movement (SO)	Motor	Money
Trigeminal	V	Mastication, facial sensation (ophthalmic, maxillary, mandibular divisions), somatosensation from anterior $2/3$ of tongue	Both	But
Abducens	VI	Eye movement (LR)	Motor	My
Facial	VII	Facial movement, taste from anterior $2/3$ of tongue, lacrimation, salivation (submandibular and sublingual glands), eyelid 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, coughing, 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 Solitarius	Visceral Sensory information (eg, taste, baroreceptors, gut distention)	VII, IX, X
Nucleus ambiguus	Motor 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

Cranial nerve reflexes

REFLEX	AFFERENT	EFFERENT
Corneal	V ₁ ophthalmic (nasociliary branch)	VII (temporal branch: orbicularis oculi)
Lacrimation	V ₁ (loss of reflex does not preclude emotional tears)	VII
Jaw jerk	V ₃ (sensory—muscle spindle from masseter)	V ₃ (motor—masseter)
Pupillary	II	III
Gag	IX	X

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 away 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 weakened tongue muscles on affected side.

Mastication muscles

3 muscles close jaw: **M**asseter, **tM**poralis, **M**edial pterygoid. 1 opens: lateral pterygoid. All are innervated by trigeminal nerve (V₃).

M's **M**unch.

Lateral **L**owers (when speaking of pterygoids with respect to jaw motion).

“It takes more muscle to keep your mouth shut.”

Facial nerve lesions

Upper motor neuron lesion

Destruction of motor cortex or connection between motor cortex and facial nucleus in pons → contralateral paralysis of lower muscles of facial expression. Forehead is spared due to its bilateral UMN innervation.

Lower motor neuron lesion

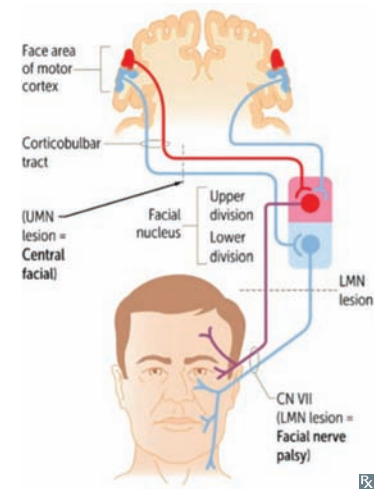
Destruction of facial nucleus or CN VII anywhere along its course → ipsilateral paralysis of upper and lower muscles of facial expression **A**, hyperacusis, loss of taste sensation to anterior tongue.

Facial nerve palsy



Clinical syndrome of peripheral CN VII (LMN) lesion. Depending on lesion location and severity, may cause partial or complete loss of function.

When idiopathic (most common), called **Bell palsy**. May also be caused by Lyme disease, herpes simplex, herpes zoster (Ramsay Hunt syndrome), sarcoidosis, tumors, diabetes mellitus. Treatment is corticosteroids, acyclovir. Most patients have gradual recovery of function.

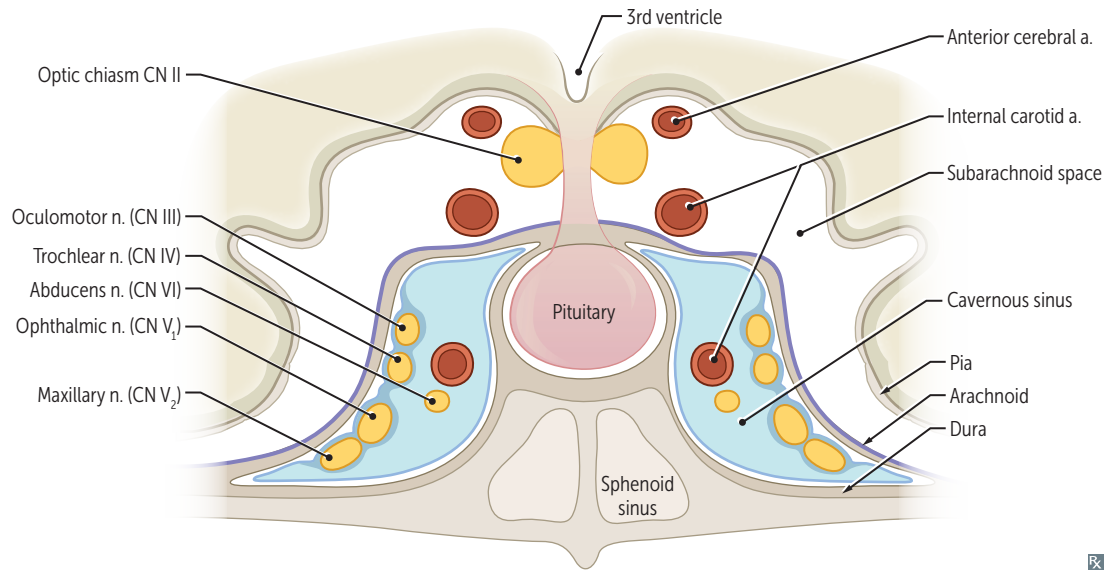


Cavernous sinus

Collection of venous sinuses on either side of pituitary. Blood from eye and superficial cortex → cavernous sinus → internal jugular vein.

CNs III, IV, V₁, VI, and occasionally V₂ 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. CN VI is most susceptible to injury.



8x

Auditory physiology

Outer ear

Visible portion of ear (pinna), includes auditory canal and eardrum. Transfers sound waves via vibration of eardrum.

Middle ear

Air-filled space with three bones called the ossicles (malleus, incus, stapes). Ossicles conduct and amplify sound from eardrum 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):

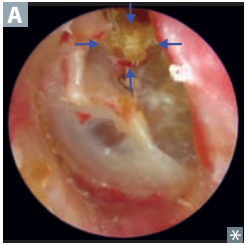
- Low frequency heard at apex near helicotrema (wide and flexible).
- High frequency heard best at base of cochlea (thin and rigid).

Hearing loss

	RINNE TEST	WEBER TEST
Conductive	Abnormal (bone > air)	Localizes to affected ear
Sensorineural	Normal (air > bone)	Localizes to unaffected ear
Noise-induced	Damage to stereociliated cells in organ of Corti; loss of high-frequency hearing 1st; sudden extremely loud noises can produce hearing loss due to tympanic membrane rupture.	

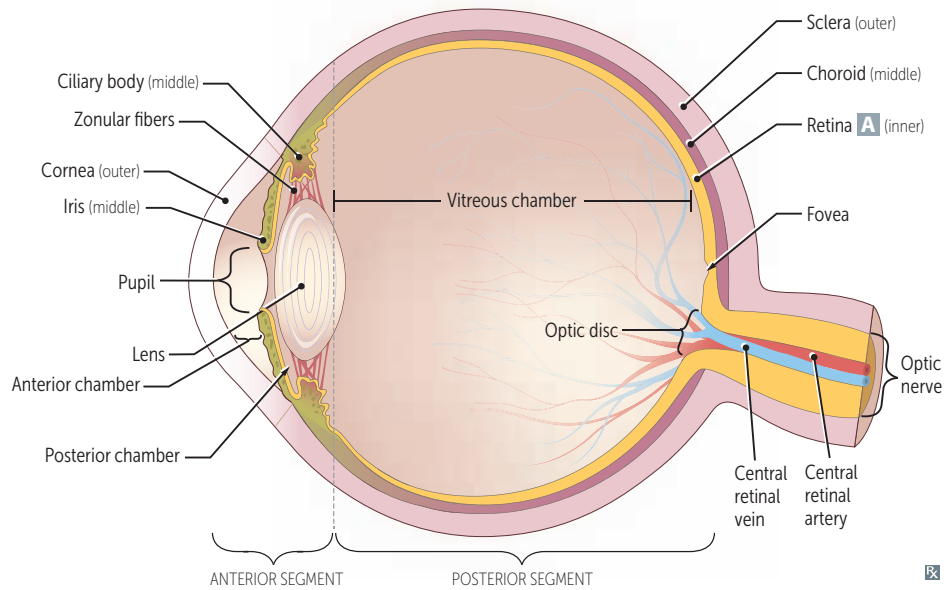
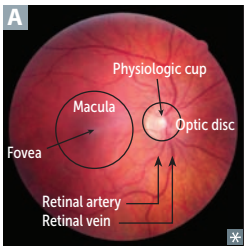
Cholesteatoma

Overgrowth of desquamated keratin debris within the middle ear space (A, blue arrows); may erode ossicles, mastoid air cells → conductive hearing loss.

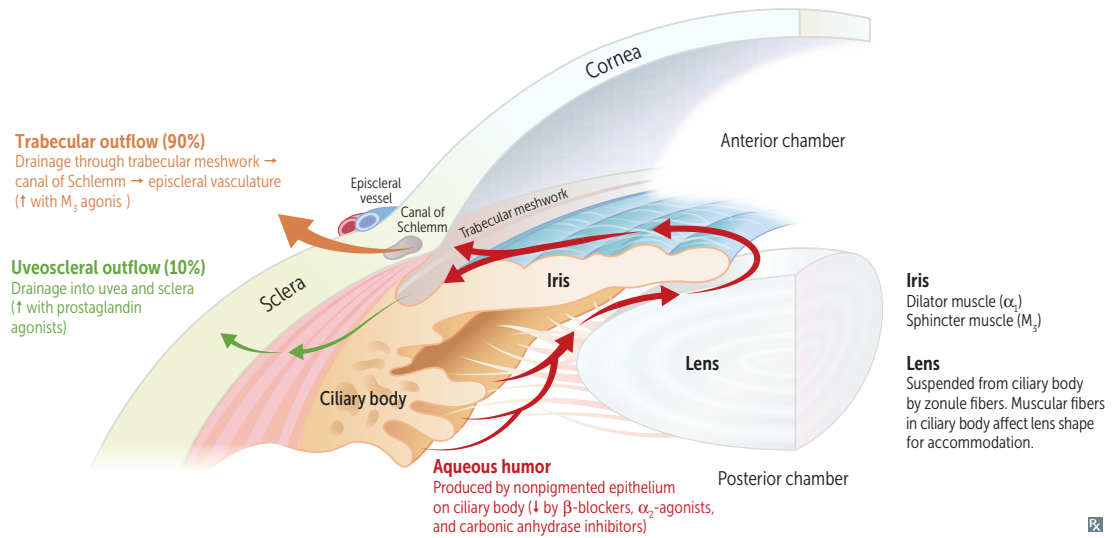


▶ NEUROLOGY—OPHTHALMOLOGY

Normal eye



Aqueous humor pathway



Refractive errors

Common cause of impaired vision, correctable with glasses.

Hyperopia

Eye too short for refractive power of cornea and lens → light focused behind retina.

Myopia

Eye too long for refractive power of cornea and lens → light focused in front of retina.

Astigmatism

Abnormal curvature of cornea → different refractive power at different axes.

Presbyopia

Age-related impaired accommodation (focusing on near objects), primarily due to ↓ lens elasticity. Often necessitates “reading glasses.”

Cataract

Painless, often bilateral, opacification of lens **A**, often resulting in ↓ vision. 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), TORCHeS infections (eg, rubella), Marfan syndrome, Alport syndrome, myotonic dystrophy, neurofibromatosis 2.



Glaucoma

Optic disc atrophy with characteristic cupping (thinning of outer rim of optic nerve head **B** versus normal **A**), usually with elevated intraocular pressure (IOP) and progressive peripheral visual field loss if untreated. Treatment is through pharmacologic or surgical lowering of the 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 narrow-angle glaucoma

Primary—enlargement or forward 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 **C** and impeding flow through trabecular meshwork.

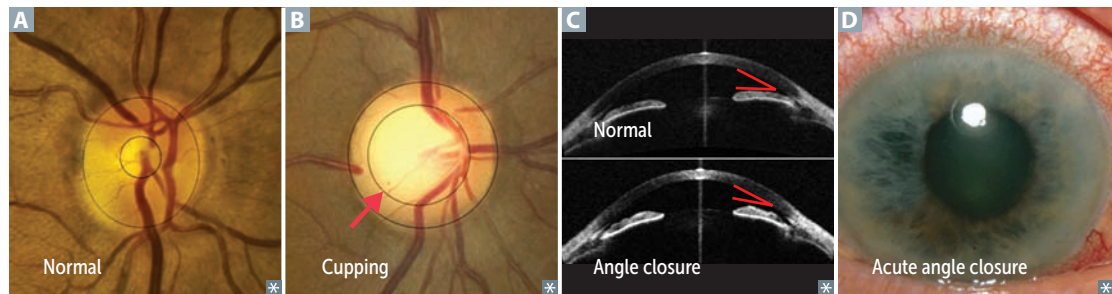
Secondary—hypoxia from retinal disease (eg, diabetes mellitus, vein occlusion) induces vasoproliferation in iris that contracts angle.

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 **D**, sudden vision loss, halos around lights, rock-hard eye, frontal headache.

Do not give epinephrine because of its mydriatic effect.

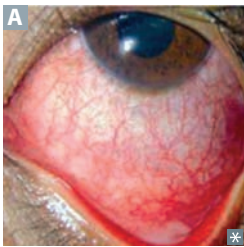
**Conjunctivitis**

Inflammation of the conjunctiva → red eye **A**.

Allergic—itchy eyes, bilateral.

Bacterial—pus; treat with antibiotics.

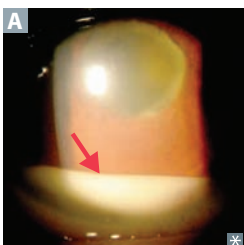
Viral—most common, often adenovirus; sparse mucous discharge, swollen preauricular node; self-resolving.

**Uveitis**

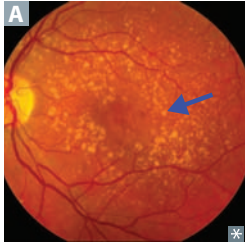
Inflammation of uvea, specific name based on location within affected eye. Anterior uveitis:

iritis; intermediate uveitis: pars planitis; 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).



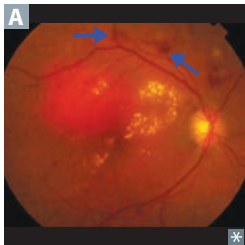
Age-related macular degeneration



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 in and between Bruch membrane and retinal pigment epithelium (“drusen”) **A** 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, ranibizumab).

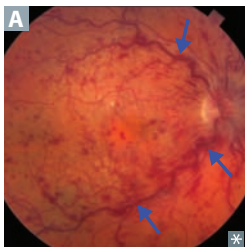
Diabetic retinopathy



Retinal damage due to chronic hyperglycemia. Two types:

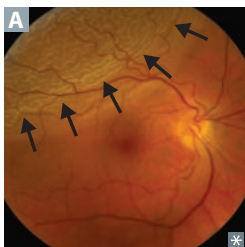
- Nonproliferative—damaged capillaries leak blood → lipids and fluid seep into retina → hemorrhages (blue arrows in **A**) and macular edema. Treatment: blood sugar control.
- Proliferative—chronic hypoxia results in new blood vessel formation with resultant traction on retina. Treatment: peripheral retinal photocoagulation, surgery, anti-VEGF.

Retinal vein occlusion



Blockage of central or branch retinal vein due to compression from nearby arterial atherosclerosis. Retinal hemorrhage and venous engorgement (blue arrows in **A**), edema in affected area.

Retinal detachment

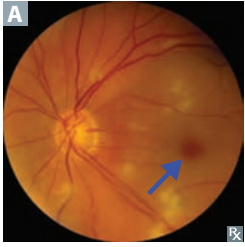


Separation of neurosensory layer of retina (photoreceptor layer with rods and cones) from outermost pigmented epithelium (normally shields excess light, supports retina) → degeneration of photoreceptors → vision loss. May be 2° to retinal breaks, diabetic traction, inflammatory effusions. Visualized on funduscopy 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.

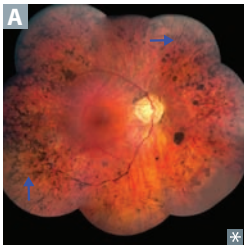
Central retinal artery occlusion

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).



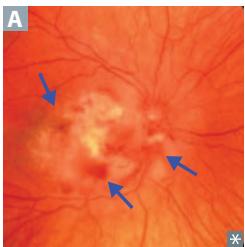
Retinitis pigmentosa

Inherited retinal degeneration. Painless, progressive vision loss beginning with night blindness (rods affected first). Bone spicule-shaped deposits around macula **A**.



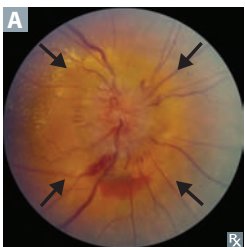
Retinitis

Retinal edema and necrosis (blue arrows in **A**) leading to scar. Often viral (CMV, HSV, VZV), but can be bacterial or parasitic. May be associated with immunosuppression.



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**.



Pupillary control

Miosis

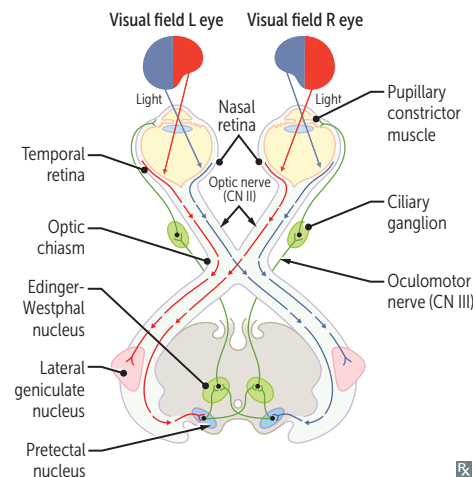
Constriction, parasympathetic:

- 1st neuron: Edinger-Westphal nucleus to ciliary ganglion via CN III
- 2nd neuron: short ciliary nerves to pupillary sphincter muscles

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 contract bilaterally (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.

Marcus Gunn pupil

Afferent pupillary defect—due to optic nerve damage or severe retinal injury. ↓ bilateral pupillary constriction when light is shone in affected eye relative to unaffected eye. Tested with “swinging flashlight test.”

Horner syndrome

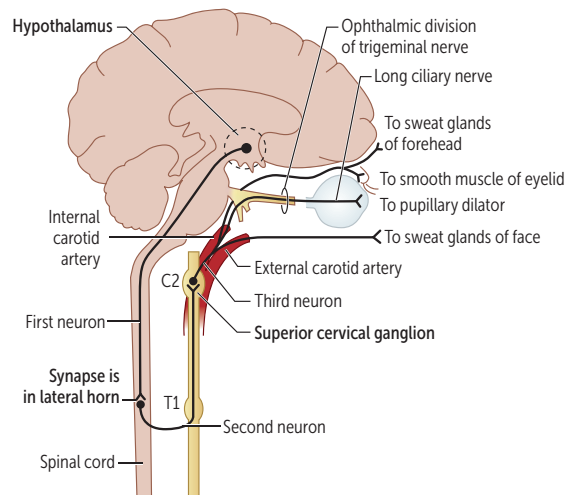
Sympathetic denervation of face →:

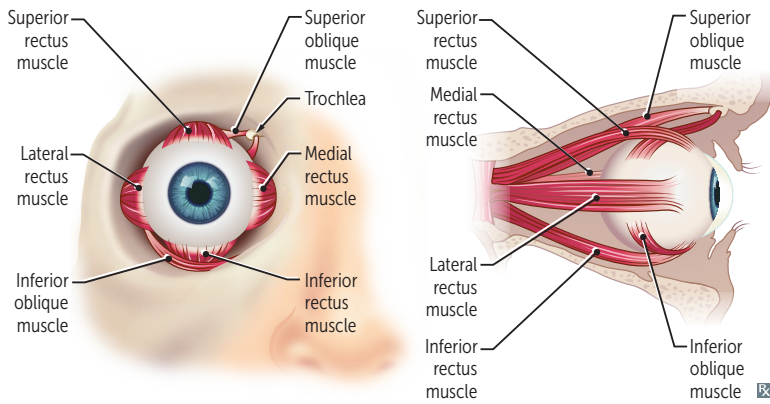
- **P**tosis (slight drooping of eyelid: superior tarsal muscle)
- **A**nhidrosis (absence of sweating) and flushing of affected side of face
- **M**iosis (pupil constriction)

Associated with lesion of spinal cord above T1 (eg, Pancoast tumor, Brown-Séquard syndrome, late-stage syringomyelia). Any interruption results in Horner syndrome.

PAM is horny (Horner).

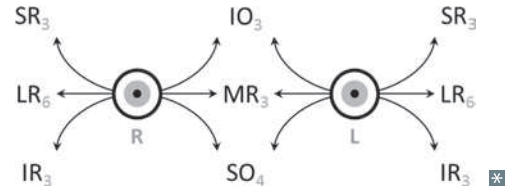
Ptos**i**s, **a**nhidros**i**s, and **m**iosis (rhyming).



Ocular motility

To test each muscle, ask patient to move his/her eye in the path diagrammed below, from neutral position toward the muscle being tested.

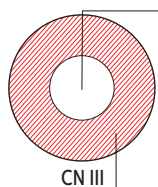
CN **VI** innervates the **Lateral Rectus**.
 CN **IV** innervates the **Superior Oblique**.
 CN **III** innervates the **Rest**.
 The “chemical formula” **LR₆SO₄R₃**.
 The superior oblique abducts, intorts, and depresses while adducted.



Obliques go **O**pposite (left SO and IO tested with patient looking right).
IOU: **IO** tested looking **U**p.

CN III, IV, VI palsies

CN III damage

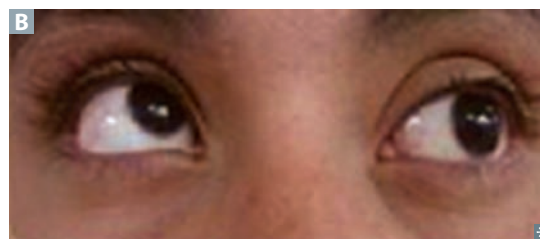


CN III has both motor (central) and parasympathetic (peripheral) components. Motor output to ocular muscles—affected primarily by vascular disease (eg, diabetes mellitus: glucose → sorbitol) due to ↓ diffusion of oxygen and nutrients to the interior fibers from compromised vasculature that resides on outside of nerve. Signs: ptosis, “down and out” gaze **A**. Parasympathetic output—fibers on the periphery are 1st affected by compression (eg, posterior communicating artery aneurysm, uncal herniation). Signs: diminished or absent pupillary light reflex, “blown pupil” often with “down-and-out” gaze.



CN IV damage

Eye moves upward, particularly with contralateral gaze **B** and head tilt toward the side of the lesion (problems going down stairs, may present with compensatory head tilt in the opposite direction).



CN VI damage

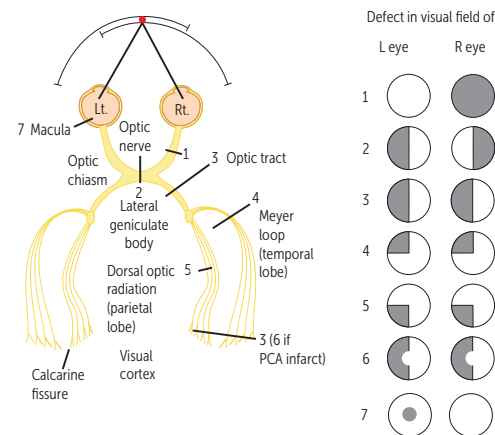
Medially directed eye that cannot abduct **C**.



Visual field defects

1. Right anopia
2. Bitemporal hemianopia (pituitary lesion, chiasm)
3. Left homonymous hemianopia
4. Left upper quadrantic anopia (right temporal lesion, MCA)
5. Left lower quadrantic anopia (right parietal lesion, MCA)
6. Left hemianopia with macular sparing (PCA infarct)
7. Central scotoma (eg, macular degeneration)

Meyer loop—inferior retina; loops around inferior horn of lateral ventricle.
Dorsal optic radiation—superior retina; takes shortest path via internal capsule.

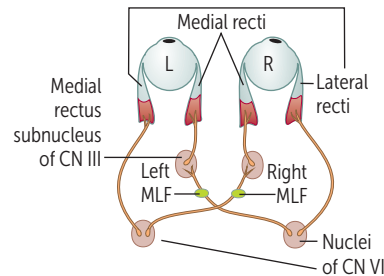


Note: When an image hits 1° visual cortex, it is upside down and left-right reversed.

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).

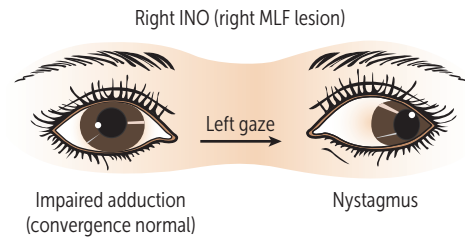
Lesion in MLF = internuclear ophthalmoplegia (INO), a conjugate horizontal gaze palsy. Lack of communication such that when CN VI nucleus activates ipsilateral lateral rectus, contralateral CN III nucleus does not stimulate medial rectus to fire. Abducting eye gets nystagmus (CN VI overfires to stimulate 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.

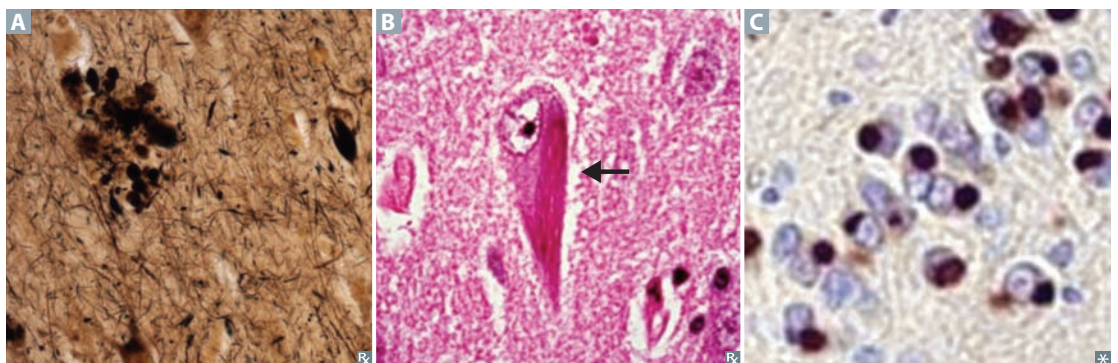
Directional term (eg, right INO, left INO) refers to which eye is paralyzed.



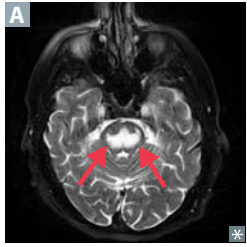
▶ NEUROLOGY—PATHOLOGY

Dementia ↓ in cognitive ability, memory, or function with intact consciousness.

DISEASE	DESCRIPTION	HISTOLOGIC/GROSS FINDINGS
Alzheimer disease	<p>Most common cause in elderly. Down syndrome patients have an ↑ risk of developing Alzheimer.</p> <p>Associated with the following altered proteins:</p> <ul style="list-style-type: none"> ▪ ApoE2: ↓ risk of sporadic form ▪ ApoE4: ↑ risk of sporadic form ▪ APP, presenilin-1, presenilin-2: familial forms (10%) with earlier onset 	<p>Widespread cortical atrophy. Narrowing of gyri and widening of sulci.</p> <p>↓ ACh.</p> <p>Senile plaques A in gray matter: extracellular β-amyloid core; may cause amyloid angiopathy → intracranial hemorrhage; Aβ (amyloid-β) synthesized by cleaving amyloid precursor protein (APP).</p> <p>Neurofibrillary tangles B: intracellular, hyperphosphorylated tau protein = insoluble cytoskeletal elements; number of tangles correlates with degree of dementia.</p>
Frontotemporal dementia	<p>Early changes in personality and behavior (behavioral variant), or aphasia (primary progressive aphasia).</p> <p>May have associated movement disorders (eg, parkinsonism, ALS-like UMN/LMN degeneration).</p> <p>Previously known as Pick disease.</p>	<p>Frontotemporal lobe degeneration.</p> <p>Inclusions of hyperphosphorylated tau (round Pick bodies; C) or ubiquitinated TDP-43.</p>
Lewy body dementia	<p>Initially dementia and visual hallucinations (“haLewycinations”) followed by parkinsonian features.</p>	<p>Intracellular Lewy bodies (insoluble aggregates of α-synuclein) primarily in cortex.</p>
Vascular dementia	<p>Result of multiple arterial infarcts and/or chronic ischemia.</p> <p>Step-wise decline in cognitive ability with late-onset memory impairment. 2nd most common cause of dementia in elderly.</p>	<p>MRI or CT shows multiple cortical and/or subcortical infarcts.</p>
Creutzfeldt-Jakob disease	<p>Rapidly progressive (weeks to months) dementia with myoclonus (“startle myoclonus”).</p>	<p>Spongiform cortex.</p> <p>Prions (PrP^c → PrP^{sc} sheet [β-pleated sheet resistant to proteases]).</p>
Other causes	<p>Syphilis; HIV; hypothyroidism; vitamins B₁, B₃, or B₁₂ deficiency; Wilson disease; normal pressure hydrocephalus.</p>	



Osmotic demyelination syndrome (central pontine myelinolysis)



Acute paralysis, dysarthria, dysphagia, diplopia, loss of consciousness. Can cause “locked-in syndrome.” Massive axonal demyelination in pontine white matter **A** 2° to osmotic changes. Commonly iatrogenic, caused by overly rapid correction of hyponatremia. In contrast, correcting hypernatremia too quickly results in cerebral edema/herniation.

Correcting serum Na⁺ too fast:

- “From low to high, your pons will die” (osmotic demyelination syndrome)
- “From high to low, your brain will blow” (cerebral edema/herniation)

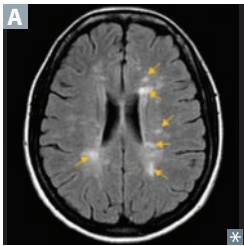
Multiple sclerosis

Autoimmune inflammation and demyelination of CNS (brain and spinal cord). Patients can present with optic neuritis (sudden loss of vision resulting in Marcus Gunn pupils), INO, hemiparesis, hemisensory symptoms, bladder/bowel dysfunction. Relapsing and remitting course. Most often affects women in their 20s and 30s; more common in whites living further from equator.

Charcot triad of MS is a **SIN**:

- **S**canning speech
- **I**ntention tremor (also **I**ncontinence and **I**nternuclear ophthalmoplegia)
- **N**ystagmus

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) with destruction of axons. Multiple white matter lesions separated in space and time.

TREATMENT

Slow progression with disease-modifying therapies (eg, β-interferon, glatiramer, natalizumab). Treat acute flares with IV steroids. Symptomatic treatment for neurogenic bladder (catheterization, muscarinic antagonists), spasticity (baclofen, GABA_B receptor agonists), pain (opioids).

Acute inflammatory demyelinating polyradiculopathy

Most common subtype of **Guillain-Barré syndrome**. Autoimmune condition that destroys Schwann cells → inflammation and demyelination of peripheral nerves and motor fibers. Results in symmetric ascending muscle weakness/paralysis beginning in lower extremities. Facial paralysis in 50% of cases. May see autonomic dysregulation (eg, cardiac irregularities, hypertension, hypotension) or sensory abnormalities. Almost all patients survive; the majority recover completely after weeks to months.

Findings: ↑ CSF protein with normal cell count (albuminocytologic dissociation). ↑ protein may cause papilledema.

Associated with infections (eg, *Campylobacter jejuni*, viral) → autoimmune attack of peripheral myelin due to molecular mimicry, inoculations, and stress, but no definitive link to pathogens.

Respiratory support is critical until recovery. Additional treatment: plasmapheresis, IV immunoglobulins. No role for steroids.

Other demyelinating and dysmyelinating diseases**Acute disseminated (postinfectious) encephalomyelitis**

Multifocal periventricular inflammation and demyelination after infection or vaccination. Presents with rapidly progressive multifocal neurologic symptoms, altered mental status.

Charcot-Marie-Tooth disease

Also known as hereditary motor and sensory neuropathy (HMSN). 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 inheritance pattern and associated with foot deformities (pes cavus), lower extremity weakness and sensory deficits.

Krabbe disease

Autosomal recessive lysosomal storage disease due to deficiency of galactocerebrosidase. Buildup of galactocerebroside and psychosine destroys myelin sheath. Findings: peripheral neuropathy, developmental delay, optic atrophy, globoid cells.

Metachromatic leukodystrophy

Autosomal recessive lysosomal storage disease, most commonly due to arylsulfatase A deficiency. Buildup of sulfatides → impaired production and destruction of myelin sheath. Findings: central and peripheral demyelination with ataxia, dementia.

Progressive multifocal leukoencephalopathy

Demyelination of CNS due to destruction of oligodendrocytes. Seen in 2–4% of AIDS patients (reactivation of latent JC virus infection). Rapidly progressive, usually fatal. ↑ risk associated with natalizumab, rituximab.

Adrenoleukodystrophy

X-linked genetic disorder typically affecting males. Disrupts metabolism of very-long-chain fatty acids → excessive buildup in nervous system, adrenal gland, testes. Progressive disease that can lead to long-term coma/death and adrenal gland crisis.

Seizures

Characterized by synchronized, high-frequency neuronal firing. Variety of forms.

Partial (focal) seizures

Affect single area of the brain. Most commonly originate in medial temporal lobe. Often preceded by seizure aura; can secondarily generalize. Types:

- **Simple partial** (consciousness intact)—motor, sensory, autonomic, psychic
- **Complex partial** (impaired consciousness)

Generalized seizures

Diffuse. Types:

- **Absence** (petit mal)—3 Hz, no postictal confusion, blank stare
- **Myoclonic**—quick, repetitive jerks
- **Tonic-clonic** (grand mal)—alternating stiffening and movement
- **Tonic**—stiffening
- **Atonic**—“drop” seizures (falls to floor); commonly mistaken for fainting

Epilepsy—a disorder of recurrent seizures (febrile seizures are not epilepsy).

Status epilepticus—continuous or recurring seizure(s) that may result in brain injury; defined as > 5 min.

Causes of seizures by age:

- Children—genetic, infection (febrile), trauma, congenital, metabolic
- Adults—tumor, trauma, stroke, infection
- Elderly—stroke, tumor, trauma, metabolic, infection

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
Cluster^a	Unilateral	15 min–3 hr; repetitive	Repetitive brief headaches. Excruciating periorbital pain with lacrimation and rhinorrhea. May present with Horner syndrome.	Acute: sumatriptan, 100% O ₂ Prophylaxis: verapamil
Tension	Bilateral	> 30 min (typically 4–6 hr); constant	Steady pain. No photophobia or phonophobia. No aura.	Analgesics, NSAIDs, acetaminophen; amitriptyline for chronic pain
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 substance P, calcitonin gene–related peptide, vasoactive peptides).	Acute: NSAIDs, triptans, dihydroergotamine Prophylaxis: lifestyle changes (eg, sleep, exercise, diet), β-blockers, calcium channel blockers, amitriptyline, topiramate, valproate. POUND —Pulsatile, One-day duration, Unilateral, Nausea, Disabling

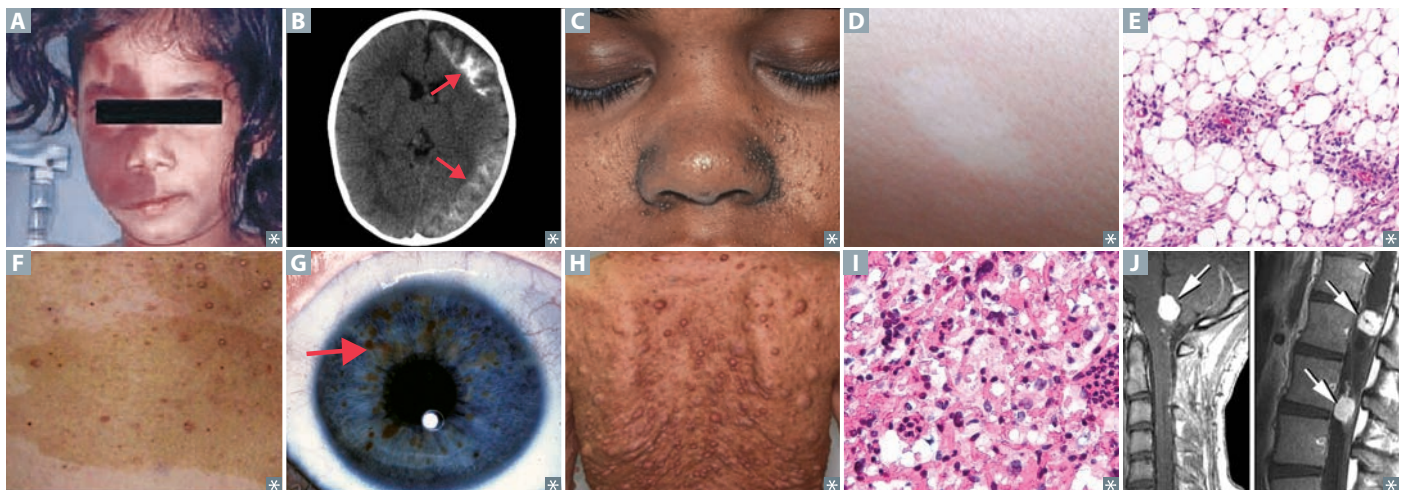
Other causes of headache include subarachnoid hemorrhage (“worst headache of my life”), meningitis, hydrocephalus, neoplasia, arteritis.

^aCompare with trigeminal neuralgia, which produces repetitive, unilateral, shooting pain in the distribution of CN V that lasts (typically) for < 1 minute.

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). Positional testing → delayed horizontal nystagmus.
Central vertigo	Brain stem or cerebellar lesion (eg, stroke affecting vestibular nuclei or posterior fossa tumor). Findings: directional change of nystagmus, skew deviation, diplopia, dysmetria. Positional testing → immediate nystagmus in any direction; may change directions. Focal neurologic findings.

Neurocutaneous disorders

Sturge-Weber syndrome (encephalotrigeminal angiomatosis)	<p>Congenital, non-inherited (somatic), developmental anomaly of neural crest derivatives due to activating mutation of <i>GNAQ</i> gene. Affects small (capillary-sized) blood vessels → port-wine stain of the face A (nevus flammeus, a non-neoplastic “birthmark” in CN V₁/V₂ distribution); ipsilateral leptomeningeal angioma B → seizures/epilepsy; intellectual disability; and episcleral hemangioma → ↑ IOP → early-onset glaucoma.</p> <p>STURGE-Weber: Sporadic, port-wine Stain; Tram track calcifications (opposing gyri); Unilateral; Retardation (intellectual disability); Glaucoma; GNAQ gene; Epilepsy.</p>
Tuberous sclerosis	<p>HAMARTOMAS: 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. ↑ incidence of subependymal astrocytomas and ungual fibromas.</p>
Neurofibromatosis type I (von Recklinghausen disease)	<p>Café-au-lait spots F, Lisch nodules (pigmented iris hamartomas G), cutaneous neurofibromas H, optic gliomas, pheochromocytomas. Mutated <i>NF1</i> tumor suppressor gene (neurofibromin, a negative regulator of RAS) on chromosome 17. Neurofibromas are derived from neural crest cells.</p>
von Hippel-Lindau disease	<p>Hemangioblastomas (high vascularity with hyperchromatic nuclei I) in retina, brain stem, cerebellum, spine J; angiomatosis (eg, cavernous hemangiomas in skin, mucosa, organs); bilateral renal cell carcinomas; pheochromocytomas.</p>



Adult primary brain tumors**Glioblastoma multiforme (grade IV astrocytoma)**

Common, highly malignant 1° brain tumor with ~1-year median survival. Found in cerebral hemispheres **A**. Can cross corpus callosum (“butterfly glioma”). “Pseudopalisading” pleomorphic tumor cells **B**—border central areas of necrosis and hemorrhage. Stain astrocytes for GFAP.

Meningioma

Common, typically benign 1° brain tumor. Most often occurs near surfaces of brain and parasagittal region. Arises from arachnoid cells, is extra-axial (external to brain parenchyma), and may have a dural attachment (“tail” **C**). Often asymptomatic; may present with seizures or focal neurologic signs. Resection and/or radiosurgery. Spindle cells concentrically arranged in a whorled pattern; psammoma bodies **D** (laminated calcifications).

Hemangioblastoma

Most often cerebellar **E**. Associated with von Hippel-Lindau syndrome when found with retinal angiomas. Can produce erythropoietin → 2° polycythemia. Closely arranged, thin-walled capillaries with minimal intervening parenchyma **F**.

Schwannoma

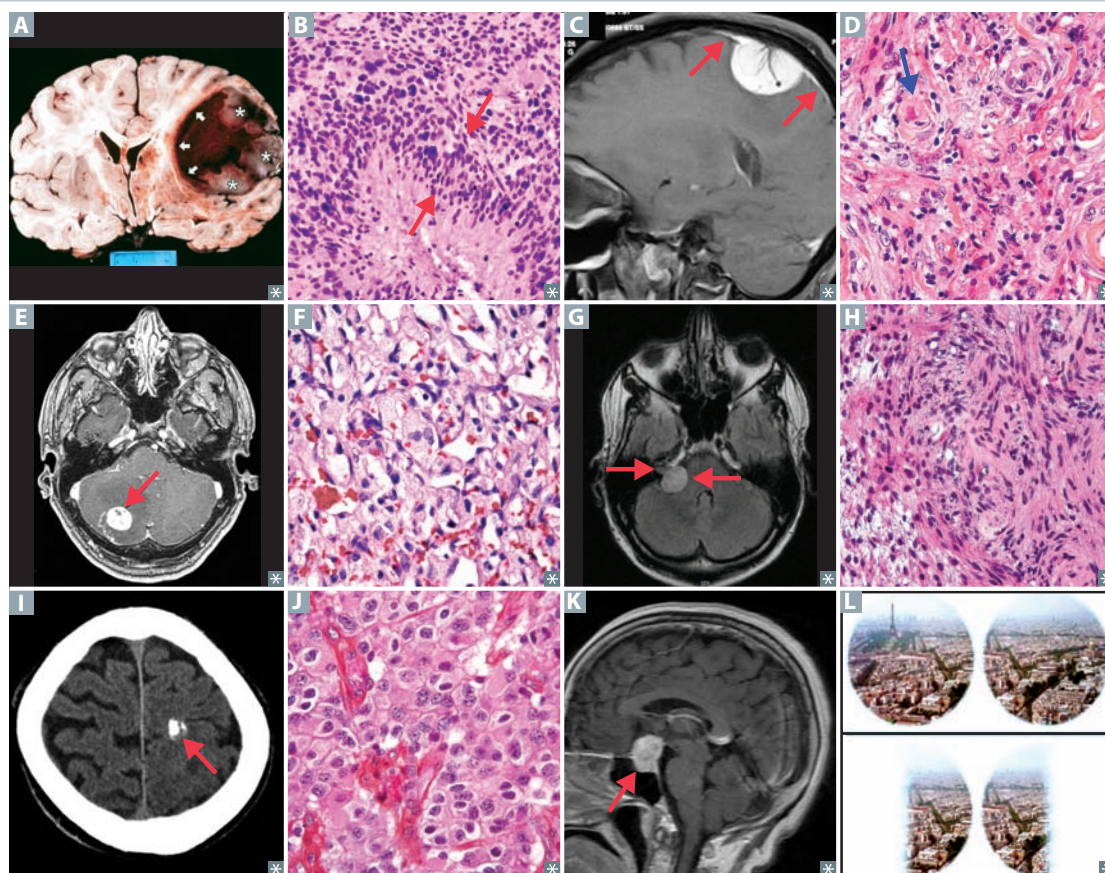
Classically at the cerebellopontine angle **G**, but can be along any peripheral nerve. Often localized to CN VIII → vestibular schwannoma. Bilateral vestibular schwannomas found in NF-2. Resection or stereotactic radiosurgery. Schwann cell origin **H**, S-100 ⊕.

Oligodendroglioma

Relatively rare, slow growing. Most often in frontal lobes **I**. “Chicken-wire” capillary pattern. Oligodendrocytes = “fried egg” cells—round nuclei with clear cytoplasm **J**. Often calcified.

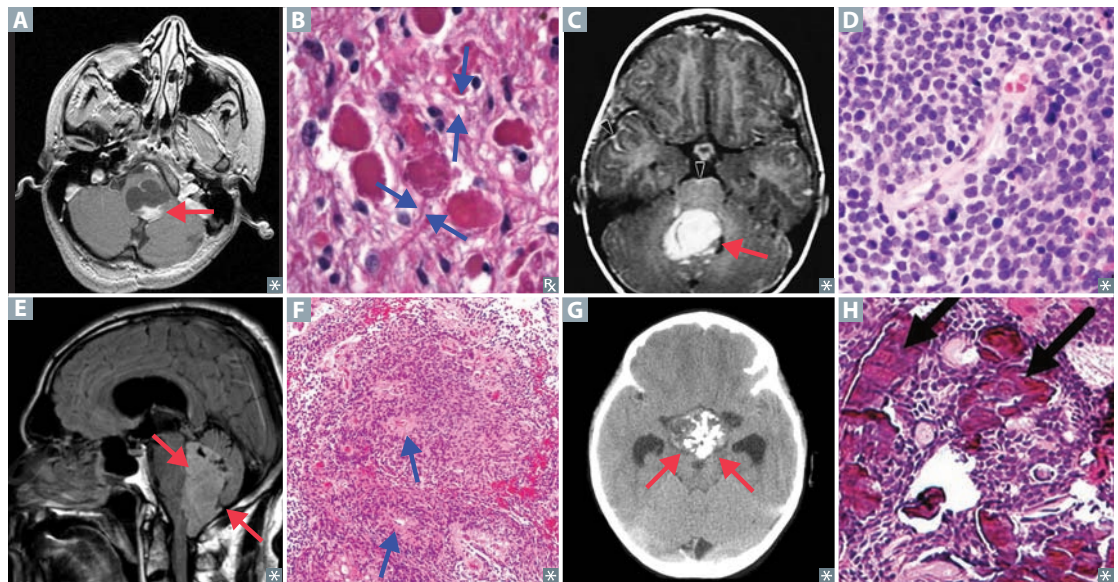
Pituitary adenoma

Most commonly prolactinoma **K** (lactotroph adenoma) or nonfunctioning adenoma. Bitemporal hemianopia due to pressure on optic chiasm (**L** shows normal visual field above, patient’s perspective below). Hyper- or hypopituitarism are sequelae. Hyperplasia of a single type of endocrine cell found in pituitary (ie, lactotroph, gonadotroph, somatotroph, corticotroph).

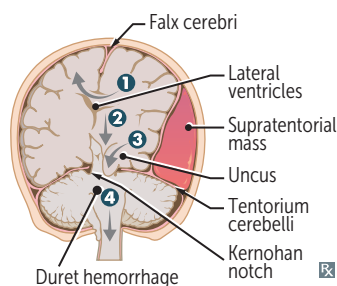


Childhood primary brain tumors

Pilocytic (low-grade) astrocytoma	Usually well circumscribed. In children, most often found in posterior fossa A (eg, cerebellum). May be supratentorial. GFAP ⊕. Benign; good prognosis. Rosenthal fibers—eosinophilic, corkscrew fibers B . Cystic + solid (gross).
Medulloblastoma	Highly malignant cerebellar tumor C . A form of primitive neuroectodermal tumor. Can compress 4th ventricle, causing noncommunicating hydrocephalus. Can send “drop metastases” to spinal cord. Homer-Wright rosettes, small blue cells D .
Ependymoma	Ependymal cell tumors most commonly found in 4th ventricle E . Can cause hydrocephalus. Poor prognosis. Characteristic perivascular rosettes F . Rod-shaped blepharoplasts (basal ciliary bodies) found near nucleus.
Craniopharyngioma	Childhood tumor, may be confused with pituitary adenoma (both can cause bitemporal hemianopia). Most common childhood supratentorial tumor. Derived from remnants of Rathke pouch. Calcification is common G H . 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 (β-hCG production). Histologically similar to germ cell tumors (eg, testicular seminoma).



Herniation syndromes



- | | |
|---|--|
| ① Cingulate (subfalcine) herniation under falx cerebri | Can compress anterior cerebral artery. |
| ② Downward transtentorial (central) herniation | Caudal displacement of brain stem → rupture of paramedian basilar artery branches → Duret hemorrhages. Usually fatal. |
| ③ Uncal herniation | Uncus = medial temporal lobe. Compresses ipsilateral CN III (blown pupil, “down-and-out” gaze), ipsilateral PCA (contralateral homonymous hemianopia with macular sparing), contralateral crus cerebri at the Kernohan notch (ipsilateral paresis; a “false localization” sign). |
| ④ Cerebellar tonsillar herniation into the foramen magnum | Coma and death result when these herniations compress the brain stem. |

▶ NEUROLOGY—PHARMACOLOGY

Glaucoma drugs

↓ IOP via ↓ amount of aqueous humor (inhibit synthesis/secretion or ↑ drainage).

DRUG	MECHANISM	ADVERSE EFFECTS
α-agonists		
Epinephrine (α_1), brimonidine (α_2)	↓ aqueous humor synthesis via vasoconstriction ↓ aqueous humor synthesis	Mydriasis (α_1); do not use in closed-angle glaucoma Blurry vision, ocular hyperemia, foreign body sensation, ocular allergic reactions, ocular pruritus
β-blockers		
Timolol, betaxolol, carteolol	↓ aqueous humor synthesis	No pupillary or vision changes
Diuretics		
Acetazolamide	↓ aqueous humor synthesis via inhibition of carbonic anhydrase	No pupillary or vision changes
Cholinomimetics (M_3)		
Direct (pilocarpine, carbachol) Indirect (physostigmine, echothiophate)	↑ outflow of aqueous humor via contraction of ciliary muscle and opening of trabecular meshwork Use pilocarpine in emergencies—very effective at opening meshwork into canal of Schlemm	Miosis (contraction of pupillary sphincter muscles) and cyclospasm (contraction of ciliary muscle)
Prostaglandin		
Bimatoprost, latanoprost ($PGF_{2\alpha}$)	↑ outflow of aqueous humor	Darkens color of iris (browning), eyelash growth

Opioid analgesics

Morphine, fentanyl, codeine, loperamide, methadone, meperidine, dextromethorphan, diphenoxylate, pentazocine.

MECHANISM

Act as agonists at opioid receptors (μ = β -endorphin, δ = enkephalin, κ = dynorphin) to modulate synaptic transmission—open K^+ channels, close Ca^{2+} channels \rightarrow \downarrow synaptic transmission. Inhibit release of ACh, norepinephrine, 5-HT, glutamate, substance P.

CLINICAL USE

Pain, cough suppression (dextromethorphan), diarrhea (loperamide, diphenoxylate), acute pulmonary edema, maintenance programs for heroin addicts (methadone, buprenorphine + naloxone).

ADVERSE EFFECTS

Addiction, respiratory depression, constipation, miosis (except meperidine \rightarrow mydriasis), additive CNS depression with other drugs. Tolerance does not develop to miosis and constipation. Toxicity treated with naloxone or naltrexone (opioid receptor antagonist).

Pentazocine**MECHANISM**

κ -opioid receptor agonist and μ -opioid receptor antagonist.

CLINICAL USE

Analgesia for moderate to severe pain.

ADVERSE EFFECTS

Can cause opioid withdrawal symptoms if patient is also taking full opioid antagonist (competition for opioid receptors).

Butorphanol**MECHANISM**

κ -opioid receptor agonist and μ -opioid receptor partial agonist; produces analgesia.

CLINICAL USE

Severe pain (eg, migraine, labor). Causes less respiratory depression than full opioid agonists.

ADVERSE EFFECTS

Can cause opioid withdrawal symptoms if patient is also taking full opioid agonist (competition for opioid receptors). Overdose not easily reversed with naloxone.

Tramadol**MECHANISM**

Very weak opioid agonist; also inhibits 5-HT and norepinephrine reuptake (works on multiple neurotransmitters—“**tram it all**” in with **tramadol**).

CLINICAL USE

Chronic pain.

ADVERSE EFFECTS

Similar to opioids. Decreases seizure threshold. Serotonin syndrome.

Epilepsy drugs

	PARTIAL (FOCAL)		GENERALIZED			MECHANISM	SIDE EFFECTS	NOTES
	SIMPLE	COMPLEX	TONIC-CLONIC	ABSENCE	STATUS EPILEPTICUS			
Ethosuximide				*		Blocks thalamic T-type Ca ²⁺ channels	GI, fatigue, headache, urticaria, Stevens-Johnson syndrome. EFGHIJ —Ethosuximide causes F atigue, G I distress, H eadache, I tching, and Stevens-Johnson syndrome	Sucks to have S ilent (absence) S eizures
Benzodiazepines (eg, diazepam, lorazepam, midazolam)					**	↑ GABA _A action	Sedation, tolerance, dependence, respiratory depression	Also for eclampsia seizures (1st line is MgSO ₄)
Phenobarbital	✓	✓	✓			↑ GABA _A action	Sedation, tolerance, dependence, induction of cytochrome P-450, cardiorespiratory depression	1st line in neonates
Phenytoin, fosphenytoin	✓	✓	*	✓	***	Blocks Na ⁺ channels; zero-order kinetics	Neurologic: nystagmus, diplopia, ataxia, sedation, peripheral neuropathy. Dermatologic: hirsutism, Stevens-Johnson syndrome, gingival hyperplasia, DRESS syndrome. Musculoskeletal: osteopenia, SLE-like syndrome. Hematologic: megaloblastic anemia. Reproductive: teratogenesis (fetal hydantoin syndrome). Other: cytochrome P-450 induction	
Carbamazepine	* ✓	* ✓	✓			Blocks Na ⁺ channels	Diplopia, ataxia, blood dyscrasias (agranulocytosis, aplastic anemia), liver toxicity, teratogenesis, induction of cytochrome P-450, SIADH, Stevens-Johnson syndrome	1st line for trigeminal neuralgia
Valproic acid	✓	✓	* ✓	✓		↑ 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	✓	✓				↑ GABA by irreversibly inhibiting GABA transaminase		
Gabapentin	✓	✓				Primarily inhibits high-voltage-activated Ca ²⁺ channels; designed as GABA analog	Sedation, ataxia	Also used for peripheral neuropathy, postherpetic neuralgia
Topiramate	✓	✓	✓			Blocks Na ⁺ channels, ↑ GABA action	Sedation, mental dulling, kidney stones, weight loss	Also used for migraine prevention
Lamotrigine	✓	✓	✓	✓		Blocks voltage-gated Na ⁺ channels	Stevens-Johnson syndrome (must be titrated slowly)	
Levetiracetam	✓	✓	✓			Unknown; may modulate GABA and glutamate release		
Tiagabine	✓	✓				↑ GABA by inhibiting reuptake		

* = 1st line; ** = 1st line for acute; *** = 1st line for prophylaxis.

Barbiturates

Phenobarbital, pentobarbital, thiopental, secobarbital.

MECHANISM

Facilitate GABA_A action by ↑ **duration** of Cl⁻ channel opening, thus ↓ neuron firing (barbiturates ↑ **duration**). Contraindicated in porphyria.

CLINICAL USE

Sedative for anxiety, seizures, insomnia, induction of anesthesia (thiopental).

ADVERSE EFFECTS

Respiratory and cardiovascular depression (can be fatal); CNS depression (can be exacerbated by alcohol use); dependence; drug interactions (induces cytochrome P-450).
Overdose treatment is supportive (assist respiration and maintain BP).

Benzodiazepines

Diazepam, lorazepam, triazolam, temazepam, oxazepam, midazolam, chlordiazepoxide, alprazolam.

MECHANISM

Facilitate GABA_A action by ↑ **frequency** of Cl⁻ channel opening. ↓ REM sleep. Most have long half-lives and active metabolites (exceptions: **Alprazolam**, **Triazolam**, **Oxazepam**, and **Midazolam** are short acting → higher addictive potential).

“**F**renzodiazepines” ↑ **f**requency.

Benzos, barbs, and alcohol all bind the GABA_A receptor, which is a ligand-gated Cl⁻ channel.

ATOM.

CLINICAL USE

Anxiety, spasticity, status epilepticus (lorazepam and diazepam), eclampsia, detoxification (especially alcohol withdrawal—DTs), night terrors, sleepwalking, general anesthetic (amnesia, muscle relaxation), hypnotic (insomnia).

ADVERSE EFFECTS

Dependence, additive CNS depression effects with alcohol. 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, **Z**aleplon, es**Z**opiclone. “All **ZZZ**s put you to sleep.”

MECHANISM

Act via the BZ1 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. Unlike older sedative-hypnotics, cause only modest day-after psychomotor depression and few amnesic effects. ↓ dependence risk than benzodiazepines.

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 ↑ solubility in lipids = ↑ potency = $\frac{1}{\text{MAC}}$

MAC = **M**inimal **A**lveolar **C**oncentration (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, in contrast, has ↑ lipid and blood solubility, and thus high potency and slow induction.

Inhaled anesthetics

Desflurane, halothane, enflurane, isoflurane, sevoflurane, methoxyflurane, N₂O.

MECHANISM

Mechanism unknown.

EFFECTS

Myocardial depression, respiratory depression, nausea/emesis, ↑ cerebral blood flow (↓ cerebral metabolic demand).

ADVERSE EFFECTS

Hepatotoxicity (halothane), nephrotoxicity (methoxyflurane), proconvulsant (enflurane), expansion of trapped gas in a body cavity (N₂O).

Malignant hyperthermia—rare, life-threatening condition in which inhaled anesthetics or succinylcholine induce fever and severe muscle contractions. Susceptibility is often inherited as autosomal dominant with variable penetrance. Mutations in voltage-sensitive ryanodine receptor cause ↑ Ca²⁺ release from sarcoplasmic reticulum. Treatment: dantrolene, a ryanodine receptor antagonist.

Intravenous anesthetics

The Mighty King Proposes Foolishly to Oprah.

**Barbiturates
(Thiopental)**

High potency, high lipid solubility, rapid entry into brain. Used for induction of anesthesia and short surgical procedures. Effect terminated by rapid redistribution into tissue and fat. ↓ cerebral blood flow.

**Benzodiazepines
(Midazolam)**

Used for endoscopy; used adjunctively with gaseous anesthetics and narcotics. May cause severe postoperative respiratory depression, ↓ BP (treat overdose with flumazenil), anterograde amnesia.

**Arylcyclohexylamines
(Ketamine)**

PCP analogs that act as dissociative anesthetics. Block NMDA receptors. Cardiovascular stimulants. Cause disorientation, hallucination, bad dreams. ↑ cerebral blood flow.

Propofol

Used for sedation in ICU, rapid anesthesia induction, short procedures. Less postoperative nausea than thiopental. Potentiates GABA_A.

Opioids

Morphine, fentanyl used with other CNS depressants during general anesthesia.

Local anesthetics

Esters—procaine, cocaine, tetracaine, benzocaine.
Amides—**I**doca**I**ne, mep**I**vaca**I**ne, bup**I**vaca**I**ne (am**I**des have **2 I**'s in name).

MECHANISM

Block Na⁺ 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).

Neuromuscular blocking drugs

Muscle paralysis in surgery or mechanical ventilation. Selective for motor (vs autonomic) nicotinic receptor.

Depolarizing

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

Tubocurarine, atracurium, mivacurium, pancuronium, vecuronium, rocuronium—competitive antagonists—compete with ACh for receptors.
Reversal of blockade—neostigmine (must be given with atropine to prevent muscarinic effects such as bradycardia), edrophonium, and other cholinesterase inhibitors.

Dantrolene**MECHANISM**

Prevents release of Ca²⁺ from the sarcoplasmic reticulum of skeletal muscle by binding to the ryanodine receptor.

CLINICAL USE

Malignant hyperthermia and neuroleptic malignant syndrome (a toxicity of antipsychotic drugs).

Baclofen**MECHANISM**

Activates GABA_B receptors at spinal cord level, inducing skeletal muscle relaxation.

CLINICAL USE

Muscle spasms (eg, acute low back pain).

Cyclobenzaprine**MECHANISM**

Centrally acting skeletal muscle relaxant. Structurally related to TCAs, similar anticholinergic side effects.

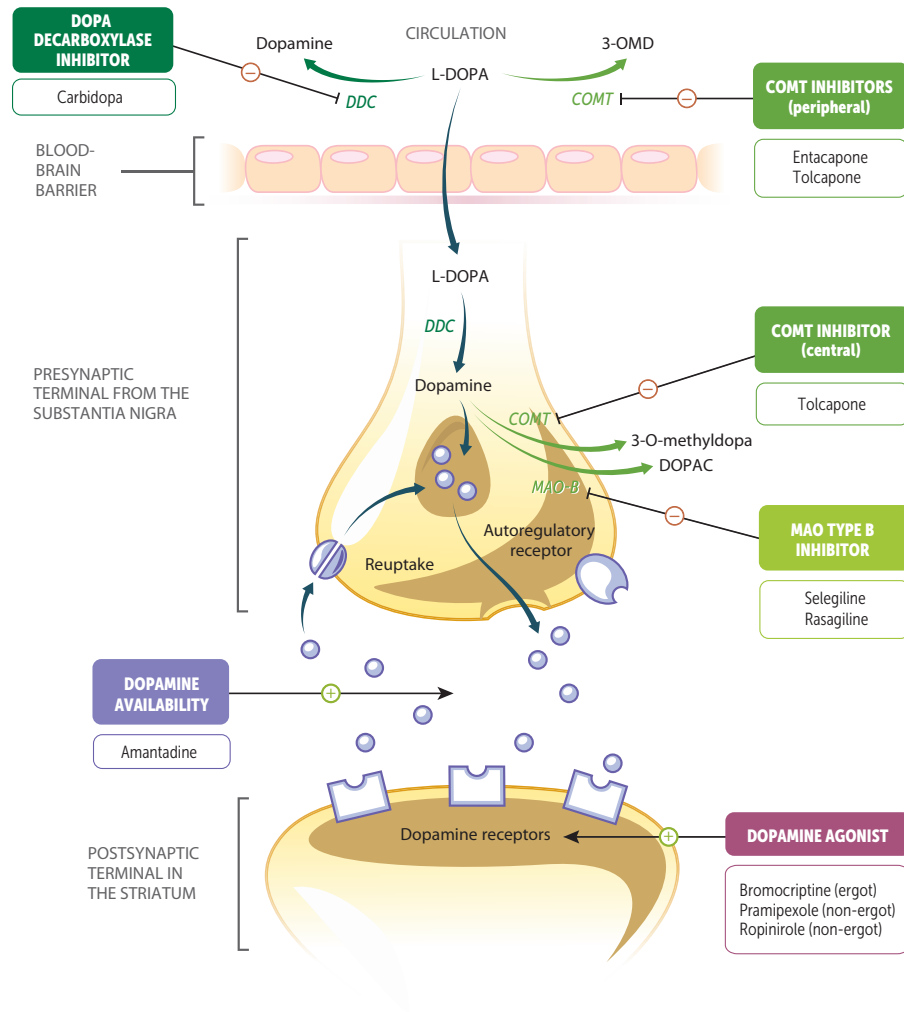
CLINICAL USE

Muscle spasms.

Parkinson disease drugs

Parkinsonism is due to loss of dopaminergic neurons and excess cholinergic activity.
Bromocriptine, **A**mantadine, **L**evodopa (with carbidopa), **S**elegiline (and COMT inhibitors),
Antimuscarinics—**BALSA**.

STRATEGY	AGENTS
Dopamine agonists	Ergot— B romocriptine Non-ergot (preferred)—pramipexole, ropinirole
↑ dopamine availability	A mantadine (↑ dopamine release and ↓ dopamine reuptake); toxicity = ataxia, livedo reticularis.
↑ L-DOPA availability	Agents prevent peripheral (pre-BBB) L-dopa degradation → ↑ L-DOPA entering CNS → ↑ central L-DOPA available for conversion to dopamine. <ul style="list-style-type: none"> ▪ 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, tolcapone—prevent peripheral L-dopa degradation to 3-O-methyldopa (3-OMD) by inhibiting COMT.
Prevent dopamine breakdown	Agents act centrally (post-BBB) to inhibit breakdown of dopamine. <ul style="list-style-type: none"> ▪ Selegiline—blocks conversion of dopamine into DOPAC by selectively inhibiting MAO-B. ▪ Tolcapone—blocks conversion of dopamine to 3-OMD by inhibiting central COMT.
Curb excess cholinergic activity	B enzotropine (A ntimuscarinic; improves tremor and rigidity but has little effect on bradykinesia in P arkinson disease). P ark your Mercedes- B enz.



L-dopa (levodopa)/carbidopa

MECHANISM	↑ level of 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 ↑ the bioavailability of L-dopa in the brain and to limit peripheral side effects.
CLINICAL USE	Parkinson disease.
ADVERSE EFFECTS	Arrhythmias from ↑ peripheral formation of catecholamines. Long-term use can lead to dyskinesia following administration (“on-off” phenomenon), akinesia between doses.

Selegiline, rasagiline

MECHANISM	Selectively inhibit MAO-B (metabolize dopamine) → ↑ dopamine availability.
CLINICAL USE	Adjunctive agent to L-dopa in treatment of Parkinson disease.
ADVERSE EFFECTS	May enhance adverse effects of L-dopa.

Alzheimer drugs**Memantine**

MECHANISM	NMDA receptor antagonist; helps prevent excitotoxicity (mediated by Ca ²⁺).
ADVERSE EFFECTS	Dizziness, confusion, hallucinations.

Donepezil, galantamine, rivastigmine, tacrine

MECHANISM	AChE inhibitors.
ADVERSE EFFECTS	Nausea, dizziness, insomnia.

Huntington disease drugs

Tetrabenazine and reserpine—inhibit vesicular monoamine transporter (VMAT) → ↓ dopamine vesicle packaging and release.
Haloperidol—D₂ receptor antagonist.

Riluzole

Treatment for ALS that modestly ↑ survival by ↓ glutamate excitotoxicity via an unclear mechanism.

For **Lou** Gehrig disease, give rilouzole.

Triptans**Sumatriptan**

MECHANISM	5-HT _{1B/1D} agonists. Inhibit trigeminal nerve activation; prevent vasoactive peptide release; induce vasoconstriction.	A SUM o wrestler TRIP s ANd falls on your head .
CLINICAL USE	Acute migraine, cluster head ache attacks.	
ADVERSE EFFECTS	Coronary vasospasm (contraindicated in patients with CAD or Prinzmetal angina), mild paresthesia.	

Psychiatry

“A Freudian slip is when you say one thing but mean your mother.”

—Anonymous

“Men will always be mad, and those who think they can cure them are the maddest of all.”

—Voltaire

“Anyone who goes to a psychiatrist ought to have his head examined.”

—Samuel Goldwyn

“Words of comfort, skillfully administered, are the oldest therapy known to man.”

—Louis Nizer

▶ Psychology	508
▶ Pathology	510
▶ Pharmacology	524

▶ PSYCHIATRY—PSYCHOLOGY

Classical conditioning	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).	Usually deals with involuntary responses. Pavlov's classical experiments with dogs—ringing the bell provoked salivation.
Operant conditioning	Learning in which a particular action is elicited because it produces a punishment or reward. Usually deals with voluntary responses.	
Reinforcement	Target behavior (response) is followed by desired reward (positive reinforcement) or removal of aversive stimulus (negative reinforcement).	
Punishment	Repeated application of aversive stimulus (positive punishment) or removal of desired reward (negative punishment) to extinguish unwanted behavior.	
Extinction	Discontinuation of reinforcement (positive or negative) eventually eliminates behavior. Can occur in operant or classical conditioning.	

Transference and countertransference

Transference	Patient projects feelings about formative or other important persons onto physician (eg, psychiatrist is seen as parent).
Countertransference	Doctor projects feelings about formative or other important persons onto patient (eg, patient reminds physician of younger sibling).

Ego defenses Mental processes (unconscious or conscious) used to resolve conflict and prevent undesirable feelings (eg, anxiety, depression).

IMMATURE DEFENSES	DESCRIPTION	EXAMPLE
Acting out	Expressing unacceptable feelings and thoughts through actions.	Tantrums.
Denial	Avoiding the awareness of some painful reality.	A common reaction in newly diagnosed AIDS and cancer patients.
Displacement	Transferring avoided ideas and feelings to a neutral person or object (vs projection).	Mother yells at her child, because her husband yelled at her.
Dissociation	Temporary, drastic change in personality, memory, consciousness, or motor behavior to avoid emotional stress.	Extreme forms can result in dissociative identity disorder (multiple personality disorder).
Fixation	Partially remaining at a more childish level of development (vs regression).	Adults fixating on video games.
Idealization	Expressing extremely positive thoughts of self and others while ignoring negative thoughts.	A patient boasts about his physician and his accomplishments while ignoring any flaws.
Identification	Modeling behavior after another person who is more powerful (though not necessarily admired).	Abused child later becomes a child abuser.

Ego defenses (continued)

IMMATURE DEFENSES	DESCRIPTION	EXAMPLE
Intellectualization	Using facts and logic to emotionally distance oneself from a stressful situation.	In a therapy session, patient diagnosed with cancer focuses only on rates of survival.
Isolation (of affect)	Separating feelings from ideas and events.	Describing murder in graphic detail with no emotional response.
Passive aggression	Failing to meet the needs/expectations of others as an indirect show of opposition.	Disgruntled employee is repeatedly late to work.
Projection	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.
Rationalization	Proclaiming logical reasons for actions actually performed for other reasons, usually to avoid self-blame.	After getting fired, claiming that the job was not important anyway.
Reaction formation	Replacing a warded-off idea or feeling by an (unconsciously derived) emphasis on its opposite (vs sublimation).	A patient with libidinous thoughts enters a monastery.
Regression	Involuntarily turning back the maturational clock and going back to earlier modes of dealing with the world (vs fixation).	Seen in children under stress such as illness, punishment, or birth of a new sibling (eg, bedwetting in a previously toilet-trained child when hospitalized).
Repression	Involuntarily 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.
Splitting	Believing that people are either all good or all bad at different times due to intolerance of ambiguity. Commonly seen in borderline personality disorder.	A patient says that all the nurses are cold and insensitive but that the doctors are warm and friendly.
MATURE DEFENSES		
Sublimation	Replacing an unacceptable wish with a course of action that is similar to the wish but does not conflict with one's value system (vs reaction formation).	Teenager's aggression toward his father is redirected to perform well in sports.
Altruism	Alleviating negative feelings via unsolicited generosity.	Mafia boss makes large donation to charity.
Suppression	Intentionally withholding an idea or feeling from conscious awareness (vs repression); temporary.	Choosing to not worry about the big game until it is time to play.
Humor	Appreciating the amusing nature of an anxiety-provoking or adverse situation.	Nervous medical student jokes about the boards.

Mature adults wear a **SASH**.

▶ PSYCHIATRY—PATHOLOGY

Psychiatric genetics

Both genetic and environmental factors are involved in development of most psychiatric disorders. For example, in bipolar disorder and schizophrenia, lifetime risk in general population (~ 1%) < parent or sibling of someone affected (~ 10%) < monozygotic twin of someone affected (~ 50%).

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)

The **4 W's**: **W**eak, **W**ordless, **W**anting (socially), **W**ary.

Deprivation for > 6 months can lead to irreversible changes.

Severe deprivation can result in infant death.

Child abuse

	Physical abuse	Sexual abuse
EVIDENCE	Fractures (eg, ribs, long bone spiral, multiple in different stages of healing), bruises (eg, trunk, ear, neck; in pattern of implement), burns (eg, cigarette, buttocks/thighs), subdural hematomas, retinal hemorrhages. During exam, children often avoid eye contact.	Genital, anal, or oral trauma; STIs; UTIs.
ABUSER	Usually biological mother.	Known to victim, usually male.
EPIDEMIOLOGY	40% of deaths in children < 1 year old.	Peak incidence 9–12 years old.

Child neglect

Failure to provide a child with adequate food, shelter, supervision, education, and/or affection. Most common form of child maltreatment. Evidence: poor hygiene, malnutrition, withdrawal, impaired social/emotional development, failure to thrive. As with child abuse, suspected child neglect must be reported to local child protective services.

Vulnerable child syndrome

Parents perceive the child as especially susceptible to illness or injury. Usually follows a serious illness or life-threatening event. Can result in missed school or overuse of medical services.

Childhood and early-onset disorders

Attention-deficit hyperactivity disorder	Onset before age 12. Limited attention span and poor impulse control. Characterized by hyperactivity, impulsivity, and/or inattention in multiple settings (school, home, places of worship, etc). Normal intelligence, but commonly coexists with difficulties in school. Continues into adulthood in as many as 50% of individuals. Treatment: stimulants (eg, methylphenidate) +/- cognitive behavioral therapy (CBT); alternatives include atomoxetine, guanfacine, clonidine.
Autism spectrum disorder	Characterized by poor social interactions, social communication deficits, repetitive/ritualized behaviors, restricted interests. Must present in early childhood. May be accompanied by intellectual disability; rarely accompanied by unusual abilities (savants). More common in boys. Associated with ↑ head/brain size.
Rett syndrome	X-linked dominant disorder seen almost exclusively in girls (affected males die in utero or shortly after birth). Symptoms usually become apparent around ages 1–4, including regression characterized by loss of development, loss of verbal abilities, intellectual disability, ataxia, stereotyped hand-wringing.
Conduct disorder	Repetitive and pervasive behavior violating the basic rights of others or societal norms (eg, aggression to people and animals, destruction of property, theft). After age 18, many of these patients will meet criteria for diagnosis of antisocial personality disorder. Treatment for both: psychotherapy such as CBT.
Oppositional defiant disorder	Enduring pattern of hostile, defiant behavior toward authority figures in the absence of serious violations of social norms. Treatment: psychotherapy such as CBT.
Separation anxiety disorder	Common onset at 7–9 years. Overwhelming fear of separation from home or loss of attachment figure. May lead to factitious physical complaints to avoid going to or staying at school. Treatment: CBT, play therapy, family therapy.
Tourette syndrome	Onset before age 18. Characterized by sudden, rapid, recurrent, nonrhythmic, stereotyped motor and vocal tics that persist for > 1 year. Coprolalia (involuntary obscene speech) found in only 10–20% of patients. Associated with OCD and ADHD. Treatment: psychoeducation, behavioral therapy. For intractable and distressing tics, high-potency antipsychotics (eg, fluphenazine, pimozide), tetrabenazine, guanfacine, and clonidine may be used.

Neurotransmitter changes with disease

DISORDER	NEUROTRANSMITTER CHANGES
Alzheimer disease	↓ ACh ↑ glutamate
Anxiety	↑ norepinephrine ↓ GABA, ↓ 5-HT
Depression	↓ norepinephrine ↓ 5-HT, ↓ dopamine
Huntington disease	↓ GABA, ↓ ACh ↑ dopamine
Parkinson disease	↓ dopamine ↑ ACh
Schizophrenia	↑ dopamine

Understanding these changes can help guide pharmacologic treatment choice.

Orientation	<p>Patient's ability to know who he or she is, where he or she is, and the date and time.</p> <p>Common causes of loss of orientation: alcohol, drugs, fluid/electrolyte imbalance, head trauma, hypoglycemia, infection, nutritional deficiencies.</p>	<p>Order of loss: 1st—time; 2nd—place; last—person.</p>
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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 (↓ acquisition of new memory).
Korsakoff syndrome	Amnesia (anterograde > retrograde) caused by vitamin B ₁ deficiency and associated destruction of mammillary bodies. Seen in alcoholics as a late neuropsychiatric manifestation of Wernicke encephalopathy. Confabulations are characteristic.
Dissociative amnesia	Inability to recall important personal information, usually subsequent to severe trauma or stress. May be accompanied by dissociative fugue (abrupt travel or wandering during a period of dissociative amnesia, associated with traumatic circumstances).

Dissociative disorders

Dissociative identity disorder	Formerly known as multiple personality disorder. Presence of 2 or more distinct identities or personality states. More common in women. Associated with history of sexual abuse, PTSD, depression, substance abuse, borderline personality, somatoform conditions.
Depersonalization/derealization disorder	Persistent feelings of detachment or estrangement from one's own body, thoughts, perceptions, and actions (depersonalization) or one's environment (derealization).

Delirium	<p>“Waxing and waning” level of consciousness with acute onset; rapid ↓ in attention span and level of arousal. Characterized by disorganized thinking, hallucinations (often visual), illusions, misperceptions, disturbance in sleep-wake cycle, cognitive dysfunction.</p> <p>Usually 2° to other illness (eg, CNS disease, infection, trauma, substance abuse/withdrawal, metabolic/electrolyte disturbances, hemorrhage, urinary/fecal retention).</p> <p>Most common presentation of altered mental status in inpatient setting. Commonly, diffuse slowing EEG.</p> <p>Treatment is aimed at identifying and addressing underlying condition. Haloperidol may be used as needed. Use benzodiazepines for alcohol withdrawal.</p>	<p>Delirium = changes in sensorium.</p> <p>May be caused by medications (eg, anticholinergics), especially in the elderly.</p> <p>Reversible.</p> <p>T-A-DA approach (Tolerate, Anticipate, Don't Agitate) helpful for management.</p>
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Dementia	<p>↓ in intellectual function without affecting level of consciousness. Characterized by memory deficits, apraxia, aphasia, agnosia, loss of abstract thought, behavioral/personality changes, impaired judgment. A patient with dementia can develop delirium (eg, patient with Alzheimer disease who develops pneumonia is at ↑ risk for delirium).</p> <p>Irreversible causes: Alzheimer disease, Lewy body dementia, Huntington disease, Pick disease, cerebral infarct, Creutzfeldt-Jakob disease, chronic substance abuse (due to neurotoxicity of drugs).</p> <p>Reversible causes: hypothyroidism, depression, vitamin B₁₂ deficiency, normal pressure hydrocephalus, neurosyphilis.</p> <p>↑ incidence with age. EEG usually normal.</p> <p>“Dementia” is characterized by memory loss. Usually irreversible.</p> <p>In elderly patients, depression and hypothyroidism may present like dementia (pseudodementia). Screen for depression and measure TSH, B₁₂ levels.</p>
Psychosis	Distorted perception of reality characterized by delusions, hallucinations, and/or disorganized thinking. Can occur in patients with medical illness, psychiatric illness, or both.
Delusions	Unique, false beliefs that persist despite the facts (eg, thinking aliens are communicating with you). Types include persecutory, referential, grandiose, erotomanic, somatic.
Disorganized thought	Speech may be incoherent (“word salad”), tangential, or derailed (“loose associations”).
Hallucinations	<p>Perceptions in the absence of external stimuli (eg, seeing a light that is not actually present). Contrast with illusions, misperceptions of real external stimuli. Types include:</p> <ul style="list-style-type: none"> ▪ Visual—more commonly a feature of medical illness (eg, drug intoxication) than psychiatric illness. ▪ Auditory—more commonly a feature of psychiatric illness (eg, schizophrenia) than medical illness. ▪ Olfactory—often occur as an aura of temporal lobe epilepsy (eg, burning rubber) and in brain tumors. ▪ Gustatory—rare, but seen in epilepsy. ▪ Tactile—common in alcohol withdrawal and stimulant use (eg, cocaine, amphetamines), delusional parasitosis, “cocaine crawlies.” ▪ Hypnagogic—occurs while going to sleep. Sometimes seen in narcolepsy. ▪ Hypnopompic—occurs while waking from sleep (“pompous upon awakening”). Sometimes seen in narcolepsy.

Schizophrenia

Chronic mental disorder with periods of psychosis, disturbed behavior and thought, and decline in functioning **lasting > 6 months**. Associated with ↑ dopaminergic activity, ↓ dendritic branching.

Diagnosis requires at least 2 of the following, and at least 1 of these should include 1–3 (first 4 are “positive symptoms”):

1. Delusions
2. Hallucinations—often auditory
3. Disorganized speech
4. Disorganized or catatonic behavior
5. Negative symptoms (affective flattening, avolition, anhedonia, asociality, alogia)

Brief psychotic disorder—lasting < 1 month, usually stress related.

Schizophreniform disorder—lasting 1–6 months.

Schizoaffective disorder—> 2 weeks of hallucinations or delusions without major mood episode (major depression or mania), plus periods of concurrent major mood episode with schizophrenic symptoms.

Frequent cannabis use is associated with psychosis/schizophrenia in teens. Lifetime prevalence—1.5% (males = females, African Americans = Caucasians). Presents earlier in men (late teens to early 20s vs late 20s to early 30s in women). Patients are at ↑ risk for suicide.

Ventriculomegaly on brain imaging. Treatment: atypical antipsychotics (eg, risperidone) are first line.

Delusional disorder

Fixed, persistent, false belief system **lasting > 1 month**. Functioning otherwise not impaired (eg, a woman who genuinely believes she is married to a celebrity when, in fact, she is not). Can be shared by individuals in close relationships (folie à deux).

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 disorder, bipolar disorder, dysthymic disorder, and cyclothymic disorder. Episodic superimposed psychotic features (delusions or hallucinations) may be present.

Manic episode

Distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently ↑ activity or energy **lasting at least 1 week**. Often disturbing to patient.

Diagnosis requires hospitalization or at least 3 of the following (manics **DIG FAST**):

- **D**istractibility
- **I**rresponsibility—seeks pleasure without regard to consequences (hedonistic)
- **G**randiosity—inflated self-esteem
- **F**light of ideas—racing thoughts
- **↑** in goal-directed **A**ctivity/psychomotor **A**gitation
- **↓** need for **S**leep
- **T**alkativeness or pressured speech

Hypomanic episode

Like manic episode except mood disturbance is not severe enough to cause marked impairment in social and/or occupational functioning or to necessitate hospitalization. No psychotic features. Lasts at least 4 consecutive days.

Bipolar disorder (manic depression)

Bipolar I defined by presence of at least 1 manic episode +/- a hypomanic or depressive episode. Bipolar II defined by presence of a hypomanic and a depressive episode.

Patient's mood and functioning usually return to normal between episodes. Use of antidepressants can precipitate mania. High suicide risk. Treatment: mood stabilizers (eg, lithium, valproic acid, carbamazepine), atypical antipsychotics.

Cyclothymic disorder—milder form of bipolar disorder lasting at least 2 years, fluctuating between mild depressive and hypomanic symptoms.

Major depressive disorder

May be self-limited disorder, with major depressive episodes usually lasting 6–12 months. Episodes characterized by at least 5 of the following 9 symptoms for 2 or more weeks (symptoms must include patient-reported depressed mood or anhedonia). Treatment: CBT and SSRIs are first line. SNRIs, mirtazapine, bupropion can also be considered. Electroconvulsive therapy (ECT) in select patients.

Persistent depressive disorder (dysthymia)—depression, often milder, lasting at least 2 years.

SIG E CAPS:

- Depressed mood
- Sleep disturbance
- Loss of Interest (anhedonia)
- Guilt or feelings of worthlessness
- Energy loss and fatigue
- Concentration problems
- Appetite/weight changes
- Psychomotor retardation or agitation
- Suicidal ideations

Patients with depression typically have the following changes in their sleep stages:

- ↓ slow-wave sleep
- ↓ REM latency
- ↑ REM early in sleep cycle
- ↑ total REM sleep
- Repeated nighttime awakenings
- Early-morning waking (terminal insomnia)

Depression with atypical features

Differs from classical forms of depression. Characterized by mood reactivity (being able to experience improved mood in response to positive events, albeit briefly), “reversed” vegetative symptoms (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 are effective but not first line because of their risk profile.

Postpartum mood disturbances	Onset within 4 weeks of delivery.	
Maternal (postpartum) “blues”	50–85% incidence rate. Characterized by depressed affect, tearfulness, and fatigue starting 2–3 days after delivery. Usually resolves within 10 days. Treatment: supportive. Follow up to assess for possible postpartum depression.	
Postpartum depression	10–15% incidence rate. Characterized by depressed affect, anxiety, and poor concentration. 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 history of bipolar or psychotic disorder, first pregnancy, family history, recent discontinuation of psychotropic medication. Treatment: hospitalization and initiation of atypical antipsychotic; if insufficient, ECT may be used.	
Grief	<p>Normal grief is characterized by shock, denial, guilt, sadness, anxiety, yearning, and somatic symptoms. Hallucinations of the deceased person are common. Duration varies widely; usually < 6 months.</p> <p>Pathologic grief is persistent and causes functional impairment. Can meet criteria for major depressive episode.</p>	
Electroconvulsive therapy	Used mainly for treatment-refractory depression, depression with psychotic symptoms, and acutely suicidal patients. Produces grand mal seizure in an anesthetized patient. Adverse effects include disorientation, temporary headache, partial anterograde/retrograde amnesia usually resolving in 6 months. Safe in pregnancy.	
Risk factors for suicide completion	<ul style="list-style-type: none"> Sex (male) Age (young adult or elderly) Depression Previous attempt Ethanol or drug use Rational thinking loss (psychosis) Sickness (medical illness) Organized plan No spouse or other social support Stated future intent 	<p>SAD PERSONS are more likely to complete suicide.</p> <p>Most common method in US is firearms; access to guns ↑ risk of suicide completion.</p> <p>Women try more often; men succeed more often.</p>
Anxiety disorder	Inappropriate experience of fear/worry and its physical manifestations (anxiety) incongruent with the magnitude of the perceived stressor. Symptoms interfere with daily functioning. Includes panic disorder, phobias, generalized anxiety disorder, and selective mutism. Treatment: CBT, SSRIs, SNRIs.	

Panic disorder

Defined by recurrent panic attacks (periods of intense fear and discomfort peaking in 10 minutes with at least 4 of the following): **P**alpitations, **P**aresthesias, **d**e**P**ersonalization or derealization, **A**bdominal distress or **N**ausea, **I**ntense fear of dying, **I**ntense fear of losing control or “going crazy,” **H**igh-headedness, **C**hest pain, **C**hills, **C**hoking, **S**weating, **S**haking, **S**hortness of breath. Strong genetic component. Treatment: CBT, SSRIs, and venlafaxine are first line. Benzodiazepines occasionally used in acute setting.

PANICS.

Diagnosis requires attack followed by 1 month (or more) of 1 (or more) of the following:

- Persistent concern of additional attacks
- Worrying about consequences of attack
- Behavioral change related to attacks

Symptoms are the systemic manifestations of fear.

Specific phobia

Severe, persistent fear or anxiety due to presence or anticipation of a specific object or situation. Person recognizes fear is excessive. Can be treated with systematic desensitization.

Social anxiety disorder—exaggerated fear of embarrassment in social situations (eg, public speaking, using public restrooms). Treatment: CBT, SSRIs, venlafaxine. For only occasional anxiety-inducing situations, benzodiazepine or β -blocker.

Agoraphobia—exaggerated fear of open or enclosed places, using public transportation, being in line or in crowds, or leaving home alone. Associated with panic disorder. Treatment: CBT, SSRIs, MAO inhibitors.

Generalized anxiety disorder

Anxiety **lasting > 6 months** unrelated to a specific person, situation, or event. Associated with restlessness, irritability, sleep disturbance, fatigue, muscle tension, difficulty concentrating. Treatment: CBT, SSRIs, SNRIs are first line. Buspirone, TCAs, benzodiazepines are second line.

Adjustment disorder—emotional symptoms (anxiety, depression) causing impairment following an identifiable psychosocial stressor (eg, divorce, illness) and **lasting < 6 months** (> 6 months in presence of chronic stressor). Treatment: CBT, SSRIs.

Obsessive-compulsive disorder

Recurring intrusive thoughts, feelings, or sensations (obsessions) that cause severe distress; relieved in part by the performance of repetitive actions (compulsions). Ego-dystonic: behavior inconsistent with one's own beliefs and attitudes (vs obsessive-compulsive personality disorder). Associated with Tourette syndrome. Treatment: CBT, SSRIs, and clomipramine are first line.

Body dysmorphic disorder—preoccupation with minor or imagined defect in appearance → significant emotional distress or impaired functioning; patients often repeatedly seek cosmetic treatment. Treatment: CBT.

Post-traumatic stress disorder

Exposure to prior trauma (eg, witnessing death, experiencing serious injury or rape) → intrusive reexperiencing of the event (nightmares, flashbacks), avoidance of associated stimuli, changes in cognition or mood (fear, horror), and persistently ↑ arousal. Disturbance **lasts > 1 month** with significant distress or impaired social-occupational functioning. Treatment: CBT, SSRIs, and venlafaxine are first line.

Acute stress disorder—lasts **between 3 days and 1 month**. Treatment: CBT; pharmacotherapy is usually not indicated.

Malingering	Patient consciously fakes, profoundly exaggerates, or claims to have a disorder in order to attain a specific 2° (external) gain (eg, avoiding work, obtaining compensation). Poor compliance with treatment or follow-up of diagnostic tests. Complaints cease after gain (vs factitious disorder).
Factitious disorders	Patient consciously creates physical and/or psychological symptoms in order to assume “sick role” and to get medical attention (1° [internal] gain).
Factitious disorder imposed on self (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.
Factitious disorder imposed on another (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	Category of disorders characterized by physical symptoms causing significant distress and impairment. Both illness production and motivation are unconscious drives. Symptoms not intentionally produced or feigned. More common in women.
Somatic symptom disorder	Variety of bodily complaints (eg, pain, fatigue) lasting for months to years. Associated with excessive, persistent thoughts and anxiety about symptoms. May co-occur with medical illness.
Conversion disorder (functional neurologic symptom disorder)	Loss of sensory or motor function (eg, paralysis, blindness, mutism), often following an acute stressor; patient is aware of but sometimes indifferent toward symptoms (“la belle indifférence”); more common in females, adolescents, and young adults.
Illness anxiety disorder	Excessive preoccupation with acquiring or having a serious illness, often despite medical evaluation and reassurance; minimal somatic symptoms.
Pseudocyesis	False, nondelusional belief of being pregnant. May have signs and symptoms of pregnancy but is not pregnant.
Personality	
Personality trait	An enduring, repetitive pattern of perceiving, relating to, and thinking about the environment and 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. Usually presents by early adulthood. Three clusters, A, B, and C; remember as Weird , Wild , and Worried based on symptoms.

Cluster A personality disorders	Odd or eccentric; inability to develop meaningful social relationships. No psychosis; genetic association with schizophrenia.	“ Weird ” (Accusatory, Aloof, Awkward).
Paranoid	Pervasive distrust and suspiciousness; projection is the major defense mechanism.	
Schizoid	Voluntary social withdrawal, limited emotional expression, content with social isolation (vs avoidant).	Schizoid = distant.
Schizotypal	Eccentric appearance, odd beliefs or magical thinking, interpersonal awkwardness.	Schizotypal = magical thinking.
Cluster B personality disorders	Dramatic, emotional, or erratic; genetic association with mood disorders and substance abuse.	“ Wild ” (Bad to the Bone).
Antisocial	Disregard for and violation of rights of others, criminality, impulsivity; males > females; must be ≥ 18 years old and have history of conduct disorder before age 15. Conduct disorder if < 18 years old.	Antisocial = sociopath.
Borderline	Unstable mood and interpersonal relationships, impulsivity, self-mutilation, suicidality, sense of emptiness; females > males; splitting is a major defense mechanism.	Treatment: dialectical behavior therapy.
Histrionic	Excessive emotionality and excitability, attention seeking, sexually provocative, overly concerned with appearance.	
Narcissistic	Grandiosity, sense of entitlement; lacks empathy and requires excessive admiration; often demands the “best” and reacts to criticism with rage.	
Cluster C personality disorders	Anxious or fearful; genetic association with anxiety disorders.	“ Worried ” (Cowardly, Compulsive, Clingy).
Avoidant	Hypersensitive to rejection, socially inhibited, timid, feelings of inadequacy, desires relationships with others (vs schizoid).	
Obsessive-compulsive	Preoccupation with order, perfectionism, and control; ego-syntonic: behavior consistent with one’s own beliefs and attitudes (vs OCD).	
Dependent	Submissive and clingy, excessive need to be taken care of, low self-confidence.	Patients often get stuck in abusive relationships.

Eating disorders	Most common in young females.
Anorexia nervosa	Excessive dieting, exercise, or binge eating/purging with BMI < 18.5 kg/m ² ; intense fear of gaining weight; and distortion or overvaluation of body image. Associated with ↓ bone density, severe weight loss, metatarsal stress fractures, amenorrhea (due to loss of pulsatile GnRH secretion), lanugo, anemia, electrolyte disturbances. Commonly coexists with depression. Psychotherapy and nutritional rehabilitation are first line. Refeeding syndrome (↑ insulin → hypophosphatemia → cardiac complications) can occur in significantly malnourished patients.
Bulimia nervosa	Binge eating with recurrent inappropriate compensatory behaviors (eg, self-induced vomiting, using laxatives or diuretics, fasting, excessive exercise) occurring weekly for at least 3 months and overvaluation of body image. Body weight often maintained within normal range. Associated with parotitis, enamel erosion, electrolyte disturbances, alkalosis, dorsal hand calluses from induced vomiting (Russell sign). Treatment: psychotherapy, nutritional rehabilitation, antidepressants.
Binge eating disorder	Regular episodes of excessive, uncontrollable eating without inappropriate compensatory behaviors. ↑ risk of diabetes. Treatment: psychotherapy such as CBT is first-line; SSRIs.
Gender dysphoria	Strong, persistent cross-gender identification that leads to persistent discomfort with sex assigned at birth, causing significant distress and/or impaired functioning. Transgender individuals may have gender dysphoric disorder. Transsexualism —desire to live as the opposite sex , often through surgery or hormone treatment. Transvestism —paraphilia, not gender dysphoria. Wearing clothes (eg, vest) of the opposite sex (cross-dressing).
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: <ul style="list-style-type: none"> ▪ Drugs (eg, antihypertensives, neuroleptics, SSRIs, ethanol) ▪ Diseases (eg, depression, diabetes, STIs) ▪ Psychological (eg, performance anxiety)
Sleep terror disorder	Periods of terror with screaming in the middle of the night; occurs during slow-wave/deep (stage N3) sleep. Most common in children. Occurs during non-REM sleep (no memory of arousal) as opposed to nightmares that occur during REM sleep (memory of a scary dream). Cause unknown, but triggers include emotional stress, fever, or lack of sleep. Usually self limited.

Narcolepsy

Disordered regulation of sleep-wake cycles; 1° characteristic is excessive daytime sleepiness (awaken feeling rested).

Caused by ↓ hypocretin (orexin) production in lateral hypothalamus.

Also associated with:

- Hypnagogic (just before sleep) or hypnopompic (just before awakening) hallucinations.
- Nocturnal and narcoleptic sleep episodes that start with REM sleep.
- Cataplexy (loss of all muscle tone following strong emotional stimulus, such as laughter) in some patients.

Strong genetic component. Treatment: daytime stimulants (eg, amphetamines, modafinil) and nighttime sodium oxybate (GHB).

Hypnagogic—going to sleep

Hypnopompic—“pompous upon awakening”

Substance use disorder

Maladaptive pattern of substance use defined as 2 or more of the following signs in 1 year:

- Tolerance—need more to achieve same effect
- Withdrawal
- Substance taken in larger amounts, or over longer time, than desired
- Persistent desire or unsuccessful attempts to cut down
- Significant energy spent obtaining, using, or recovering from substance
- Important social, occupational, or recreational activities reduced because of substance use
- Continued use despite knowing substance causes physical and/or psychological problems
- Craving
- Recurrent use in physically dangerous situations
- Failure to fulfill major obligations at work, school, or home due to use
- Social or interpersonal conflicts related to substance use

Stages of change in overcoming substance addiction

1. **Precontemplation**—not yet acknowledging that there is a problem
2. **Contemplation**—acknowledging that there is a problem, but not yet ready or willing to make a change
3. **Preparation/determination**—getting ready to change behaviors
4. **Action/willpower**—changing behaviors
5. **Maintenance**—maintaining the behavior changes
6. **Relapse**—returning to old behaviors and abandoning new changes

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. AST value is twice ALT value.	Mild alcohol withdrawal: symptoms similar to other depressants. Severe alcohol withdrawal can cause autonomic hyperactivity and DTs (5–15% mortality rate). Treatment for DTs: benzodiazepines.
Opioids	Euphoria, respiratory and CNS depression, ↓ gag reflex, pupillary constriction (pinpoint pupils), seizures (overdose). Most common cause of drug overdose death. Treatment: naloxone, naltrexone.	Sweating, dilated pupils, piloerection (“cold turkey”), fever, rhinorrhea, yawning, nausea, stomach cramps, diarrhea (“flu-like” symptoms). Treatment: long-term support, methadone, buprenorphine.
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, rebound anxiety, seizure.
Stimulants		
	Nonspecific: mood elevation, 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 and attention, hypertension, tachycardia, anorexia, paranoia, fever. Severe: cardiac arrest, seizures. Treatment: benzodiazepines for agitation and seizures.	
Cocaine	Impaired judgment, pupillary dilation, hallucinations (including tactile), paranoid ideations, angina, sudden cardiac death. Treatment: α -blockers, benzodiazepines. β -blockers not recommended.	
Caffeine	Restlessness, ↑ diuresis, muscle twitching.	Headache, difficulty concentrating, flu-like symptoms.
Nicotine	Restlessness.	Irritability, anxiety, restlessness, difficulty concentrating. Treatment: nicotine patch, gum, or lozenges; bupropion/varenicline.

Psychoactive drug intoxication and withdrawal (continued)

DRUG	INTOXICATION	WITHDRAWAL
Hallucinogens		
Phencyclidine	Violence, impulsivity, psychomotor agitation, nystagmus, tachycardia, hypertension, analgesia, psychosis, delirium, seizures. Trauma is most common complication. Treatment: benzodiazepines, rapid-acting antipsychotic.	
Lysergic acid diethylamide	Perceptual distortion (visual, auditory), depersonalization, anxiety, paranoia, psychosis, possible flashbacks.	
Marijuana (cannabinoid)	Euphoria, anxiety, paranoid delusions, perception of slowed time, impaired judgment, social withdrawal, ↑ appetite, dry mouth, conjunctival injection, hallucinations. Pharmaceutical form is dronabinol (tetrahydrocannabinol isomer): used as antiemetic (chemotherapy) and appetite stimulant (in AIDS).	Irritability, anxiety, depression, insomnia, restlessness, ↓ appetite. Generally detectable in urine for up to 1 month.
MDMA (ecstasy)	Hallucinogenic stimulant: euphoria, disinhibition, hyperactivity. Life-threatening effects include hypertension, tachycardia, hyperthermia, hyponatremia, serotonin syndrome.	Depression, fatigue, change in appetite, difficulty concentrating, anxiety.
Heroin addiction		
	Users at ↑ risk for hepatitis, HIV, abscesses, bacteremia, right-heart endocarditis. Treatment is described below.	
Methadone	Long-acting oral opiate used for heroin detoxification or long-term maintenance.	
Naloxone + buprenorphine	Antagonist + partial agonist. Naloxone is not orally bioavailable, so withdrawal symptoms occur only if injected (lower abuse potential).	
Naltrexone	Long-acting opioid antagonist used for relapse prevention once detoxified.	
Alcoholism		
	Physiologic tolerance and dependence with symptoms of withdrawal (tremor, tachycardia, hypertension, malaise, nausea, DTs) when intake is interrupted. Complications: alcoholic cirrhosis, hepatitis, pancreatitis, peripheral neuropathy, testicular atrophy. Treatment: disulfiram (to condition the patient to abstain from alcohol use), acamprosate, naltrexone, supportive care. Support groups such as Alcoholics Anonymous are helpful in sustaining abstinence and supporting patient and family.	
Wernicke-Korsakoff syndrome	Caused by vitamin B ₁ (thiamine) deficiency. Triad of confusion, ophthalmoplegia, ataxia (Wernicke encephalopathy). May progress to irreversible memory loss, confabulation, personality change (Korsakoff syndrome). Associated with periventricular hemorrhage/necrosis of mammillary bodies. Treatment: IV vitamin B ₁ .	
Mallory-Weiss syndrome	Partial thickness tear at gastroesophageal junction caused by excessive/forceful vomiting. Often presents with hematemesis and misdiagnosed as ruptured esophageal varices.	

Delirium tremens

Life-threatening alcohol withdrawal syndrome that peaks 2–4 days after last drink.

Characterized by autonomic hyperactivity (eg, tachycardia, tremors, anxiety, seizures). Classically occurs in hospital setting (eg, 2–4 days postsurgery) in alcoholics not able to drink as inpatients.

Treatment: benzodiazepines.

Alcoholic hallucinosis is a distinct condition characterized by visual hallucinations 12–48 hours after last drink. Treatment: benzodiazepines (eg, chlordiazepoxide, lorazepam, diazepam).

▶ PSYCHIATRY—PHARMACOLOGY

Preferred medications for selected psychiatric conditions

PSYCHIATRIC CONDITION	PREFERRED DRUGS
ADHD	Stimulants (methylphenidate, amphetamines)
Alcohol withdrawal	Benzodiazepines (eg, chlordiazepoxide, lorazepam, diazepam)
Bipolar disorder	Lithium, valproic acid, 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
Tourette syndrome	Performance only: β -blockers, benzodiazepines Antipsychotics (eg, fluphenazine, pimozide), tetrabenazine

CNS stimulants

Methylphenidate, dextroamphetamine, methamphetamine.

MECHANISM

↑ catecholamines in the synaptic cleft, especially norepinephrine and dopamine.

CLINICAL USE

ADHD, narcolepsy, appetite control.

Antipsychotics (neuroleptics)

Haloperidol, trifluoperazine, fluphenazine, thioridazine, chlorpromazine (haloperidol + “-azines”).

MECHANISM	All typical antipsychotics block dopamine D ₂ receptors (↑ [cAMP]).	High potency: T rifluoperazine, F luphenazine, H aloperidol (Try to Fly High)—neurologic side effects (eg, extrapyramidal symptoms [EPS]).
CLINICAL USE	Schizophrenia (primarily positive symptoms), psychosis, bipolar disorder, delirium, Tourette syndrome, Huntington disease, OCD.	Low potency: C hlorpromazine, T hioridazine (Cheating Thieves are low)—non-neurologic side effects (anticholinergic, antihistamine, and α ₁ -blockade effects).
ADVERSE EFFECTS	Highly lipid soluble and stored in body fat; thus, very slow to be removed from body. Extrapyramidal system side effects (eg, dyskinesias). Treatment: benztropine, diphenhydramine, benzodiazepines. Endocrine side effects (eg, dopamine receptor antagonism → hyperprolactinemia → galactorrhea, oligomenorrhea, gynecomastia). Side effects arising from blocking muscarinic (dry mouth, constipation), α ₁ (orthostatic hypotension), and histamine (sedation) receptors. Can cause QT prolongation.	C hlorpromazine— C orneal deposits; T hioridazine— r e T inal deposits; haloperidol—NMS, tardive dyskinesia. Onset of EPS: ADAPT <ul style="list-style-type: none"> ▪ Hours to days: Acute Dystonia (muscle spasm, stiffness, oculogyric crisis) ▪ Days to months: Akathisia (restlessness) and Parkinsonism (bradykinesia). ▪ Months to years: Tardive dyskinesia For NMS, think FEVER : <ul style="list-style-type: none"> Fever Encephalopathy Vitals unstable Enzymes ↑ Rigidity of muscles
OTHER TOXICITIES	Neuroleptic malignant syndrome (NMS) —rigidity, myoglobinuria, autonomic instability, hyperpyrexia. Treatment: dantrolene, D ₂ agonists (eg, bromocriptine). Tardive dyskinesia —orofacial chorea as a result of long-term antipsychotic use.	

Atypical antipsychotics

Aripiprazole, asenapine, clozapine, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, ziprasidone.

MECHANISM	Not completely understood. Most are D ₂ antagonists; aripiprazole is D ₂ partial agonist. Varied effects on 5-HT ₂ , dopamine, and α- and H ₁ -receptors.	
CLINICAL USE	Schizophrenia—both positive and negative symptoms. Also used for bipolar disorder, OCD, anxiety disorder, depression, mania, Tourette syndrome.	
ADVERSE EFFECTS	All—prolonged QT interval, fewer EPS and anticholinergic side effects than typical antipsychotics. “-pines”—metabolic syndrome (weight gain, diabetes, hyperlipidemia). Clozapine—agranulocytosis (monitor WBC weekly). Risperidone—hyperprolactinemia (amenorrhea, galactorrhea, gynecomastia).	Must watch bone marrow clozely with clozapine . O lanzapine → O besity

Lithium

MECHANISM

Not established; possibly related to inhibition of phosphoinositol cascade.

CLINICAL USE

Mood stabilizer for bipolar disorder; blocks relapse and acute manic events.

ADVERSE EFFECTS

Tremor, 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 with Na⁺. Thiazide use is implicated in lithium toxicity in bipolar patients.

LMNOP—Lithium side effects:

- M**ovement (tremor)
- N**ephrogenic diabetes insipidus
- HypO**thyroidism
- P**regnancy problems

Buspirone

MECHANISM

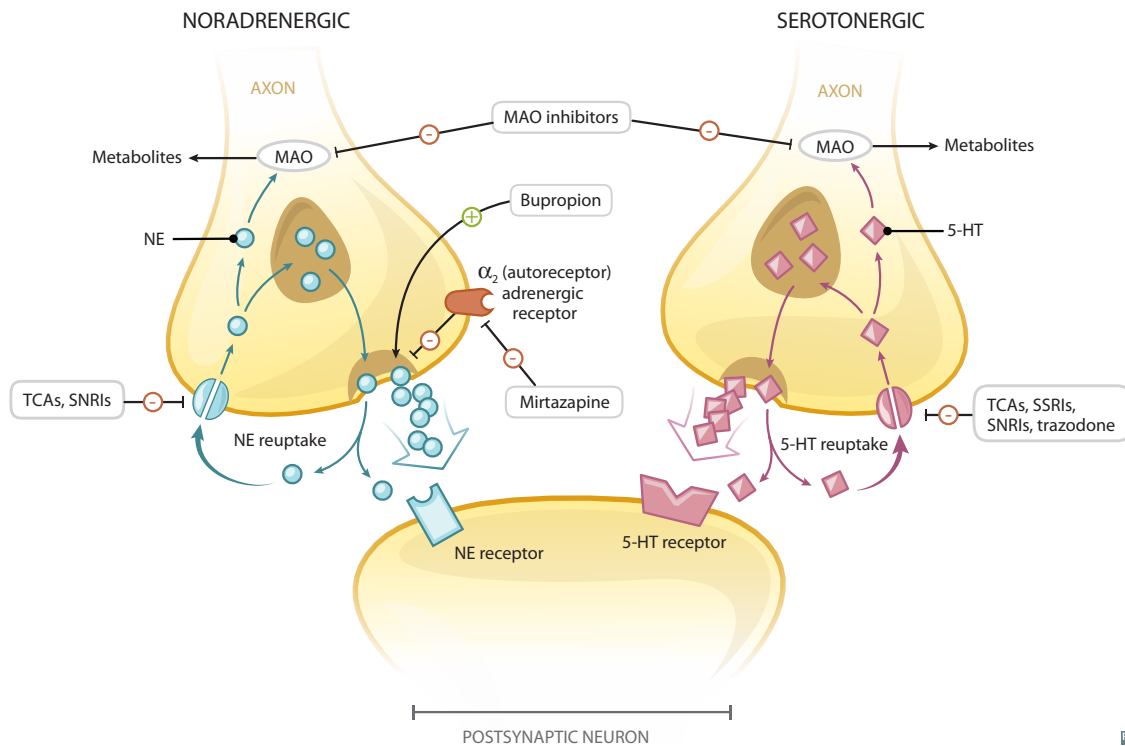
Stimulates 5-HT_{1A} receptors.

CLINICAL USE

Generalized anxiety disorder. Does not cause sedation, addiction, or tolerance. Takes 1–2 weeks to take effect. Does not interact with alcohol (vs barbiturates, benzodiazepines).

I'm always anxious if the **bus** will be **on** time, so I take **buspirone**.

Antidepressants



Selective serotonin reuptake inhibitors

Fluoxetine, paroxetine, sertraline, citalopram.

Flashbacks paralyze senior citizens.

MECHANISM	5-HT-specific reuptake inhibitors.	It normally takes 4–8 weeks for antidepressants to have an effect.
CLINICAL USE	Depression, generalized anxiety disorder, panic disorder, OCD, bulimia, social anxiety disorder, PTSD, premature ejaculation, premenstrual dysphoric disorder.	
ADVERSE EFFECTS	Fewer than TCAs. GI distress, SIADH, sexual dysfunction (anorgasmia, ↓ libido).	

Serotonin-norepinephrine reuptake inhibitors

Venlafaxine, desvenlafaxine, duloxetine, levomilnacipran, milnacipran.

MECHANISM	Inhibit 5-HT and norepinephrine reuptake.
CLINICAL USE	Depression, general anxiety disorder, diabetic neuropathy. Venlafaxine is also indicated for social anxiety disorder, panic disorder, PTSD, OCD.
ADVERSE EFFECTS	↑ BP most common; also stimulant effects, sedation, nausea.

Serotonin syndrome

Can occur with any drug that ↑ 5-HT (eg, MAO inhibitors, SNRIs, TCAs). Characterized by **3 A's**: neuromuscular **A**ctivity (clonus, hyperreflexia, hypertonia, tremor, seizure), **A**utonomic stimulation (hyperthermia, diaphoresis, diarrhea), and **A**gitation. Treatment: cyproheptadine (5-HT₂ receptor antagonist).

Tricyclic antidepressants

Amitriptyline, nortriptyline, imipramine, desipramine, clomipramine, doxepin, amoxapine.

MECHANISM	Block reuptake of norepinephrine and 5-HT.
CLINICAL USE	Major depression, OCD (clomipramine), peripheral neuropathy, chronic pain, migraine prophylaxis.
ADVERSE EFFECTS	Sedation, α ₁ -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-C's : C onvulsions, C oma, C ardiotoxicity (arrhythmia due to Na ⁺ channel inhibition); also respiratory depression, hyperpyrexia. Confusion and hallucinations in elderly due to anticholinergic side effects (use nortriptyline). Treatment: NaHCO ₃ 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.

ADVERSE EFFECTS

Hypertensive crisis (most notably with ingestion of tyramine, which is found in many foods such as aged cheese and wine); CNS stimulation. Contraindicated with SSRIs, TCAs, St. John's wort, meperidine, dextromethorphan (to prevent serotonin syndrome).
Wait 2 weeks after stopping MAO inhibitors before starting serotonergic drugs or stopping dietary restrictions.

Atypical antidepressants**Bupropion**

↑ norepinephrine and dopamine via unknown mechanism. Also used for smoking cessation. Toxicity: stimulant effects (tachycardia, insomnia), headache, seizures in anorexic/bulimic patients. No sexual side effects.

Mirtazapine

α_2 -antagonist (↑ release of NE and 5-HT), potent 5-HT₂ and 5-HT₃ receptor antagonist and H₁ antagonist. Toxicity: sedation (which may be desirable in depressed patients with insomnia), ↑ appetite, weight gain (which may be desirable in elderly or anorexic patients), dry mouth.

Trazodone

Primarily blocks 5-HT₂, α_1 -adrenergic, and H₁ 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. Called traZZZobone due to sedative and male-specific side effects.

Varenicline

Nicotinic ACh receptor partial agonist. Used for smoking cessation. Toxicity: sleep disturbance.

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

▶ Embryology	530
▶ Anatomy	532
▶ Physiology	533
▶ Pathology	544
▶ Pharmacology	556

▶ RENAL—EMBRYOLOGY

Kidney embryology

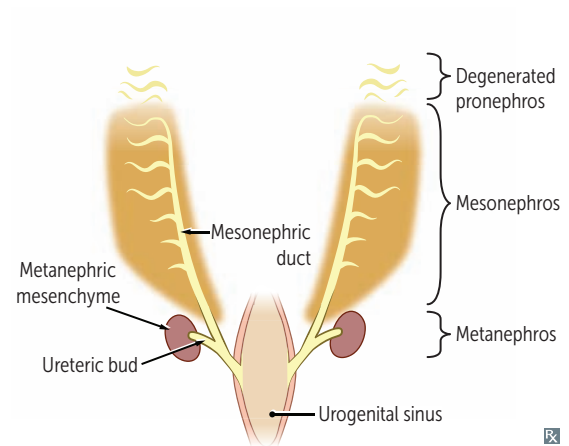
Pronephros—week 4; then degenerates.

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 32–36 weeks of gestation.

- Ureteric bud—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

Ureteropelvic junction—last to canalize → most common site of obstruction (hydronephrosis) in fetus.

**Potter sequence (syndrome)**

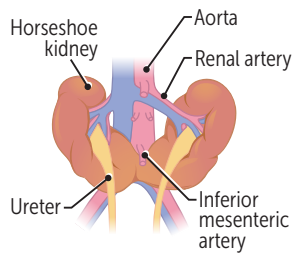
Oligohydramnios → compression of developing fetus → limb deformities, facial anomalies (eg, low-set ears and retrognathia **A**, flattened nose), compression of chest and lack of amniotic fluid aspiration into fetal lungs → pulmonary hypoplasia (cause of death).

Causes include ARPKD, obstructive uropathy (eg, posterior urethral valves), bilateral renal agenesis, chronic placental insufficiency.

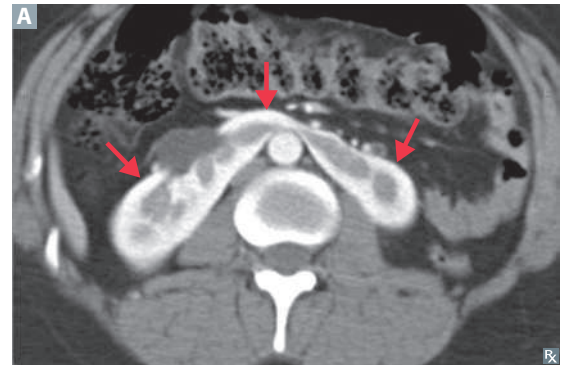
Babies who can't "Pee" in utero develop **P**otter sequence.

POTTER sequence associated with:

- P**ulmonary hypoplasia
- O**ligohydramnios (trigger)
- T**wisted face
- T**wisted skin
- E**xtrernity defects
- R**enal failure (in utero)

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, chromosomal aneuploidy syndromes (eg, Turner syndrome; trisomies 13, 18, 21), and rarely renal cancer.

**Unilateral renal agenesis**

Ureteric bud fails to develop and induce differentiation of metanephric mesenchyme → complete absence of kidney and ureter. Often diagnosed prenatally via ultrasound.

Multicystic dysplastic kidney

Ureteric bud fails to induce differentiation of metanephric mesenchyme → nonfunctional kidney consisting of cysts and connective tissue. Often diagnosed prenatally via ultrasound.

Duplex collecting system

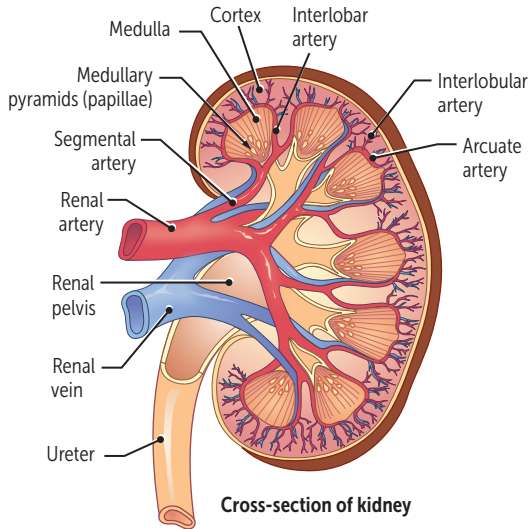
Bifurcation of ureteric bud before it enters the metanephric blastema creates a Y-shaped bifid ureter. Duplex collecting system can alternatively occur through two ureteric buds reaching and interacting with metanephric blastema. Strongly associated with vesicoureteral reflux and/or ureteral obstruction, ↑ risk for UTIs.

Congenital solitary functioning kidney

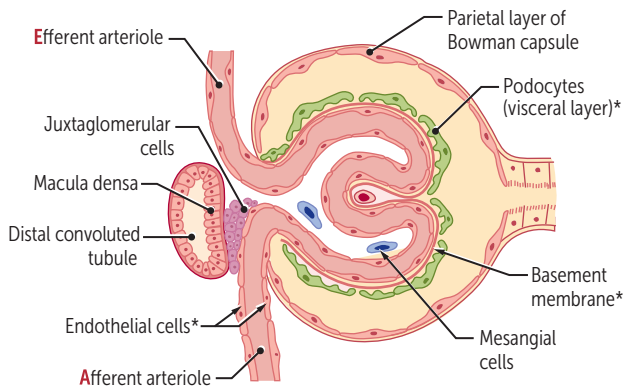
Condition of being born with only one functioning kidney. Majority asymptomatic with compensatory hypertrophy of contralateral kidney, but anomalies in contralateral kidney are common.

► RENAL—ANATOMY

Kidney anatomy and glomerular structure



Cross-section of kidney



*Components of glomerular filtration barrier.

Cross-section of glomerulus **A**

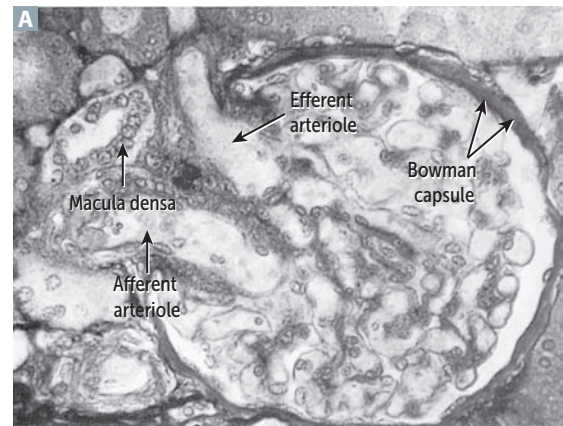
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Left kidney is taken during donor transplantation because it has a longer renal vein.

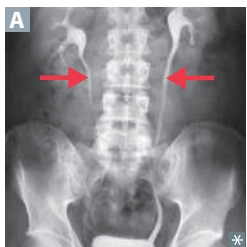
Afferent = **A**rriving.

Efferent = **E**xiting.

Renal blood flow: renal artery → segmental artery → interlobar artery → arcuate artery → interlobular artery → afferent arteriole → glomerulus → efferent arteriole → vasa recta/peritubular capillaries → venous outflow.



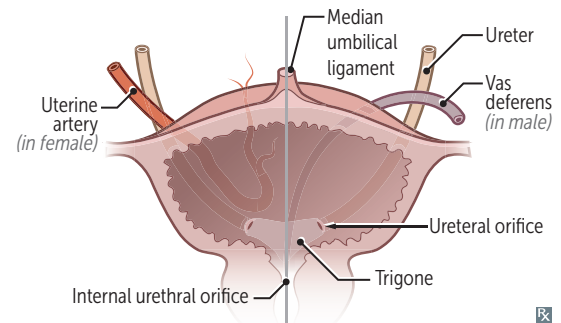
Ureters: course



Ureters **A** pass **under** uterine artery or **under** vas deferens (retroperitoneal).

Gynecologic procedures (eg, ligation of uterine or ovarian vessels) may damage ureter → ureteral obstruction or leak.

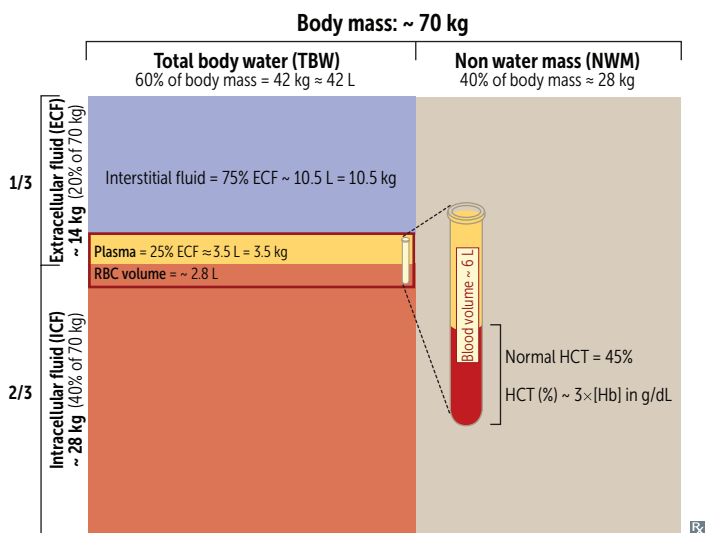
“Water (ureters) **under** the bridge (uterine artery, vas deferens).”



B

▶ RENAL—PHYSIOLOGY

Fluid compartments



HIKIN: High K^+ INtracellularly.

60–40–20 rule (% of body weight for average person):

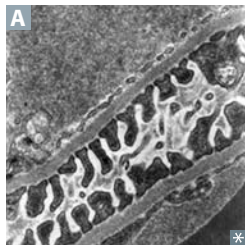
- 60% total body water
- 40% ICF
- 20% ECF

Plasma volume can be measured by radiolabeling albumin.

Extracellular volume can be measured by inulin or mannitol.

Osmolality = 285–295 mOsm/kg H_2O .

Glomerular filtration barrier



Responsible for filtration of plasma according to size and net charge.

Composed of:

- Fenestrated capillary endothelium (size barrier)
- Fused basement membrane with heparan sulfate (negative charge and size barrier)
- Epithelial layer consisting of podocyte foot processes **A** (negative charge barrier)

Charge barrier is lost in nephrotic syndrome → albuminuria, hypoproteinemia, generalized edema, hyperlipidemia.

Renal clearance

$C_x = U_x V / P_x$ = volume of plasma from which the substance is completely cleared per unit time.

If $C_x < GFR$: net tubular reabsorption of X.

If $C_x > GFR$: net tubular secretion of X.

If $C_x = GFR$: no net secretion or reabsorption.

C_x = clearance of X (mL/min).

U_x = urine concentration of X (eg, mg/mL).

P_x = plasma concentration of X (eg, mg/mL).

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.

$$\text{GFR} = U_{\text{inulin}} \times V / P_{\text{inulin}} = C_{\text{inulin}} \\ = K_f [(P_{\text{GC}} - P_{\text{BS}}) - (\pi_{\text{GC}} - \pi_{\text{BS}})]$$

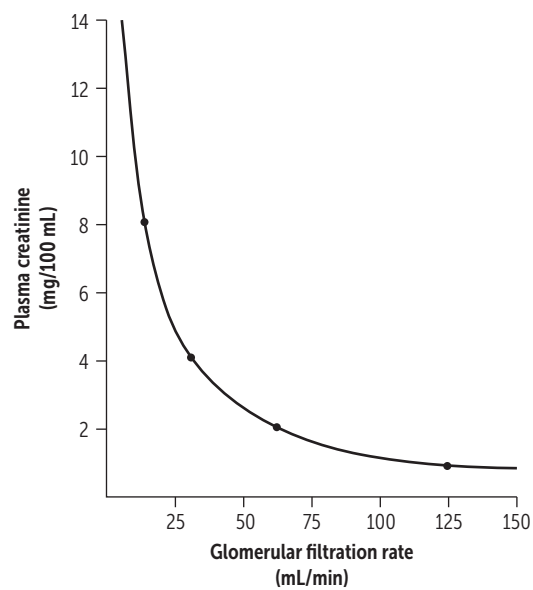
(GC = glomerular capillary; BS = Bowman space.)

π_{BS} normally equals zero; K_f = filtration constant.

Normal GFR \approx 100 mL/min.

Creatinine clearance is an approximate measure of GFR. Slightly overestimates GFR because creatinine is moderately secreted by renal tubules.

Incremental reductions in GFR define the stages of chronic kidney disease.

**Effective renal plasma flow**

Effective renal plasma flow (eRPF) can be estimated using *para*-aminohippuric acid (PAH) clearance because between filtration and secretion there is nearly 100% excretion of all PAH that enters the kidney.

$$\text{eRPF} = U_{\text{PAH}} \times V / P_{\text{PAH}} = C_{\text{PAH}}$$

$$\text{Renal blood flow (RBF)} = \text{RPF} / (1 - \text{Hct}).$$

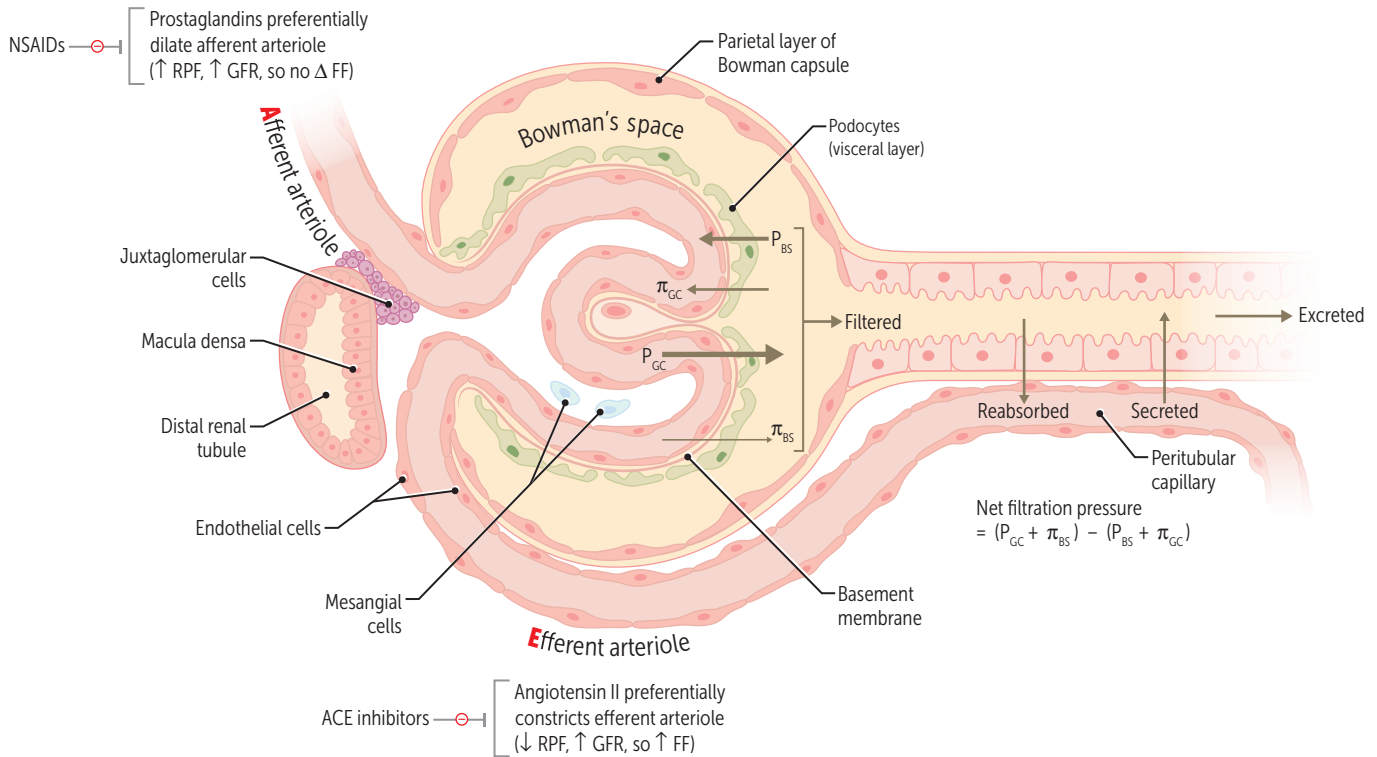
Plasma = 1 - hematocrit.

eRPF underestimates true renal plasma flow (RPF) slightly.

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.



Changes in glomerular dynamics

Effect	GFR	RPF	FF (GFR/RPF)
Afferent arteriole constriction	↓	↓	—
Efferent arteriole constriction	↑	↓	↑
↑ plasma protein concentration	↓	—	↓
↓ plasma protein concentration	↑	—	↑
Constriction of ureter	↓	—	↓
Dehydration	↓	↓	↑

Calculation of reabsorption and secretion rate

Filtered load = GFR × P_x.
 Excretion rate = V × U_x.
 Reabsorption = filtered – excreted.
 Secretion = excreted – filtered.
 $FE_{Na} = Na^+ \text{ excreted} / Na^+ \text{ filtered} = V \times U_{Na} / GFR \times P_{Na}$ (GFR = U_{Cr} × V/P_{Cr}) =
 $P_{Cr} \times U_{Na} / U_{Cr} \times P_{Na}$

Glucose clearance

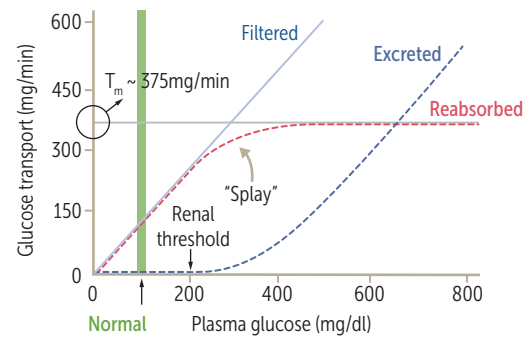
Glucose at a normal plasma level (range 60–120 mg/dL) is completely reabsorbed in proximal convoluted tubule (PCT) by Na⁺/glucose cotransport.

In adults, at plasma glucose of ~ 200 mg/dL, glucosuria begins (threshold). At rate of ~ 375 mg/min, all transporters are fully saturated (T_m).

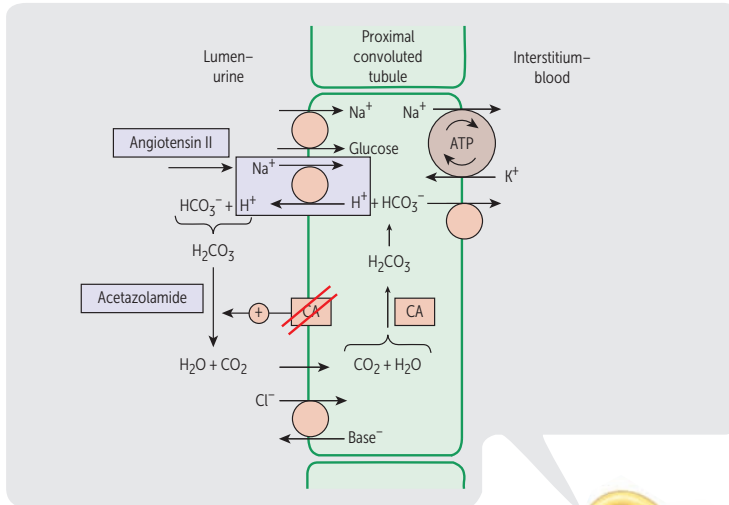
Normal pregnancy may decrease ability of PCT to reabsorb glucose and amino acids → glucosuria and aminoaciduria.

Glucosuria is an important clinical clue to diabetes mellitus.

Splay is the region of substance clearance between threshold and T_m ; due to the heterogeneity of nephrons.

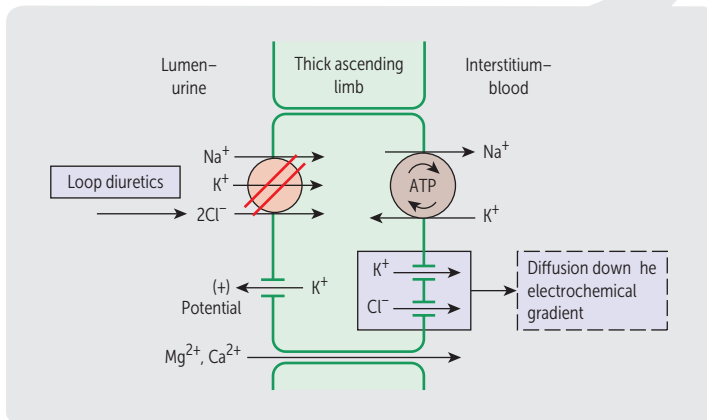


Nephron physiology

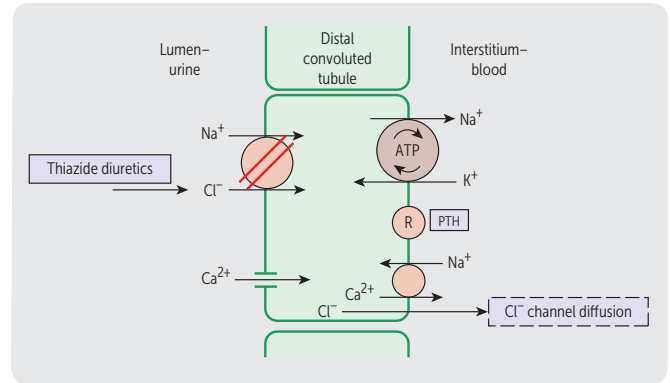


Early PCT—contains brush border. Reabsorbs all glucose and amino acids and most HCO_3^- , Na^+ , Cl^- , PO_4^{3-} , K^+ , H_2O , and uric acid. Isotonic absorption. Generates and secretes NH_3 , which acts as a buffer for secreted H^+ .
 PTH—inhibits $\text{Na}^+/\text{PO}_4^{3-}$ cotransport → PO_4^{3-} excretion.
 AT II—stimulates Na^+/H^+ exchange → ↑ Na^+ , H_2O , and HCO_3^- reabsorption (permitting contraction alkalosis).
 65–80% Na^+ reabsorbed.

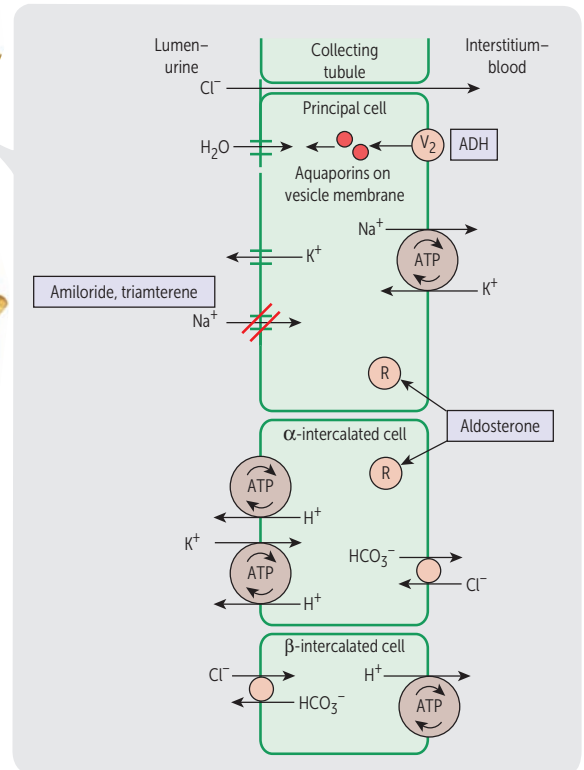
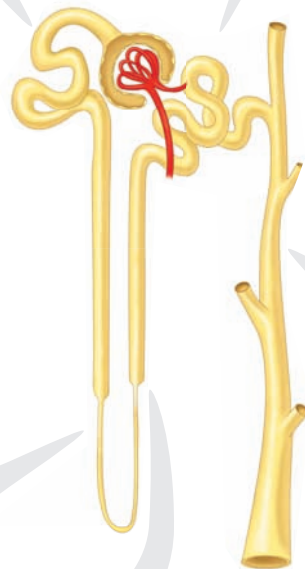
Thin descending loop of Henle—passively reabsorbs H_2O via medullary hypertonicity (impermeable to Na^+). Concentrating segment. Makes urine hypertonic.



Thick ascending loop of Henle—reabsorbs Na^+ , K^+ , and Cl^- . Indirectly induces paracellular reabsorption of Mg^{2+} and Ca^{2+} through ⊕ lumen potential generated by K^+ backleak. Impermeable to H_2O . Makes urine less concentrated as it ascends.
 10–20% Na^+ reabsorbed.



Early DCT—reabsorbs Na^+ , Cl^- . Makes urine fully dilute (hypotonic).
 PTH—↑ $\text{Ca}^{2+}/\text{Na}^+$ exchange → Ca^{2+} reabsorption.
 5–10% Na^+ reabsorbed.



Collecting tubule—reabsorbs Na^+ in exchange for secreting K^+ and H^+ (regulated by aldosterone).
 Aldosterone—acts on mineralocorticoid receptor → mRNA → protein synthesis. In principal cells: ↑ apical K^+ conductance, ↑ Na^+/K^+ pump, ↑ epithelial Na^+ channel (ENaC) activity → lumen negativity → K^+ secretion. In α -intercalated cells: lumen negativity → ↑ H^+ ATPase activity → ↑ H^+ secretion → ↑ $\text{HCO}_3^-/\text{Cl}^-$ exchanger activity.
 ADH—acts at V_2 receptor → insertion of aquaporin H_2O channels on apical side.
 3–5% Na^+ reabsorbed.

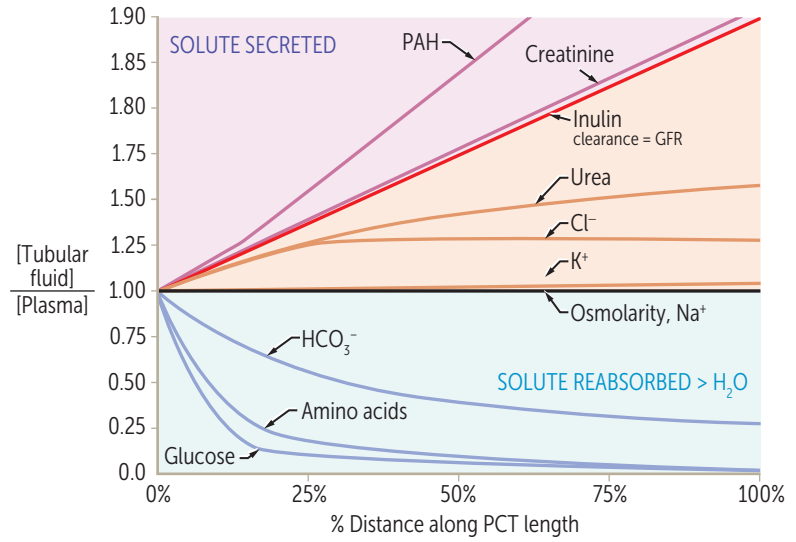
Renal tubular defects	Fanconi syndrome is first (PCT), the rest are in alphabetic order.
Fanconi syndrome	Generalized reabsorptive defect in PCT. Associated with ↑ excretion of nearly all amino acids, glucose, HCO_3^- , and PO_4^{3-} . May result in metabolic acidosis (proximal renal tubular acidosis). Causes include hereditary defects (eg, Wilson disease, tyrosinemia, glycogen storage disease, cystinosis), ischemia, multiple myeloma, nephrotoxins/drugs (eg, ifosfamide, cisplatin, tenofovir, expired tetracyclines), lead poisoning.
Bartter syndrome	Reabsorptive defect in thick ascending loop of Henle. Autosomal recessive. Affects $\text{Na}^+/\text{K}^+/\text{2Cl}^-$ cotransporter. Presents similarly to chronic loop diuretic use. Results in hypokalemia and metabolic alkalosis with hypercalciuria.
Gitelman syndrome	Reabsorptive defect of NaCl in DCT. Similar to using lifelong thiazide diuretics. Autosomal recessive. Less severe than Bartter syndrome. Leads to hypokalemia, hypomagnesemia, metabolic alkalosis, hypocalciuria.
Liddle syndrome	Gain of function mutation → ↑ Na^+ reabsorption in collecting tubules (↑ activity of epithelial Na^+ channel). Presents like hyperaldosteronism, but aldosterone is nearly undetectable. Autosomal dominant. Results in hypertension, hypokalemia, metabolic alkalosis, ↓ aldosterone. Treatment: Amiloride.
Syndrome of Apparent Mineralocorticoid Excess	Hereditary deficiency of 11β -hydroxysteroid dehydrogenase, which normally converts cortisol (can activate mineralocorticoid receptors) to cortisone (inactive on mineralocorticoid receptors) in cells containing mineralocorticoid receptors. Excess cortisol in these cells from enzyme deficiency → ↑ mineralocorticoid receptor activity → hypertension, hypokalemia, metabolic alkalosis. Low serum aldosterone levels. Can acquire disorder from glycyrrhetic acid (present in licorice), which blocks activity of 11β -hydroxysteroid dehydrogenase. Treatment: corticosteroids (exogenous corticosteroids ↓ endogenous cortisol production → ↓ mineralocorticoid receptor activation). Cortisol tries to be the SAME as aldosterone.

Relative concentrations along proximal convoluted tubules

[TF/P] > 1 when solute is reabsorbed less quickly than water

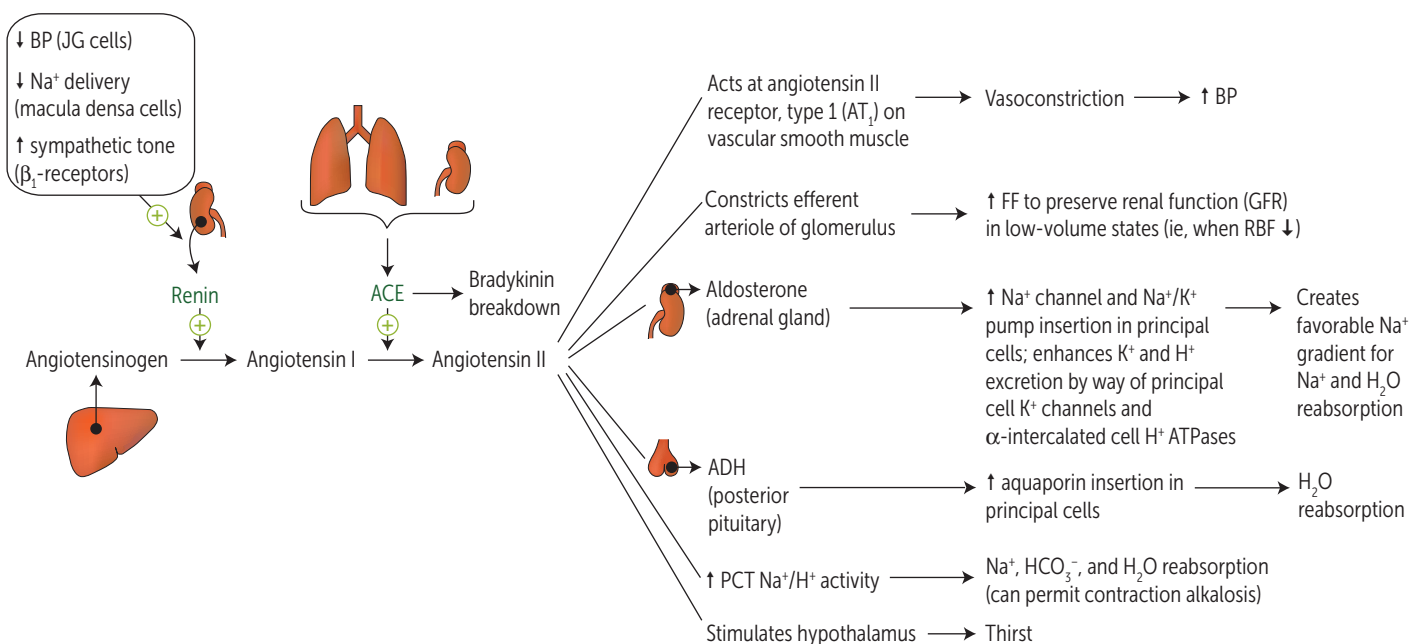
[TF/P] = 1 when solute and water are reabsorbed at the same rate

[TF/P] < 1 when solute is reabsorbed more quickly than water



Tubular inulin ↑ in concentration (but not amount) along the PCT as a result of water reabsorption. Cl⁻ reabsorption occurs at a slower rate than Na⁺ in early PCT and then matches the rate of Na⁺ reabsorption more distally. Thus, its relative concentration ↑ before it plateaus.

Renin-angiotensin-aldosterone system



Renin	Secreted by JG cells in response to ↓ renal arterial pressure and ↑ renal sympathetic discharge (β ₁ effect).
AT II	Affects baroreceptor function; limits reflex bradycardia, which would normally accompany its pressor effects. Helps maintain blood volume and blood pressure.
ANP, BNP	Released from atria (ANP) and ventricles (BNP) in response to ↑ volume; may act as a “check” on renin-angiotensin-aldosterone system; relaxes vascular smooth muscle via cGMP → ↑ GFR, ↓ renin. Dilates afferent arteriole, constricts efferent arteriole, promotes natriuresis.
ADH	Primarily regulates osmolarity; also responds to low blood volume states.
Aldosterone	Primarily regulates ECF volume and Na ⁺ content; responds to low blood volume states.

Juxtaglomerular apparatus

Consists of mesangial cells, JG cells (modified smooth muscle of afferent arteriole) and the macula densa (NaCl sensor, part of DCT). JG cells secrete renin in response to ↓ renal blood pressure and ↑ sympathetic tone (β₁). Macula densa cells sense ↓ NaCl delivery to DCT → ↑ renin release → efferent arteriole vasoconstriction → ↑ GFR.

JGA maintains GFR via renin-angiotensin-aldosterone system.

β-blockers can decrease BP by inhibiting β₁-receptors of the JGA → ↓ renin release.

Kidney endocrine functions

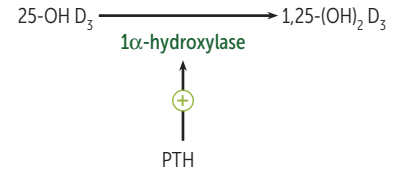
Erythropoietin

Released by interstitial cells in peritubular capillary bed in response to hypoxia.

Stimulates RBC proliferation in bone marrow. Erythropoietin often supplemented in chronic kidney disease.

Caciferol

PCT cells convert 25-OH vitamin D₃ to 1,25-(OH)₂ vitamin D₃ (calcitriol, active form).



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 renal failure 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.

Hormones acting on kidney

Atrial natriuretic peptide

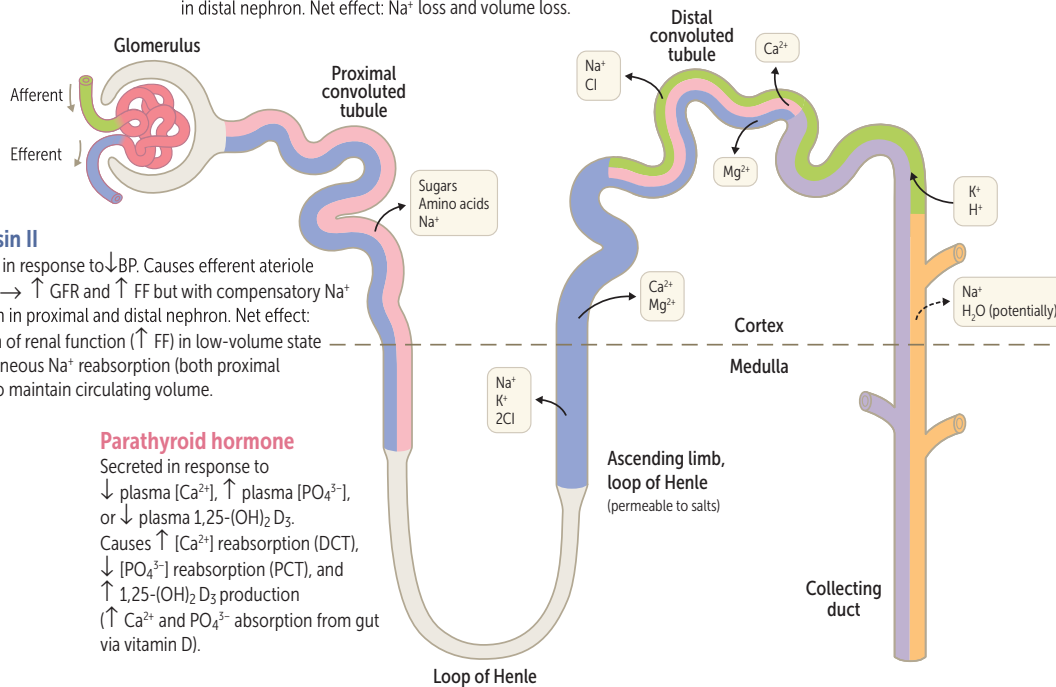
Secreted in response to ↑ atrial pressure. Causes ↑ GFR and ↑ Na⁺ filtration with no compensatory Na⁺ reabsorption in distal nephron. Net effect: Na⁺ loss and volume loss.

Angiotensin II

Synthesized in response to ↓ BP. Causes efferent arteriole constriction → ↑ GFR and ↑ FF but with compensatory Na⁺ reabsorption in proximal and distal nephron. Net effect: preservation of renal function (↑ FF in low-volume state with simultaneous Na⁺ reabsorption (both proximal and distal) to maintain circulating volume.

Parathyroid hormone

Secreted in response to ↓ plasma [Ca²⁺], ↑ plasma [PO₄³⁻], or ↓ plasma 1,25-(OH)₂D₃. Causes ↑ [Ca²⁺] reabsorption (DCT), ↓ [PO₄³⁻] reabsorption (PCT), and ↑ 1,25-(OH)₂D₃ production (↑ Ca²⁺ and PO₄³⁻ absorption from gut via vitamin D).



Aldosterone

Secreted in response to ↓ blood volume (via AT II) and ↑ plasma [K⁺]; causes ↑ Na⁺ reabsorption, ↑ K⁺ secretion, ↑ H⁺ secretion.

ADH (vasopressin)

Secreted in response to ↑ plasma osmolarity and ↓ blood volume. Binds to receptors on principal cells, causing ↑ number of aquaporins and ↑ H₂O reabsorption.



Potassium shiftsSHIFTS K⁺ OUT OF CELL (CAUSING HYPERKALEMIA)SHIFTS K⁺ INTO CELL (CAUSING HYPOKALEMIA)**D**igitalis (blocks Na⁺/K⁺ ATPase)Hyper**O**smolarity**L**ysis of cells (eg, crush injury, rhabdomyolysis, tumor lysis syndrome)**A**cidosis**β**-blockerHigh blood **S**ugar (insulin deficiency)Patient with hyperkalemia? **DO LAßS.**

Hypo-osmolarity

Alkalosis

β-adrenergic agonist (↑ Na⁺/K⁺ ATPase)Insulin (↑ Na⁺/K⁺ ATPase)**I**nsulin shifts K⁺ **into** cells**Electrolyte disturbances**

ELECTROLYTE	LOW SERUM CONCENTRATION	HIGH SERUM CONCENTRATION
Na ⁺	Nausea and malaise, stupor, coma, seizures	Irritability, stupor, coma
K ⁺	U waves and flattened T waves on ECG, arrhythmias, muscle cramps, spasm, weakness	Wide QRS and peaked T waves on ECG, arrhythmias, muscle weakness
Ca ²⁺	Tetany, seizures, QT prolongation, twitching (Chvostek sign), spasm (Trousseau sign)	S tones (renal), b ones (pain), g roans (abdominal pain), t hrones (↑ urinary frequency), p sychiatric o vertones (anxiety, altered mental status), but not necessarily calciuria
Mg ²⁺	Tetany, torsades de pointes, hypokalemia	↓ DTRs, lethargy, bradycardia, hypotension, cardiac arrest, hypocalcemia
PO ₄ ³⁻	Bone loss, osteomalacia (adults), rickets (children)	Renal stones, metastatic calcifications, hypocalcemia

Features of renal disorders

CONDITION	BLOOD PRESSURE	PLASMA RENIN	ALDOSTERONE	SERUM Mg ²⁺	URINE Ca ²⁺
Bartter syndrome	—	↑	↑		↑
Gitelman syndrome	—	↑	↑	↓	↓
Liddle syndrome	↑	↓	↓		
SIADH	↑	↓	↓		
Primary hyperaldosteronism (Conn syndrome)	↑	↓	↑		
Renin-secreting tumor	↑	↑	↑		

Acid-base physiology

	pH	P _{CO₂}	[HCO ₃ ⁻]	COMPENSATORY RESPONSE
Metabolic acidosis	↓	↓	↓	Hyperventilation (immediate)
Metabolic alkalosis	↑	↑	↑	Hypoventilation (immediate)
Respiratory acidosis	↓	↑	↑	↑ renal [HCO ₃ ⁻] reabsorption (delayed)
Respiratory alkalosis	↑	↓	↓	↓ renal [HCO ₃ ⁻] reabsorption (delayed)

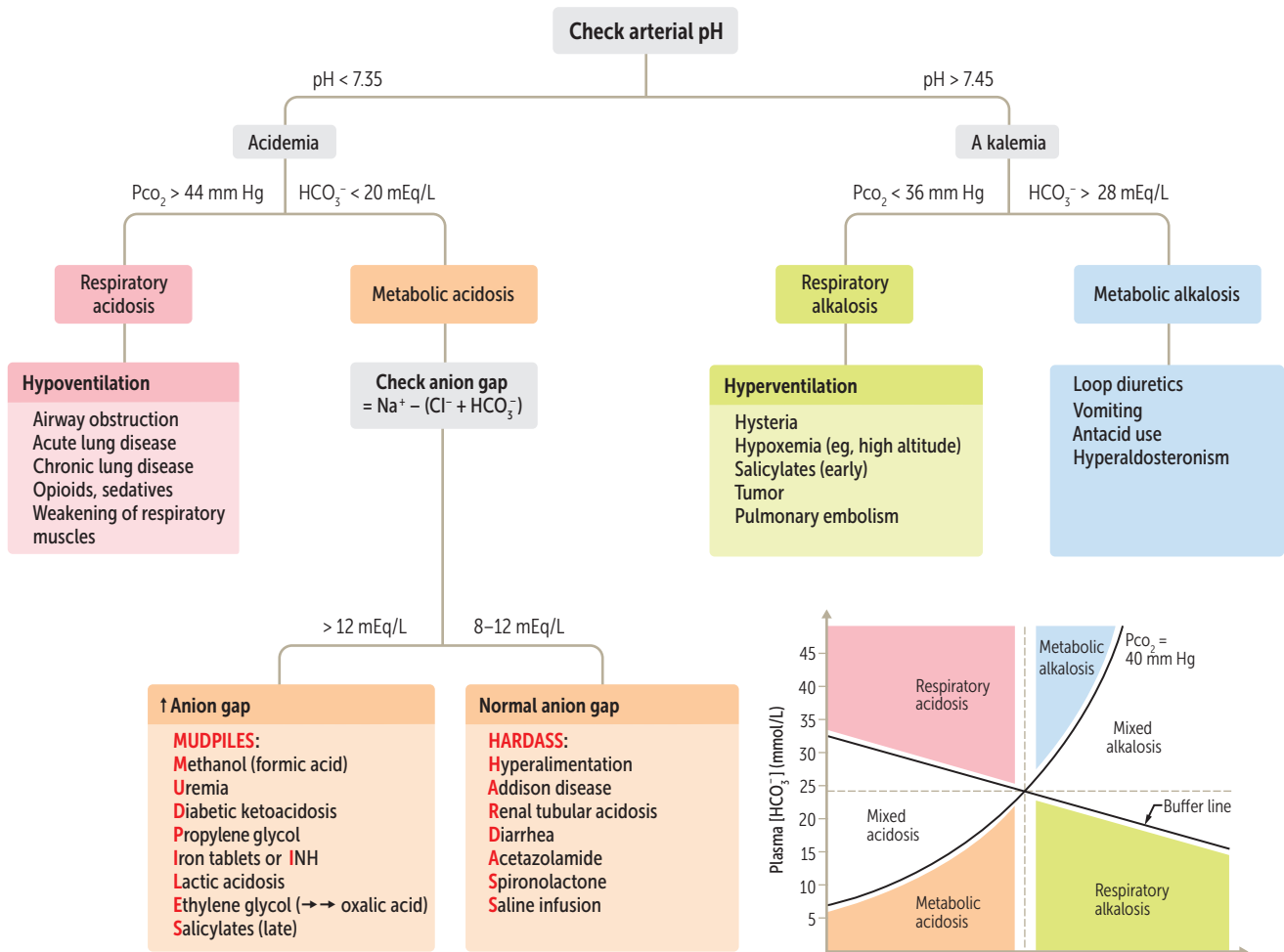
Key: ↑ ↓ = 1° disturbance; ↓ ↑ = compensatory response.

Henderson-Hasselbalch equation: $pH = 6.1 + \log \frac{[HCO_3^-]}{0.03 P_{CO_2}}$

Predicted respiratory compensation for a simple metabolic acidosis can be calculated using the Winters formula. If measured P_{CO₂} > predicted P_{CO₂} → concomitant respiratory acidosis; if measured P_{CO₂} < predicted P_{CO₂} → concomitant respiratory alkalosis:

$$P_{CO_2} = 1.5 [HCO_3^-] + 8 \pm 2$$

Acidosis/alkalosis



RTA TYPE	NOTES
Renal tubular acidosis	A disorder of the renal tubules that leads to normal anion gap (hyperchloremic) metabolic acidosis.
Distal renal tubular acidosis (type 1)	Urine pH > 5.5. Defect in ability of α intercalated cells to secrete H^+ → no new HCO_3^- is generated → metabolic acidosis. Associated with hypokalemia , ↑ risk for calcium phosphate kidney stones (due to ↑ urine pH and ↑ bone turnover). Causes: amphotericin B toxicity, analgesic nephropathy, congenital anomalies (obstruction) of urinary tract.
Proximal renal tubular acidosis (type 2)	Urine pH < 5.5. Defect in PCT HCO_3^- reabsorption → ↑ excretion of HCO_3^- in urine and subsequent metabolic acidosis. Urine is acidified by α -intercalated cells in collecting tubule. Associated with hypokalemia , ↑ risk for hypophosphatemic rickets. Causes: Fanconi syndrome and carbonic anhydrase inhibitors.
Hyperkalemic renal tubular acidosis (type 4)	Urine pH < 5.5. Hypoaldosteronism → hyperkalemia → ↓ NH_3 synthesis in PCT → ↓ NH_4^+ excretion. Causes: ↓ 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).

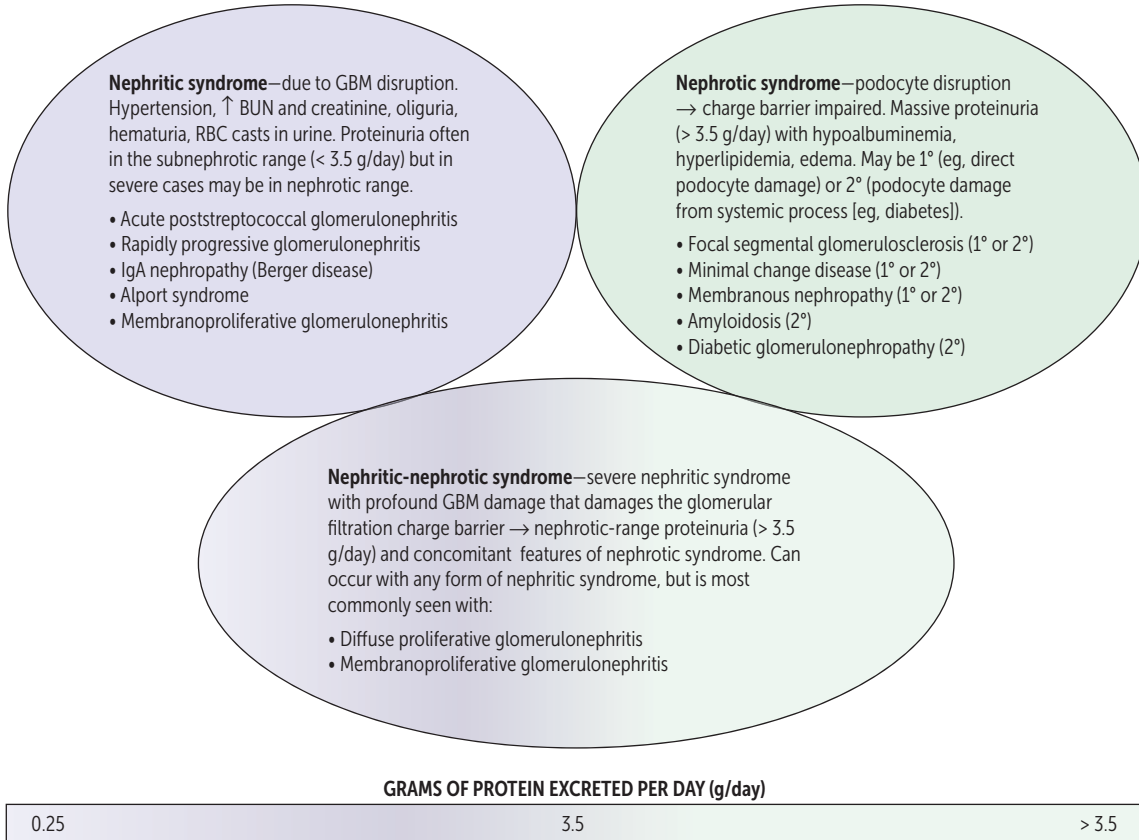
► RENAL—PATHOLOGY

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	Glomerulonephritis, malignant hypertension.
WBC casts	Tubulointerstitial inflammation, acute pyelonephritis, transplant rejection.
Fatty casts (“oval fat bodies”)	Nephrotic syndrome. Associated with “Maltese cross” sign.
Granular (“muddy brown”) casts	Acute tubular necrosis.
Waxy casts	End-stage renal disease/chronic renal failure.
Hyaline casts	Nonspecific, can be a normal finding, often seen in concentrated urine samples.

Nomenclature of glomerular disorders

TYPE	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	A 1° disease of the kidney specifically impacting the glomeruli	Minimal change disease
Secondary glomerular disease	A systemic disease or disease of another organ system that also impacts the glomeruli	SLE, diabetic nephropathy

Glomerular diseases



Nephritic syndrome

Nephritic syndrome = Inflammatory process. When it involves glomeruli, it leads to hematuria and RBC casts in urine. Associated with azotemia, oliguria, hypertension (due to salt retention), proteinuria.

Acute poststreptococcal glomerulonephritis

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 immune complex (IC) humps.

Most frequently seen in children. Occurs ~ 2–4 weeks after group A streptococcal infection of pharynx or skin. Resolves spontaneously. Type III hypersensitivity reaction.
Presents with peripheral and periorbital edema, cola-colored urine, hypertension.
Positive strep titers/serologies, ↓ complement levels due to consumption.

Rapidly progressive (crescentic) glomerulonephritis

LM and IF—crescent moon shape **C**. Crescents consist of fibrin and plasma proteins (eg, C3b) with glomerular parietal cells, monocytes, macrophages.
Several disease processes may result in this pattern, in particular:
▪ **Goodpasture syndrome**—type II hypersensitivity; antibodies to GBM and alveolar basement membrane → linear IF
▪ Granulomatosis with polyangiitis (Wegener)
▪ Microscopic polyangiitis

Poor prognosis. Rapidly deteriorating renal function (days to weeks).

Hematuria/hemoptysis.
Treatment: emergent plasmapheresis.
PR3-ANCA/c-ANCA. Pauci-immune (no Ig/C3 deposition).
MPO-ANCA/p-ANCA. Pauci-immune (no Ig/C3 deposition).

Diffuse proliferative glomerulonephritis

Due to SLE or membranoproliferative glomerulonephritis.
LM—“**wire looping**” of capillaries.
EM—subendothelial and sometimes intramembranous IgG-based ICs often with C3 deposition.
IF—granular.

A common cause of death in SLE (think “**wire lupus**”). DPGN and MPGN often present as nephrotic syndrome and nephritic syndrome concurrently.

IgA nephropathy (Berger disease)

LM—mesangial proliferation.
EM—mesangial IC deposits.
IF—IgA-based IC deposits in mesangium.
Renal pathology of Henoch-Schönlein purpura.

Episodic gross hematuria that occurs concurrently with respiratory or GI tract infections (IgA is secreted by mucosal linings).
Not to be confused with Buerger disease (thromboangiitis obliterans).

Nephritic syndrome (continued)**Alport syndrome**

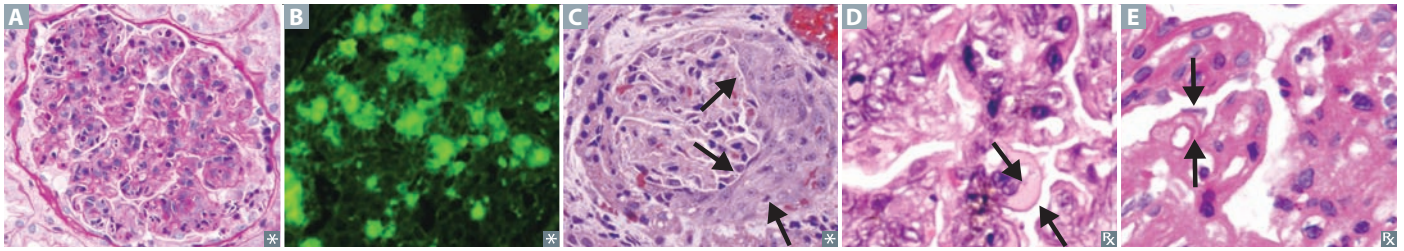
Mutation in type IV collagen → thinning and splitting of glomerular basement membrane. Most commonly X-linked dominant.

Eye problems (eg, retinopathy, lens dislocation), glomerulonephritis, sensorineural deafness; “can’t see, can’t pee, can’t hear a bee.” “Basket-weave” appearance on EM.

Membrano-proliferative glomerulonephritis (MPGN)

Type I—subendothelial immune complex (IC) deposits with granular IF; “tram-track” appearance on PAS stain **D** and H&E stain **E** due to GBM splitting caused by mesangial ingrowth.
Type II—also called dense deposit disease.

MPGN is a nephritic syndrome that often copresents with nephrotic syndrome. Type I may be 2° to hepatitis B or C infection. May also be idiopathic. Type II is associated with C3 nephritic factor (stabilizes C3 convertase → ↓ serum C3 levels).



LM = light microscopy; EM = electron microscopy; IF = immunofluorescence.

Nephrotic syndrome

Nephrotic syndrome—massive proteinuria (> 3.5 g/day) with hypoalbuminemia, resulting edema, hyperlipidemia. Frothy urine with fatty casts. Due to podocyte damage disrupting glomerular filtration charge barrier. May be 1° (eg, direct sclerosis of podocytes) or 2° (systemic process [eg, diabetes] secondarily damages podocytes). Associated with hypercoagulable state (eg, thromboembolism) due to antithrombin (AT) III loss in urine and ↑ risk of infection (due to loss of immunoglobulins in urine and soft tissue compromise by edema).

Severe nephritic syndrome may present with nephrotic syndrome features (nephritic-nephrotic syndrome) if damage to GBM is severe enough to damage charge barrier.

Minimal change disease (lipoid nephrosis)

LM—normal glomeruli (lipid may be seen in PCT cells).

IF ⊖.

EM—effacement of foot processes **A**.

Most common cause of nephrotic syndrome in children. Often 1° (idiopathic) and may be triggered by recent infection, immunization, immune stimulus. Rarely, may be 2° to lymphoma (eg, cytokine-mediated damage). 1° disease has excellent response to corticosteroids.

Focal segmental glomerulosclerosis

LM—segmental sclerosis and hyalinosis **B**.

IF—often ⊖, but may be ⊕ for nonspecific focal deposits of IgM, C3, C1.

EM—effacement of foot process similar to minimal change disease.

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, chronic kidney disease due to congenital malformations). 1° disease has inconsistent response to steroids. May progress to chronic renal disease.

Membranous nephropathy (membranous glomerulonephritis)

LM—diffuse capillary and GBM thickening **C**.

IF—granular as a result of immune complex deposition. Nephrotic presentation of SLE.

EM—“spike and dome” appearance with subepithelial deposits.

Most common cause of 1° nephrotic syndrome in Caucasian adults. Can be 1° (eg, antibodies to phospholipase A₂ receptor) or 2° to drugs (eg, NSAIDs, penicillamine), infections (eg, HBV, HCV), SLE, or solid tumors. 1° disease has poor response to steroids. May progress to chronic renal disease.

Amyloidosis

LM—Congo red stain shows apple-green birefringence under polarized light due to amyloid deposition in the mesangium.

Kidney is the most commonly involved organ (systemic amyloidosis). Associated with chronic conditions that predispose to amyloid deposition (eg, AL amyloid, AA amyloid).

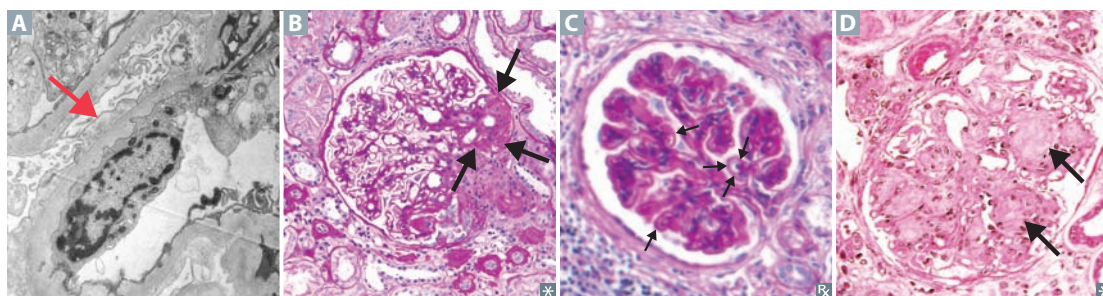
Diabetic glomerulonephropathy

LM—mesangial expansion, GBM thickening, eosinophilic nodular glomerulosclerosis (Kimmelstiel-Wilson lesions, arrows in **D**).

Nonenzymatic glycosylation of GBM
→ ↑ permeability, thickening.

Nonenzymatic glycosylation of efferent arterioles
→ ↑ GFR → mesangial expansion.

Most common cause of end-stage renal disease in the United States.

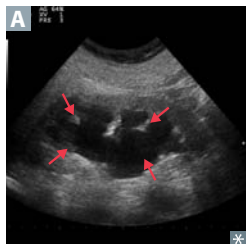


Kidney stones

Can lead to severe complications such as hydronephrosis, pyelonephritis. Presents with unilateral flank tenderness, colicky pain radiating to groin, hematuria. Treat and prevent by encouraging fluid intake. Most common kidney stone presentation: calcium oxalate stone in patient with hypercalciuria and normocalcemia.

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. Hypocitraturia often associated with ↓ urine pH. Can result from ethylene glycol (antifreeze) ingestion, vitamin C abuse, hypocitraturia, malabsorption (eg, Crohn disease). Treatment: thiazides, citrate, low-sodium diet.
	Calcium phosphate: ↑ pH	Radiopaque	Radiopaque	Wedge-shaped prism	Treatment: thiazides.
Ammonium magnesium phosphate	↑ pH	Radiopaque	Radiopaque	Coffin lid B	Also known as struvite; account for 15% of stones. Caused by infection with urease ⊕ bugs (eg, <i>Proteus mirabilis</i> , <i>Staphylococcus saprophyticus</i> , <i>Klebsiella</i>) that hydrolyze urea to ammonia → urine alkalization. Commonly form staghorn calculi C . Treatment: eradication of underlying infection, surgical removal of stone.
Uric acid	↓ pH	Radiolucent	Minimally visible	Rhomboid D or rosettes	About 5% of all stones. Risk factors: ↓ urine volume, arid climates, acidic pH. Visible on ultrasound. Strong association with hyperuricemia (eg, gout). Often seen in diseases with ↑ cell turnover, such as leukemia. Treatment: alkalization of urine, allopurinol.
Cystine	↓ pH	Radiolucent	Sometimes visible	Hexagonal E	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, alkalization of urine, chelating agents if refractory.



Hydronephrosis

Distention/dilation of renal pelvis and calyces **A**. Usually caused by urinary tract obstruction (eg, renal stones, BPH, cervical cancer, injury to ureter); other causes include retroperitoneal fibrosis, vesicoureteral reflux. Dilation occurs proximal to site of pathology. Serum creatinine becomes elevated only if obstruction is bilateral or if patient has only one kidney. Leads to compression and possible atrophy of renal cortex and medulla.

Renal cell carcinoma

Originates from PCT cells → polygonal clear cells **A** filled with accumulated lipids and carbohydrates. Often golden-yellow **B** due to ↑ lipid content. Most common in men 50–70 years old. ↑ incidence with smoking and obesity. Manifests clinically with hematuria, palpable mass, 2° polycythemia, flank pain, fever, weight loss. Invades renal vein then IVC and spreads hematogenously; metastasizes to lung and bone.

Treatment: resection if localized disease.

Immunotherapy (eg, aldesleukin) or targeted therapy for advanced/metastatic disease.

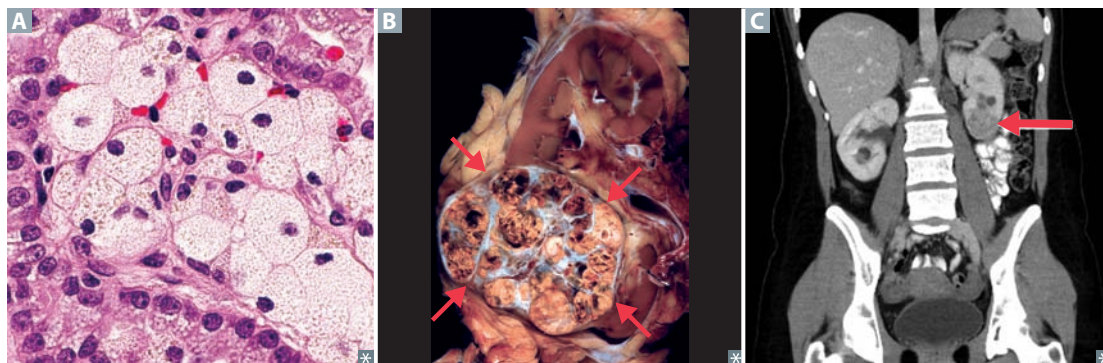
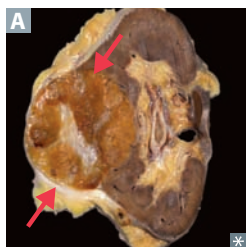
Resistant to chemotherapy and radiation therapy.

Most common 1° renal malignancy **C**.

Associated with gene deletion on chromosome 3 (sporadic or inherited as von Hippel-Lindau syndrome). **RCC = 3** letters = chromosome **3**.

Associated with paraneoplastic syndromes (eg, ectopic EPO, ACTH, PTHrP, renin).

“Silent” cancer because commonly presents as a metastatic neoplasm.

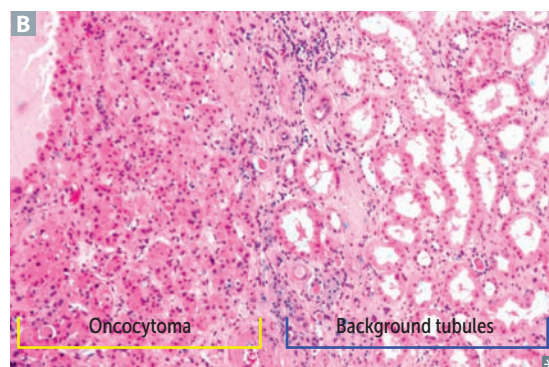
**Renal oncocytoma**

Benign epithelial cell tumor arising from collecting ducts (arrows in **A** point to well-circumscribed mass with central scar).

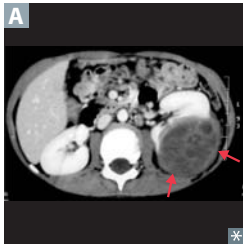
Large eosinophilic cells with abundant mitochondria without perinuclear clearing **B** (vs chromophobe renal cell carcinoma).

Presents with painless hematuria, flank pain, abdominal mass.

Often resected to exclude malignancy (eg, renal cell carcinoma).



Wilms tumor (nephroblastoma)

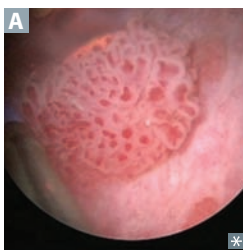


Most common renal malignancy of early childhood (ages 2–4). Contains embryonic glomerular structures. Presents with large, palpable, unilateral flank mass **A** and/or hematuria. “Loss of function” mutations of tumor suppressor genes *WT1* or *WT2* on chromosome 11.

May be a part of several syndromes:

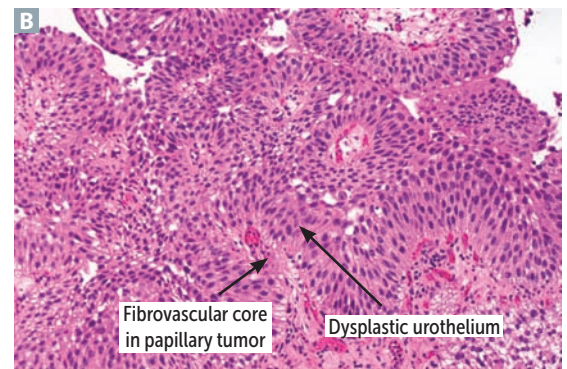
- **WAGR** complex: **W**ilms tumor, **A**niridia (absence of iris), **G**enitourinary malformations, mental **R**etardation/intellectual disability (*WT1* deletion)
- Denys-Drash: Wilms tumor, early-onset nephrotic syndrome, male pseudohermaphroditism (*WT1* mutation)
- Beckwith-Wiedemann: Wilms tumor, macroglossia, organomegaly, hemihypertrophy (*WT2* mutation)

Transitional cell carcinoma



Most common tumor of urinary tract system (can occur in renal calyces, renal pelvis, ureters, and bladder) **A B**. Painless hematuria (no casts) suggests bladder cancer.

Associated with problems in your **Pee SAC**: **P**henacetin, **S**moking, **A**niline dyes, and **C**yclophosphamide.



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.

Urinary incontinence

Stress incontinence

Outlet incompetence (urethral hypermobility or intrinsic sphincteric deficiency) → leak with ↑ intra-abdominal pressure (eg, sneezing, lifting). ↑ risk with obesity, vaginal delivery, prostate surgery. ⊕ bladder stress test (directly observed leakage from urethra upon coughing or Valsalva maneuver). Treatment: pelvic floor muscle strengthening (Kegel) exercises, weight loss, pessaries.

Urgency incontinence

Overactive bladder (detrusor instability) → leak with urge to void immediately. Treatment: Kegel exercises, bladder training (timed voiding, distraction or relaxation techniques), antimuscarinics (eg, oxybutynin).

Mixed incontinence

Features of both stress and urgency incontinence.

Overflow incontinence

Incomplete emptying (detrusor underactivity or outlet obstruction) → leak with overfilling. ↑ post-void residual (urinary retention) on catheterization or ultrasound. Treatment: catheterization, relieve obstruction (eg, α-blockers for BPH).

Urinary tract infection (acute bacterial 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 gender (short urethra), sexual intercourse (“honeymoon cystitis”), 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.

Lab findings: ⊕ leukocyte esterase. ⊕ nitrites (indicate gram ⊖ organisms, especially *E coli*). Sterile pyuria and ⊖ urine cultures suggest urethritis by *Neisseria gonorrhoeae* or *Chlamydia trachomatis*.

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.

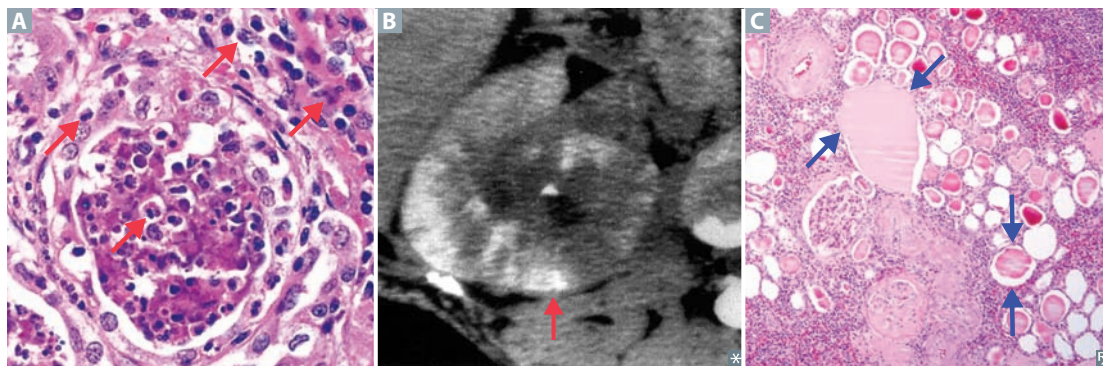
Treatment: antibiotics.

Chronic pyelonephritis

The result of recurrent 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 **C** (thyroidization of kidney).

Xanthogranulomatous pyelonephritis—rare; characterized by widespread kidney damage due to granulomatous tissue containing foamy macrophages.



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 osteodystrophy Hypocalcemia, hyperphosphatemia, and failure of vitamin D hydroxylation associated with chronic renal disease → 2° hyperparathyroidism. Hyperphosphatemia also independently ↓ serum Ca²⁺ by causing tissue calcifications, whereas ↓ 1,25-(OH)₂D₃ → ↓ intestinal Ca²⁺ absorption. Causes subperiosteal thinning of bones.

Acute kidney injury (acute renal failure) Acute kidney injury is defined as an abrupt decline in renal function as measured by ↑ creatinine and ↑ BUN.

Prerenal azotemia Due to ↓ RBF (eg, hypotension) → ↓ GFR. Na⁺/H₂O and BUN retained by kidney in an attempt to conserve volume → ↑ BUN/creatinine ratio (BUN is reabsorbed, creatinine is not) and ↓ FENa.

Intrinsic renal failure Generally due to acute tubular necrosis or ischemia/toxins; less commonly due to acute glomerulonephritis (eg, RPGN, hemolytic uremic syndrome) or acute interstitial nephritis. In ATN, patchy necrosis → debris obstructing tubule and fluid backflow across necrotic tubule → ↓ GFR. Urine has epithelial/granular casts. BUN reabsorption is impaired → ↓ BUN/creatinine ratio.

Postrenal azotemia Due to outflow obstruction (stones, BPH, neoplasia, congenital anomalies). Develops only with bilateral obstruction.

	Prerenal	Intrinsic renal	Postrenal
Urine osmolality (mOsm/kg)	> 500	< 350	< 350
Urine Na ⁺ (mEq/L)	< 20	> 40	> 40
FENa	< 1%	> 2%	> 1% (mild) > 2% (severe)
Serum BUN/Cr	> 20	< 15	Varies

Consequences of renal failure Inability to make urine and excrete nitrogenous wastes. 2 forms of renal failure: acute (eg, ATN) and chronic (eg, hypertension, diabetes mellitus, congenital anomalies).
 Consequences (**MAD HUNGER**):

- **M**etabolic **A**cidosis
- **D**yslipidemia (especially ↑ triglycerides)
- **H**yperkalemia
- **U**remia—clinical syndrome marked by ↑ BUN:
 - Nausea and anorexia
 - Pericarditis
 - Asterixis
 - Encephalopathy
 - Platelet dysfunction
- **N**a⁺/H₂O retention (HF, pulmonary edema, hypertension)
- **G**rowth retardation and developmental delay
- **E**rythropoietin failure (anemia)
- **R**enal osteodystrophy

Acute interstitial nephritis (tubulointerstitial nephritis)

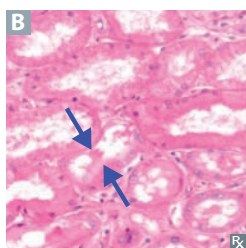
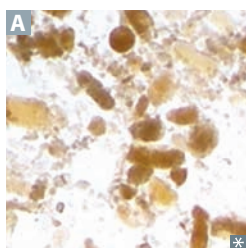
Acute interstitial renal inflammation. Pyuria (classically eosinophils) and azotemia occurring after administration of drugs that act as haptens, inducing hypersensitivity (eg, diuretics, penicillin derivatives, proton pump inhibitors, sulfonamides, rifampin, NSAIDs). Less commonly may be 2° to other processes such as systemic infections (eg, mycoplasma) or autoimmune diseases (eg, Sjögren syndrome, SLE, sarcoidosis).

Associated with fever, rash, hematuria, and costovertebral angle tenderness, but can be asymptomatic.

Remember these **P's**:

- **P**ee (diuretics)
- **P**ain-free (NSAIDs)
- **P**enicillins and cephalosporins
- **P**roton pump inhibitors
- Rifam**P**in

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. ↑ FENa.

Key finding: granular (“muddy brown”) casts **A**.

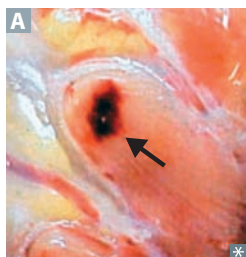
3 stages:

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

Can be caused by ischemic or nephrotoxic injury:

- Ischemic—2° to ↓ renal blood flow (eg, hypotension, shock, sepsis, hemorrhage, HF). Results in death of tubular cells that may slough into tubular lumen **B** (PCT and thick ascending limb are highly susceptible to injury).
- Nephrotoxic—2° to injury resulting from toxic substances (eg, aminoglycosides, radiocontrast agents, lead, cisplatin), crush injury (myoglobinuria), hemoglobinuria. PCT is particularly susceptible to injury.

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, NSAIDs, diabetes mellitus.

SAAD papa with papillary necrosis:

- S**ickle cell disease or trait
- A**cute pyelonephritis
- A**nalgesics (NSAIDs)
- D**iabetes mellitus

Renal cyst disorders**Autosomal dominant polycystic kidney disease**

Numerous cysts in cortex and medulla **A** causing bilateral enlarged kidneys ultimately destroy kidney parenchyma. Presents with flank pain, hematuria, hypertension, urinary infection, progressive renal failure in ~ 50% of individuals.

Mutation in *PKD1* (85% of cases, chromosome 16) or *PKD2* (15% of cases, chromosome 4). Death from complications of chronic kidney disease or hypertension (caused by ↑ renin production).

Associated with berry aneurysms, mitral valve prolapse, benign hepatic cysts.

Treatment: 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.

Medullary cystic disease

Inherited disease causing tubulointerstitial fibrosis and progressive renal insufficiency with inability to concentrate urine. Medullary cysts usually not visualized; shrunken kidneys on ultrasound. Poor prognosis.

Simple vs complex renal cysts

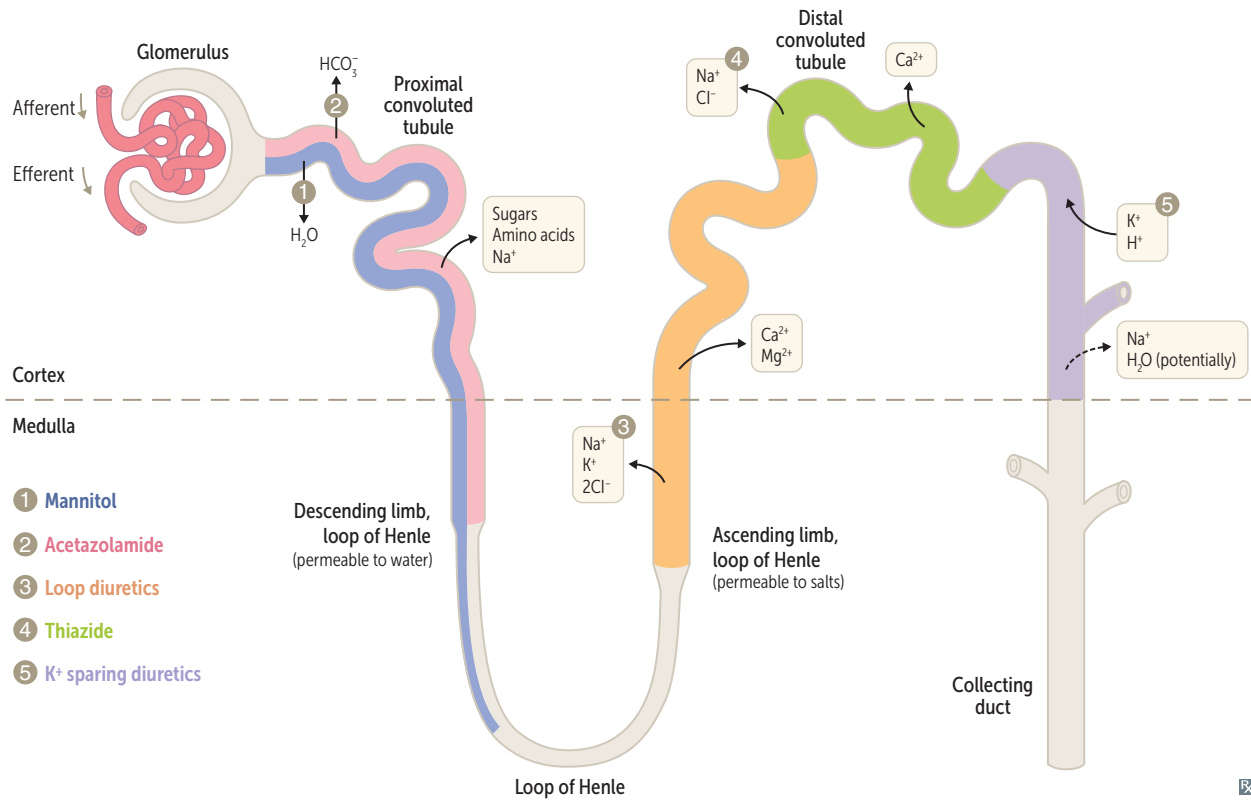
Simple cysts are filled with ultrafiltrate (anechoic on ultrasound **C**). Very common and account for majority of all renal masses. Found incidentally and typically asymptomatic.

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.



► RENAL—PHARMACOLOGY

Diuretics: site of action

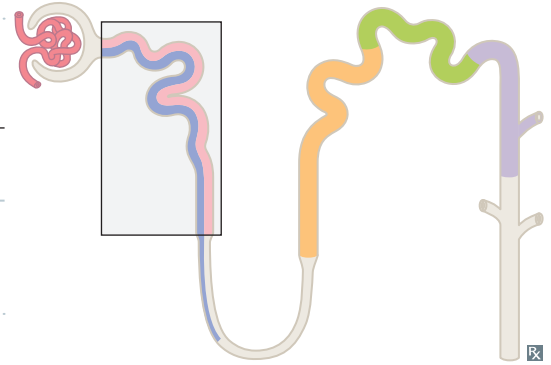


Mannitol

MECHANISM	Osmotic diuretic. ↑ tubular fluid osmolarity → ↑ urine flow, ↓ intracranial/intraocular pressure.
CLINICAL USE	Drug overdose, elevated intracranial/intraocular pressure.
ADVERSE EFFECTS	Pulmonary edema, dehydration. Contraindicated in anuria, HF.

Acetazolamide

MECHANISM	Carbonic anhydrase inhibitor. Causes self-limited NaHCO_3 diuresis and ↓ total body HCO_3^- stores.
CLINICAL USE	Glaucoma, urinary alkalinization, metabolic alkalosis, altitude sickness, pseudotumor cerebri.
ADVERSE EFFECTS	Proximal renal tubular acidosis, paresthesias, NH_3 toxicity, sulfa allergy.

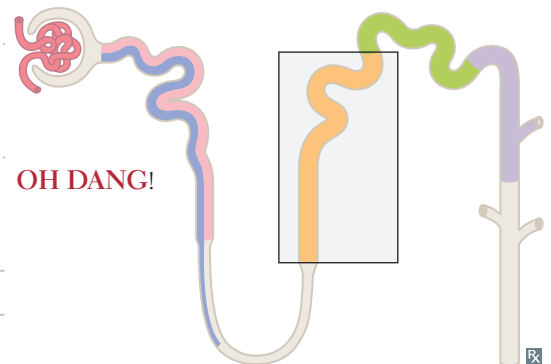


“ACID”azolamide causes ACIDosis.

Loop diuretics

Furosemide, bumetanide, torsemide

MECHANISM	Sulfonamide loop diuretics. Inhibit cotransport system ($\text{Na}^+/\text{K}^+/2\text{Cl}^-$) of thick ascending limb of loop of Henle. Abolish hypertonicity of medulla, preventing concentration of urine. Stimulate PGE release (vasodilatory effect on afferent arteriole); inhibited by NSAIDs. ↑ Ca^{2+} excretion. L oops L ose Ca^{2+} .
CLINICAL USE	Edematous states (HF, cirrhosis, nephrotic syndrome, pulmonary edema), hypertension, hypercalcemia.
ADVERSE EFFECTS	O totoxicity, H ypokalemia, D ehydration, A llergy (sulfa)/metabolic A lkalosis, N ephritis (interstitial), G out.



OH DANG!

Ethacrynic acid

MECHANISM	Nonsulfonamide inhibitor of cotransport system ($\text{Na}^+/\text{K}^+/2\text{Cl}^-$) 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.

Thiazide diuretics

Hydrochlorothiazide, chlorthalidone, metolazone.

MECHANISM

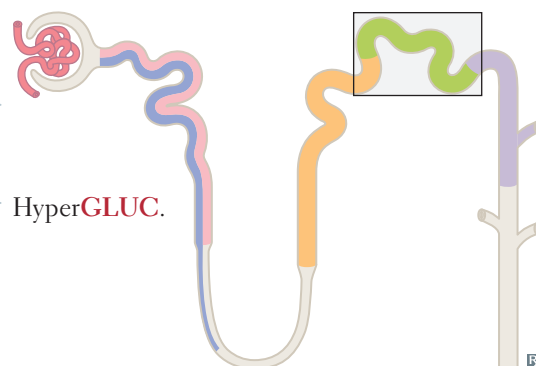
Inhibit NaCl reabsorption in early DCT
→ ↓ diluting capacity of nephron. ↓ Ca²⁺ excretion.

CLINICAL USE

Hypertension, HF, idiopathic hypercalciuria, nephrogenic diabetes insipidus, osteoporosis.

ADVERSE EFFECTS

Hypokalemic metabolic alkalosis, hyponatremia, hyper**G**lycemia, hyper**L**ipidemia, hyper**U**ricemia, hyper**C**alcemia. Sulfa allergy.

**Potassium-sparing diuretics**

Spironolactone and eplerenone; **T**riamterene, and **A**mloride.

The K⁺ **STA**ys.

MECHANISM

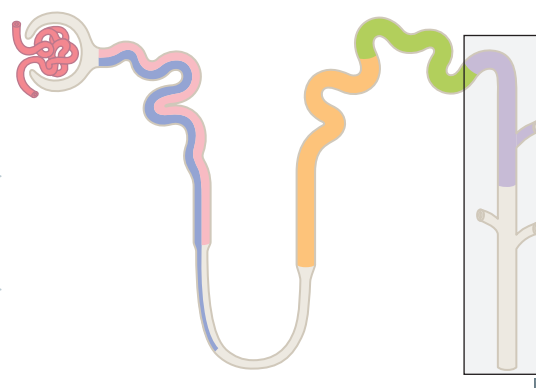
Spironolactone and eplerenone are competitive aldosterone receptor antagonists in cortical collecting tubule. Triamterene and amiloride act at the same part of the tubule by blocking Na⁺ channels in the cortical collecting tubule.

CLINICAL USE

Hyperaldosteronism, K⁺ depletion, HF, hepatic ascites (spironolactone), nephrogenic DI (amiloride).

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 potency of diuretic effect). Serum NaCl may decrease as a result.

Urine K⁺

↑ especially with loop and thiazide diuretics. Serum K⁺ may decrease as a result.

Blood pH

↓ (**acidemia**): carbonic anhydrase inhibitors: ↓ HCO₃⁻ reabsorption. K⁺ sparing: aldosterone blockade prevents K⁺ secretion and H⁺ secretion. Additionally, hyperkalemia leads to K⁺ entering all cells (via H⁺/K⁺ exchanger) in exchange for H⁺ exiting cells.

↑ (**alkalemia**): loop diuretics and thiazides cause alkalemia through several mechanisms:

- Volume contraction → ↑ AT II → ↑ Na⁺/H⁺ exchange in PCT → ↑ HCO₃⁻ reabsorption (“contraction alkalosis”)
- K⁺ loss leads to K⁺ exiting all cells (via H⁺/K⁺ exchanger) in exchange for H⁺ entering cells
- In low K⁺ state, H⁺ (rather than K⁺) is exchanged for Na⁺ in cortical collecting tubule → alkalemia and “paradoxical aciduria”

Urine Ca²⁺

↑ with loop diuretics: ↓ paracellular Ca²⁺ reabsorption → hypocalcemia.
↓ with thiazides: enhanced Ca²⁺ reabsorption.

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 (↓ mortality), proteinuria, diabetic nephropathy. Prevent unfavorable heart remodeling as a result of chronic hypertension.	In diabetic nephropathy, ↓ intraglomerular pressure, slowing GBM thickening.
ADVERSE EFFECTS	C ough, A ngioedema (due to ↑ bradykinin; contraindicated in CI esterase inhibitor deficiency), T eratogen (fetal renal malformations), ↑ C reatinine (↓ GFR), H yperkalemia, and H ypotension. Used with caution in bilateral renal artery stenosis, because ACE inhibitors will further ↓ GFR → renal failure.	

Angiotensin II receptor blockers

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 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.	
CLINICAL USE	Hypertension.	
ADVERSE EFFECTS	Hyperkalemia, ↓ GFR, hypotension. Relatively contraindicated in patients already taking ACE inhibitors or ARBs.	

Reproductive

“Artificial insemination is when the farmer does it to the cow instead of the bull.”

—Student essay

“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

“I think you can say that life is a system in which proteins and nucleic acids interact in ways that allow the structure to grow and reproduce. It’s that growth and reproduction, the ability to make more of yourself, that’s important.”

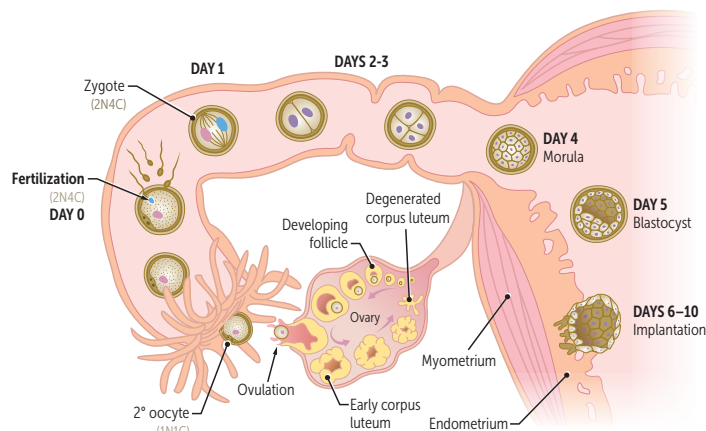
—Andrew H. Knloo

▶ Embryology	562
▶ Anatomy	573
▶ Physiology	577
▶ Pathology	585
▶ Pharmacology	600

▶ REPRODUCTIVE—EMBRYOLOGY

Important genes of embryogenesis

Sonic hedgehog gene	Produced at base of limbs in zone of polarizing activity. Involved in patterning along anteroposterior axis and CNS development; mutation can cause holoprosencephaly.
Wnt-7 gene	Produced at apical ectodermal ridge (thickened ectoderm at distal end of each developing limb). Necessary for proper organization along dorsal-ventral axis.
FGF gene	Produced at apical ectodermal ridge. Stimulates mitosis of underlying mesoderm, providing for lengthening of limbs.
Homeobox (Hox) genes	Involved in segmental organization of embryo in a craniocaudal direction. Code for transcription factors. Hox mutations → appendages in wrong locations.

Early fetal development**Early embryonic development**

Within week 1	hCG secretion begins around the time of implantation of blastocyst.	Blastocyst “sticks” at day 6
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.	

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; epidermis; anal canal below the pectinate line; parotid, sweat, mammary glands.	Craniopharyngioma —benign Rathke pouch tumor with cholesterol crystals, calcifications.
Neuroectoderm	Brain (neurohypophysis, CNS neurons, oligodendrocytes, astrocytes, ependymal cells, pineal gland), retina spinal cord.	Neuroectoderm—think CNS.
Neural crest	PNS (dorsal root ganglia, cranial nerves, autonomic ganglia, Schwann cells), melanocytes, chromaffin cells of adrenal medulla, parafollicular (C) cells of thyroid, pia and arachnoid, bones of the skull, odontoblasts, aorticopulmonary septum, endocardial cushions.	Neural crest—think PNS and non-neural structures nearby.
Mesoderm		Middle/“meat” layer.
	Muscle, bone, connective tissue, serous linings of body cavities (eg, peritoneum), spleen (derived from foregut mesentery), cardiovascular structures, lymphatics, blood, wall of gut tube, upper vagina, kidneys, adrenal cortex, dermis, testes, ovaries. Notochord induces ectoderm to form neuroectoderm (neural plate). Its only postnatal derivative is the nucleus pulposus of the intervertebral disc.	Mesodermal defects = VACTERL : V ertebral defects A nal atresia C ardiac defects T racheo- E sophageal fistula R enal defects L imb defects (bone and muscle)
Endoderm		“Enternal” layer.
	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 cells).	

Types of errors in organ 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; 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).

Teratogens Most susceptible in 3rd–8th weeks (embryonic period—organogenesis) of pregnancy. Before week 3, “all-or-none” effects. After week 8, growth and function affected.

TERATOGEN	EFFECTS ON FETUS	NOTES
Medications		
ACE inhibitors	Renal damage	
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	Vaginal clear cell adenocarcinoma, congenital Müllerian anomalies	
Folate antagonists	Neural tube defects	Includes trimethoprim, methotrexate, antiepileptic drugs.
Isotretinoin	Multiple severe birth defects	Contraception mandatory. Iso TERAT inoin.
Lithium	Ebstein anomaly (apical displacement of tricuspid valve)	
Methimazole	Aplasia cutis congenita	
Tetracyclines	Discolored teeth, inhibited bone growth	“ Teeth racyclines.”
Thalidomide	Limb defects (phocomelia, micromelia—“flipper” limbs)	Limb defects with “tha- limb -domide.”
Warfarin	Bone deformities, fetal hemorrhage, abortion, ophthalmologic abnormalities	Do not wage warfare on the baby; keep it heppy with heparin (does not cross placenta).
Substance abuse		
Alcohol	Common cause of birth defects and intellectual disability; 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	Nicotine → vasoconstriction. CO → impaired O ₂ delivery.
Other		
Iodine (lack or excess)	Congenital goiter or hypothyroidism (cretinism)	
Maternal diabetes	Caudal regression syndrome (anal atresia to sirenomelia), congenital heart defects, neural tube defects, macrosomia	
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.

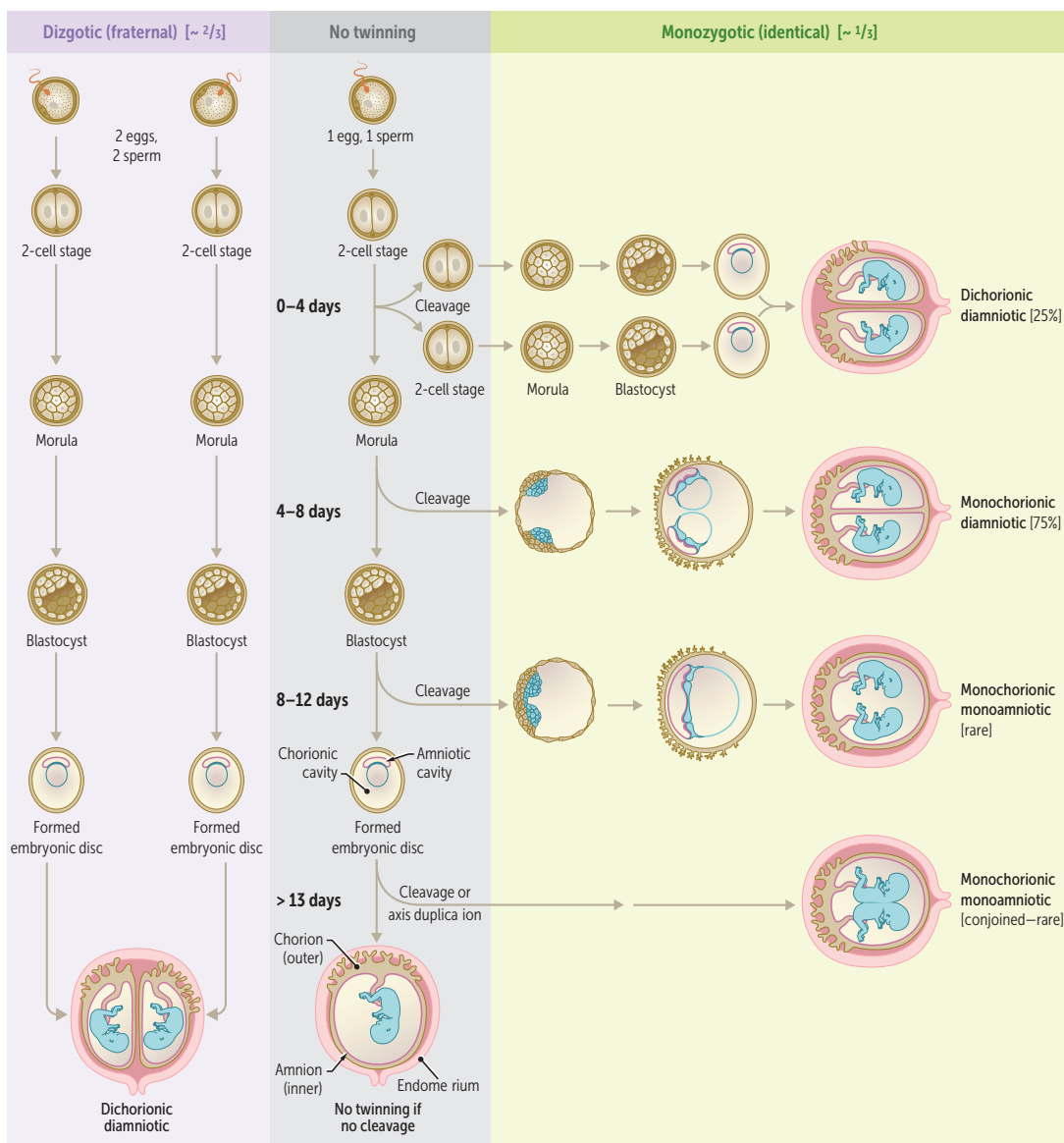
Fetal alcohol syndrome



Leading cause of intellectual disability in the US. Newborns of alcohol-consuming mothers have ↑ incidence of congenital abnormalities, including pre- and postnatal developmental retardation, microcephaly, facial abnormalities **A** (eg, smooth philtrum, thin vermilion border [upper lip], small palpebral fissures), limb dislocation, heart defects. Heart-lung fistulas and holoprosencephaly in most severe form. Mechanism is failure of cell migration.

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).



Placenta1^o site of nutrient and gas exchange between mother and fetus.**Fetal component****Cytotrophoblast**

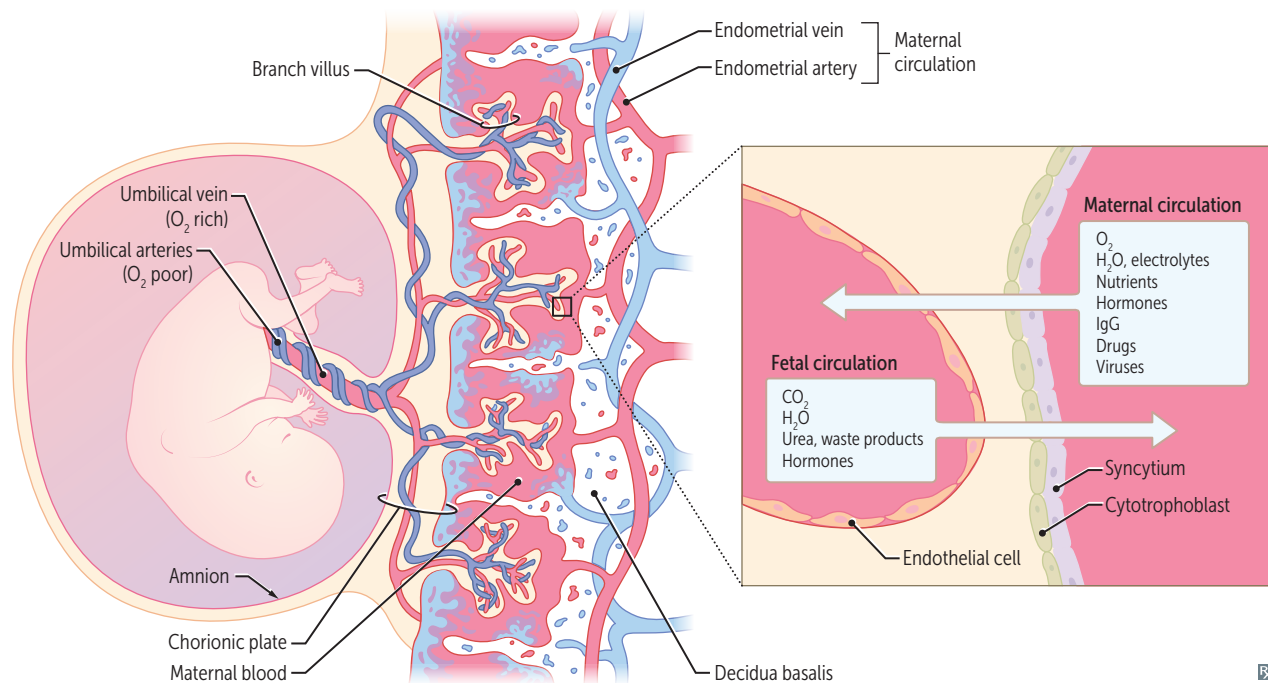
Inner layer of chorionic villi.

Cytotrophoblast makes **C**ells.**Syncytiotrophoblast**

Outer layer of chorionic villi; synthesizes and secretes hormones, eg, hCG (structurally similar to LH; stimulates corpus luteum to secrete progesterone during first trimester).

Syncytiotrophoblast **s**ynthesizes hormones. Lacks MHC-I expression → ↓ chance of attack by maternal immune system.**Maternal component****Decidua basalis**

Derived from endometrium. Maternal blood in lacunae.



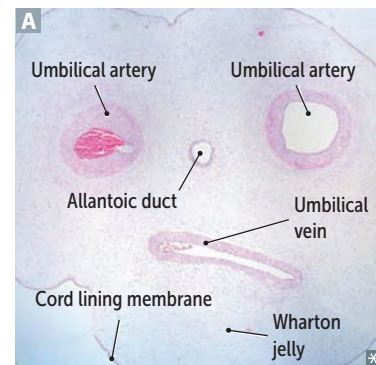
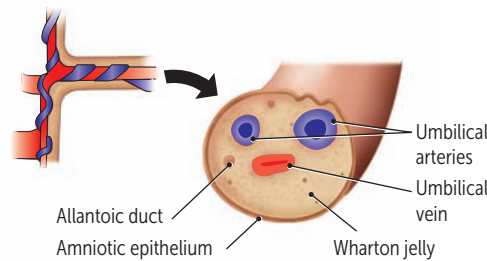
Umbilical cord

Umbilical arteries (2)—return deoxygenated blood from fetal internal iliac arteries to placenta **A**.

Umbilical vein (1)—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

In the 3rd week the yolk sac forms the allantois, which extends into urogenital sinus. Allantois becomes the urachus, a duct between fetal bladder and umbilicus.

Patent urachus

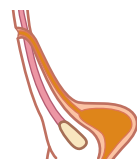
Total failure of urachus to obliterate → urine discharge from umbilicus.

Urachal cyst

Partial failure of urachus to obliterate; fluid-filled cavity lined with uroepithelium, between umbilicus and bladder. Can lead to infection, adenocarcinoma.

Vesicourachal diverticulum

Slight failure of urachus to obliterate → outpouching of bladder.



Patent urachus



Urachal cyst



Vesicourachal diverticulum **A**

Vitelline duct

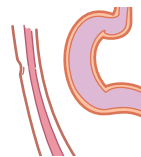
7th week—obliteration of vitelline duct (omphalo-mesenteric duct), which connects yolk sac to midgut lumen.

Vitelline fistula

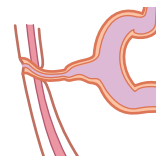
Vitelline duct fails to close → meconium discharge from umbilicus.

Meckel diverticulum

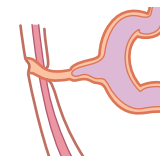
Partial closure of vitelline duct, with patent portion attached to ileum (true diverticulum). May have heterotopic gastric and/or pancreatic tissue → melena, hematochezia, abdominal pain.



Normal

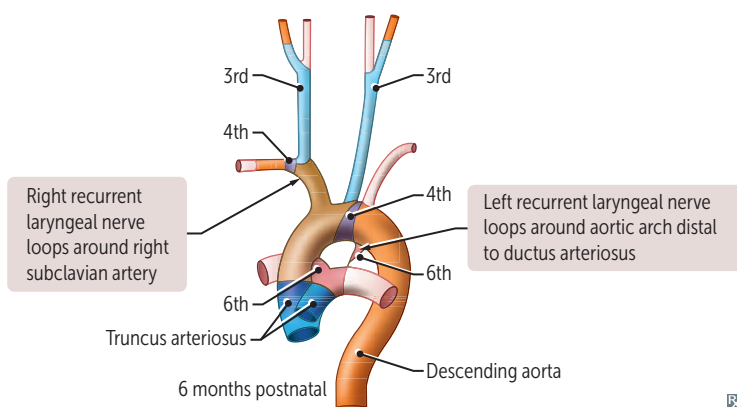


Vitelline fistula



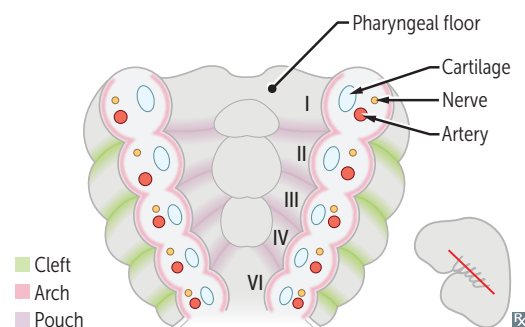
Meckel diverticulum **A**

Aortic arch derivatives	Develop into arterial system.	
1st	Part of max illary artery (branch of external carotid).	1st arch is max imal.
2nd	S tapedial artery and hyoid artery.	Second = S tapedial.
3rd	C ommon C arotid artery and proximal part of internal C arotid 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).



Branchial (pharyngeal) apparatus Composed of branchial clefts, arches, pouches. Branchial **c**lefts—derived from **e**ctoderm. Also called branchial grooves. Branchial **a**rches—derived from mesoderm (muscles, arteries) and neural crest (bones, cartilage). Branchial **p**ouches—derived from endoderm.

CAP covers outside to inside:
Clefts = ectoderm
Arches = mesoderm + neural crest
Pouches = endoderm



Branchial 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 → branchial cleft cyst within lateral neck, anterior to sternocleidomastoid muscle. Immobile during swallowing.

Branchial arch derivatives

ARCH	CARTILAGE	MUSCLES	NERVES ^a	ABNORMALITIES/COMMENTS
1st 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, tensor veli palatini	CN V ₂ and V ₃ chew	Pierre Robin sequence — micrognathia, glossoptosis, cleft palate, airway obstruction Treacher Collins syndrome —neural crest dysfunction → mandibular hypoplasia, facial abnormalities
2nd 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 arch	Greater horn of hyoid	Stylopharyngeus (think of stylopharyngeus innervated by glossopharyngeal nerve)	CN IX (stylo- pharyngeus) swallow stylishly	
4th–6th 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 laryngeal branch) speak	Arches 3 and 4 form posterior 1/3 of tongue; arch 5 makes no major developmental contributions

^aThese are the only CNs with both motor and sensory components (except V₂, which is sensory only).

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).

Branchial pouch derivatives

POUCH	DERIVATIVES	NOTES	MNEMONIC
1st pouch	Middle ear cavity, eustachian tube, mastoid air cells.	1st pouch contributes to endoderm-lined structures of ear.	Ear, tonsils, bottom-to-top: 1 (ear), 2 (tonsils), 3 dorsal (bottom for inferior parathyroids), 3 ventral (to = thymus), 4 (top = superior parathyroids).
2nd pouch	Epithelial lining of palatine tonsil.		
3rd pouch	Dorsal wings → inferior parathyroids. Ventral wings → thymus.	3rd pouch contributes to 3 structures (thymus, left and right inferior parathyroids). 3rd-pouch structures end up below 4th-pouch structures.	
4th pouch	Dorsal wings → superior parathyroids. Ventral wings → ultimobranchial body → parafollicular (C) cells of thyroid.		

DiGeorge syndrome

Chromosome 22q11 deletion. Aberrant development of 3rd and 4th pouches → T-cell deficiency (thymic aplasia) and hypocalcemia (failure of parathyroid development). Associated with cardiac defects (conotruncal anomalies).

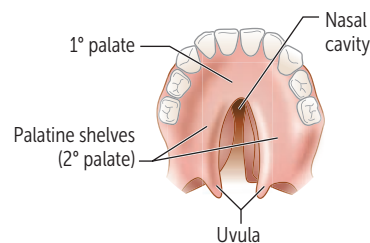
Cleft lip and cleft palate

Cleft lip

Cleft lip—failure of fusion of the maxillary and medial nasal processes (formation of 1° palate).

Cleft palate—failure of fusion of the two lateral palatine shelves or failure of fusion of lateral palatine shelves with the nasal septum and/or median palatine shelf (formation of 2° palate).

Cleft lip and cleft palate have distinct, multifactorial etiologies, but often occur together.



Cleft palate (partial)

Genital embryology

Female

Default development. Mesonephric duct degenerates and paramesonephric duct develops.

Male

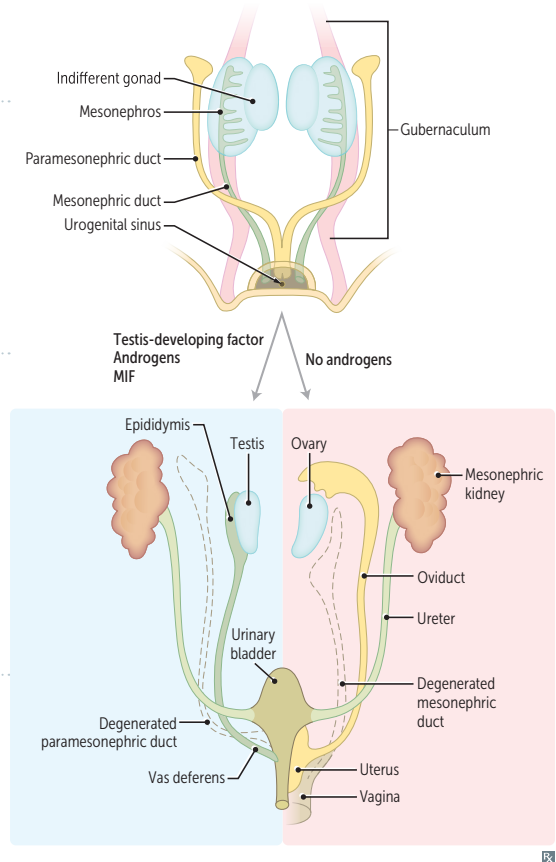
SRY gene on Y chromosome—produces testis-determining factor → testes development. Sertoli cells secrete Müllerian inhibitory factor (MIF) that suppresses development of paramesonephric ducts. Leydig cells secrete androgens that stimulate development of mesonephric ducts.

Paramesonephric (Müllerian) duct

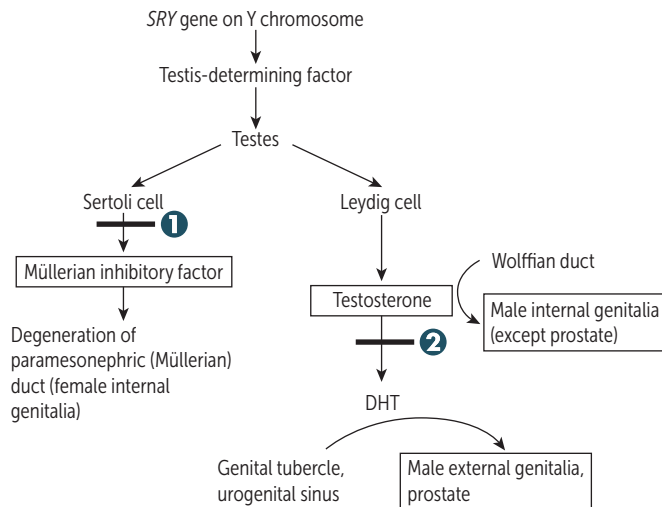
Develops into female internal structures—fallopian tubes, uterus, upper portion of vagina (lower portion from urogenital sinus). Male remnant is appendix testis. **Müllerian agenesis (Mayer-Rokitansky-Küster-Hauser syndrome)**—may present as 1° amenorrhea (due to a lack of uterine development) in females with fully developed 2° sexual characteristics (functional ovaries).

Mesonephric (Wolffian) duct

Develops into male internal structures (except prostate)—**S**eminal vesicles, **E**pididymis, **E**jaculatory duct, **D**uctus deferens (**SEED**). In females, remnant of mesonephric duct → Gartner duct.



SRY gene



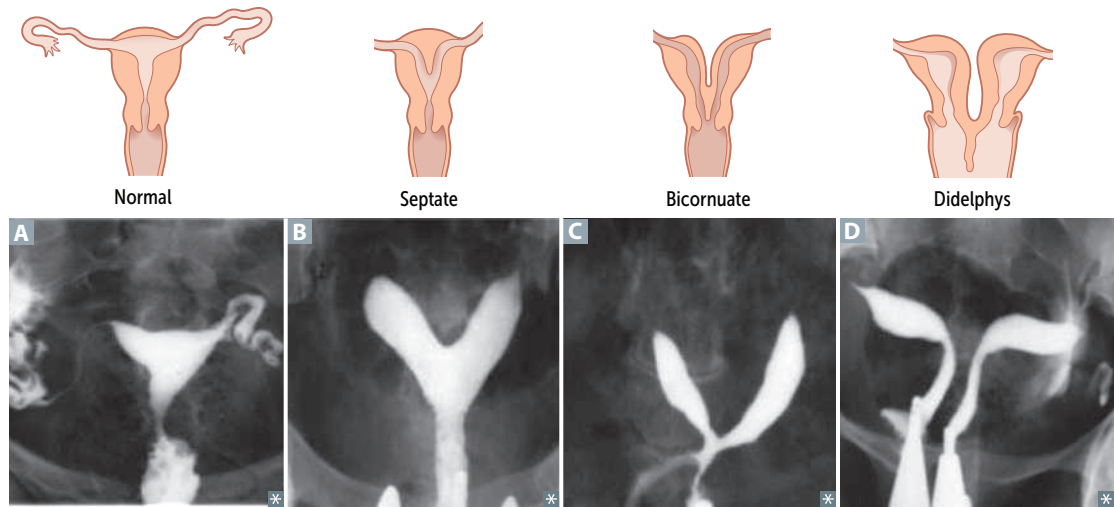
- 1 No Sertoli cells or lack of Müllerian inhibitory factor → develop both male and female internal genitalia and male external genitalia
- 2 5α-reductase deficiency—inability to convert testosterone into DHT → male internal genitalia, ambiguous external genitalia until puberty (when ↑ testosterone levels cause masculinization)

Uterine (Müllerian duct) anomalies

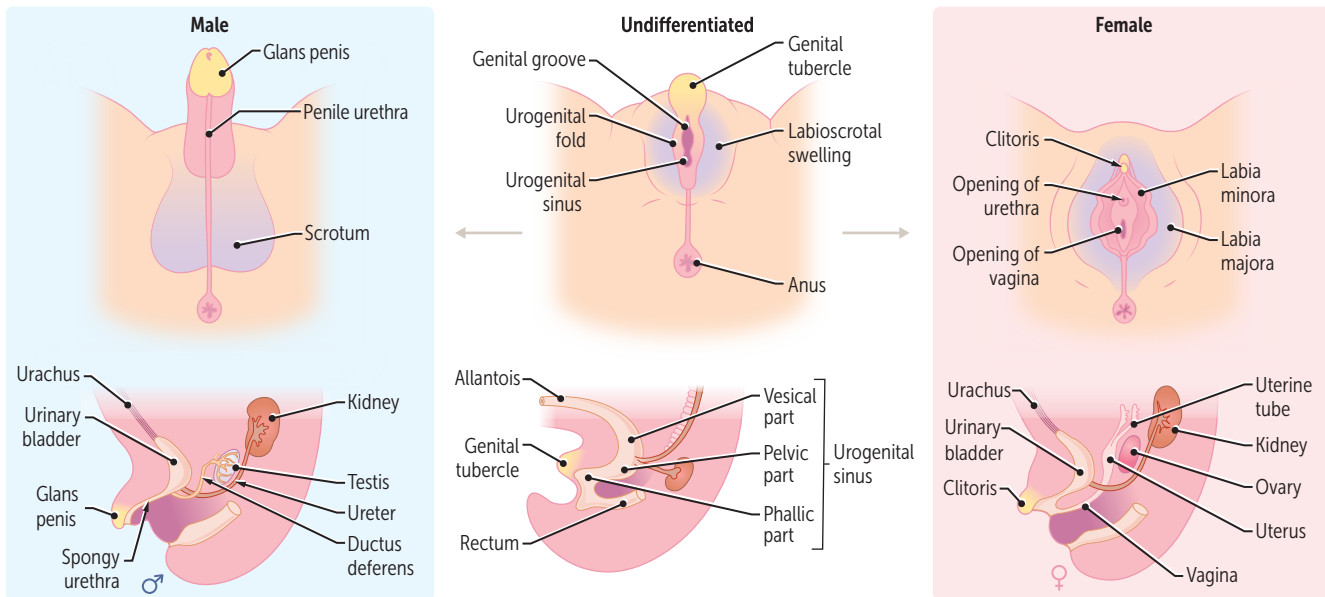
Septate uterus Common anomaly vs normal **A** uterus. Incomplete resorption of septum **B**. ↓ fertility. Treat with septoplasty.

Bicornuate uterus Incomplete fusion of Müllerian ducts **C**. ↑ risk of complicated pregnancy.

Uterus didelphys Complete failure of fusion → double uterus, vagina, and cervix **D**. Pregnancy possible.



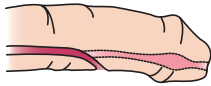
Male/female genital homologs



Dihydrotestosterone		Estrogen	
Glans penis	←	Genital tubercle	→ Glans clitoris
Corpus cavernosum and spongiosum	←	Genital tubercle	→ Vestibular bulbs
Bulbourethral glands (of Cowper)	←	Urogenital sinus	→ Greater vestibular glands (of Bartholin)
Prostate gland	←	Urogenital sinus	→ Urethral and paraurethral glands (of Skene)
Ventral shaft of penis (penile urethra)	←	Urogenital folds	→ Labia minora
Scrotum	←	Labioscrotal swelling	→ Labia majora

Congenital penile abnormalities

Hypospadias

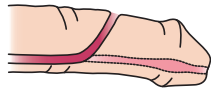


Abnormal opening of penile urethra on ventral surface of penis due to failure of urethral folds to fuse.

Hypospadias is more common than epispadias. Associated with inguinal hernia and cryptorchidism.

Hypo is below.

Epispadias



Abnormal opening of penile urethra on dorsal surface of penis due to faulty positioning of genital tubercle.

Exstrophy of the bladder is associated with **E**pispadias.

When you have **E**pispadias, you hit your **E**ye when you p**EE**.

Descent of testes and ovaries

	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.	Obliterated.

▶ REPRODUCTIVE—ANATOMY

Gonadal drainage

Venous drainage

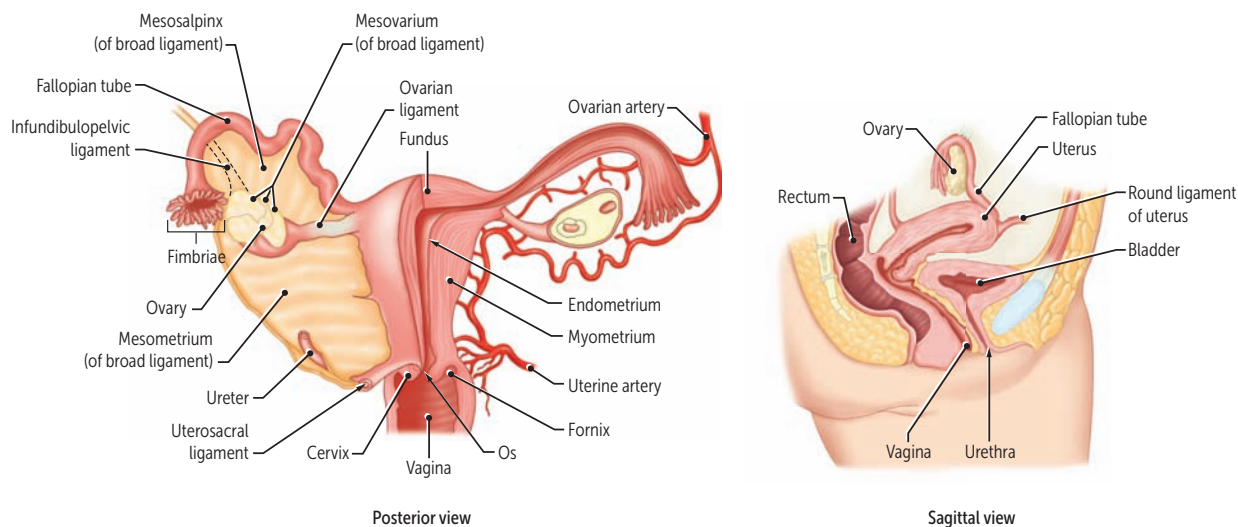
Left ovary/testis → left gonadal vein → left renal vein → IVC.
 Right ovary/testis → right gonadal vein → IVC.

“**L**eft gonadal vein takes the **L**ongest way.”
 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

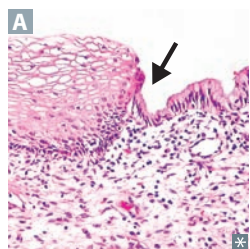
Ovaries/testes → para-aortic lymph nodes.
 Body of uterus/cervix/superior bladder → external iliac nodes.
 Prostate/cervix/corpus cavernosum/proximal vagina → internal iliac nodes.
 Distal vagina/vulva/scrotum/distal anus → superficial inguinal nodes.
 Glans penis → deep inguinal nodes.

Female reproductive anatomy

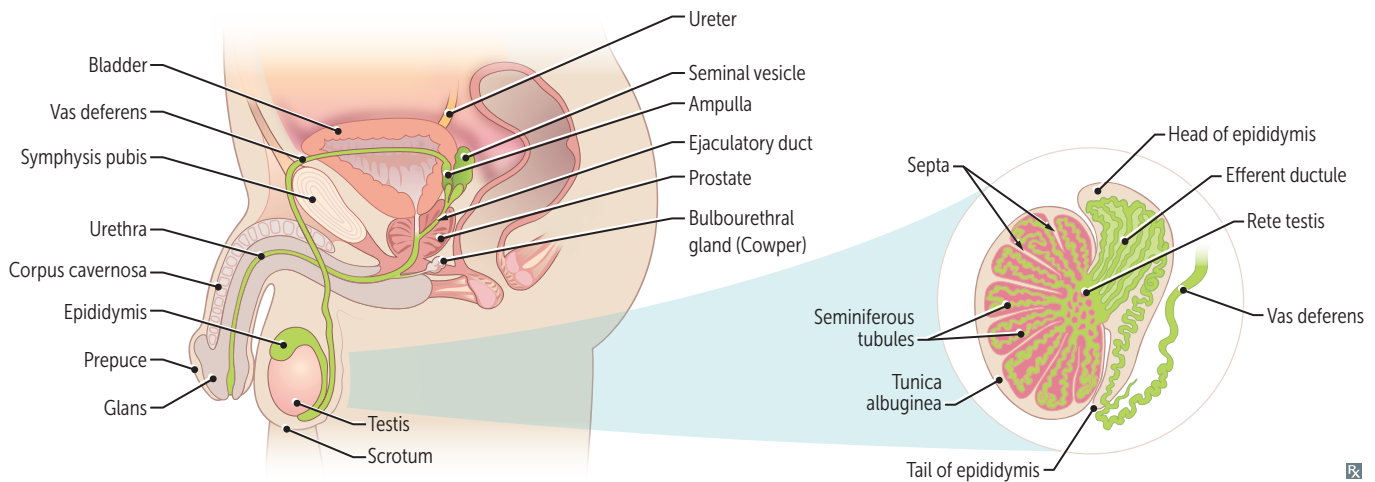


LIGAMENT	CONNECTS	STRUCTURES CONTAINED	NOTES
Infundibulopelvic ligament (suspensory ligament of the ovary)	Ovaries to lateral pelvic wall	Ovarian vessels	Ligate vessels during oophorectomy to avoid bleeding. Ureter courses retroperitoneally, close to gonadal vessels → at risk of injury during ligation of ovarian vessels.
Cardinal ligament (not labeled)	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 fundus 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 lateral uterus	—	Derivative of gubernaculum. Ovarian L igament L atches to L ateral uterus.

Female reproductive epithelial histology



TISSUE	HISTOLOGY/NOTES
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
Epididymis
Vas deferens
Ejaculatory ducts
(Nothing)
Urethra
Penis

Urethral injury

Suspect if blood seen at urethral meatus.

Posterior urethra—membranous urethra prone to injury from pelvic fracture. Injury can cause urine to leak into retropubic space.

Anterior urethra—bulbar and penile urethra at risk of damage due to perineal straddle injury. Can cause urine to leak beneath deep fascia of Buck. If fascia is torn, urine escapes into superficial perineal space.

Autonomic innervation of the male sexual response

Erection—**P**arasympathetic nervous system (pelvic nerve):

- NO → ↑ cGMP → smooth muscle relaxation → vasodilation → proerectile.
- Norepinephrine → ↑ $[Ca^{2+}]_{in}$ → smooth muscle contraction → vasoconstriction → antierectile.

Emission—**S**ympathetic nervous system (hypogastric nerve).

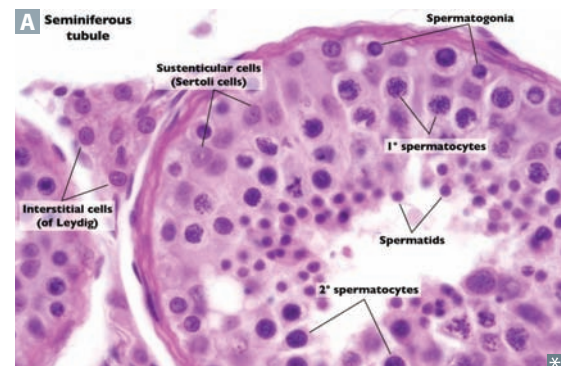
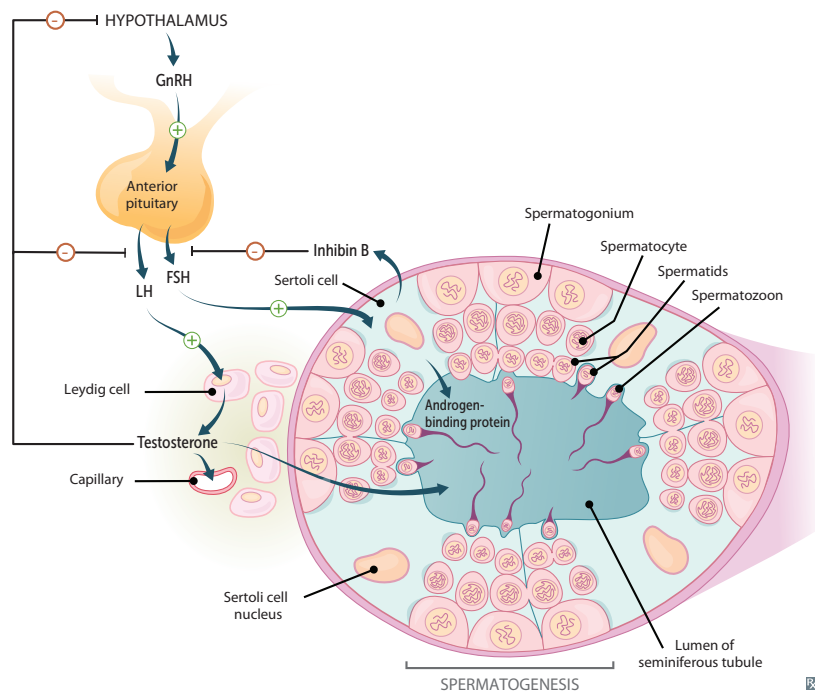
Ejaculation—visceral and **S**omatic nerves (pudendal nerve).

Point, **S**queeze, and **S**hoot.

PDE-5 inhibitors (eg, sildenafil) ↓ cGMP breakdown.

Seminiferous tubules

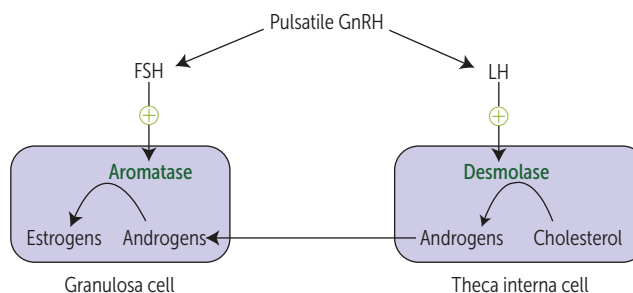
CELL	FUNCTION	LOCATION/NOTES
Spermatogonia (germ cells)	Maintain germ pool and produce 1° spermatocytes.	Line seminiferous tubules A
Sertoli cells (non-germ cells)	Secrete inhibin B → inhibit FSH. Secrete androgen-binding protein → maintain local levels of testosterone. Produce MIF. Tight junctions between adjacent Sertoli cells form blood-testis barrier → isolate gametes from autoimmune attack. Support and nourish developing spermatozoa. Regulate spermatogenesis. Temperature sensitive; ↓ sperm production and ↓ inhibin B with ↑ temperature.	Line seminiferous tubules Convert testosterone and androstenedione to estrogens via aromatase Sertoli cells Support Sperm Synthesis Homolog of female granulosa cells
Leydig cells (endocrine cells)	Secrete testosterone in the presence of LH; testosterone production unaffected by temperature.	Interstitial Homolog of female theca interna cells



▶ REPRODUCTIVE—PHYSIOLOGY

Estrogen

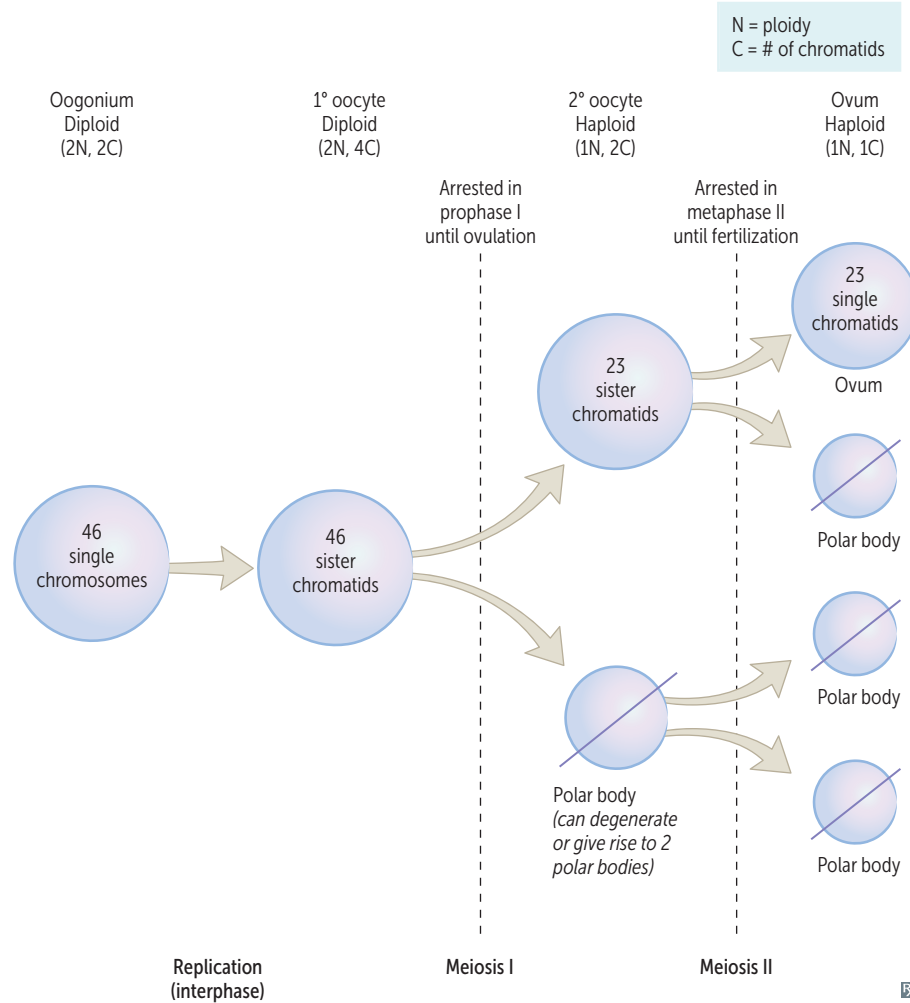
SOURCE	Ovary (17β -estradiol), placenta (estriol), adipose tissue (estrone via aromatization).	Potency: estradiol > estrone > estriol
FUNCTION	<p>Development of genitalia and breast, female fat distribution.</p> <p>Growth of follicle, endometrial proliferation, ↑ myometrial excitability.</p> <p>Upregulation of estrogen, LH, and progesterone receptors; feedback inhibition of FSH and LH, then LH surge; stimulation of prolactin secretion.</p> <p>↑ transport proteins, SHBG; ↑ HDL; ↓ LDL.</p>	<p>Pregnancy:</p> <ul style="list-style-type: none"> ▪ 50-fold ↑ in estradiol and estrone ▪ 1000-fold ↑ in estriol (indicator of fetal well-being) <p>Estrogen receptors expressed in cytoplasm; translocate to nucleus when bound by estrogen</p>

**Progesterone**

SOURCE	Corpus luteum, placenta, adrenal cortex, testes.	Fall in progesterone after delivery disinhibits prolactin → lactation. ↑ progesterone is indicative of ovulation.
FUNCTION	<p>Stimulation of endometrial glandular secretions and spiral artery development.</p> <p>Maintenance of pregnancy.</p> <p>↓ myometrial excitability.</p> <p>Production of thick cervical mucus, which inhibits sperm entry into uterus.</p> <p>↑ body temperature.</p> <p>Inhibition of gonadotropins (LH, FSH).</p> <p>Uterine smooth muscle relaxation (preventing contractions).</p> <p>↓ estrogen receptor expression.</p> <p>Prevents endometrial hyperplasia.</p>	<p>Progesterone is pro-gestation.</p> <p>Prolactin is pro-lactation.</p>

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 **met**aphase 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.

Menstrual cycle

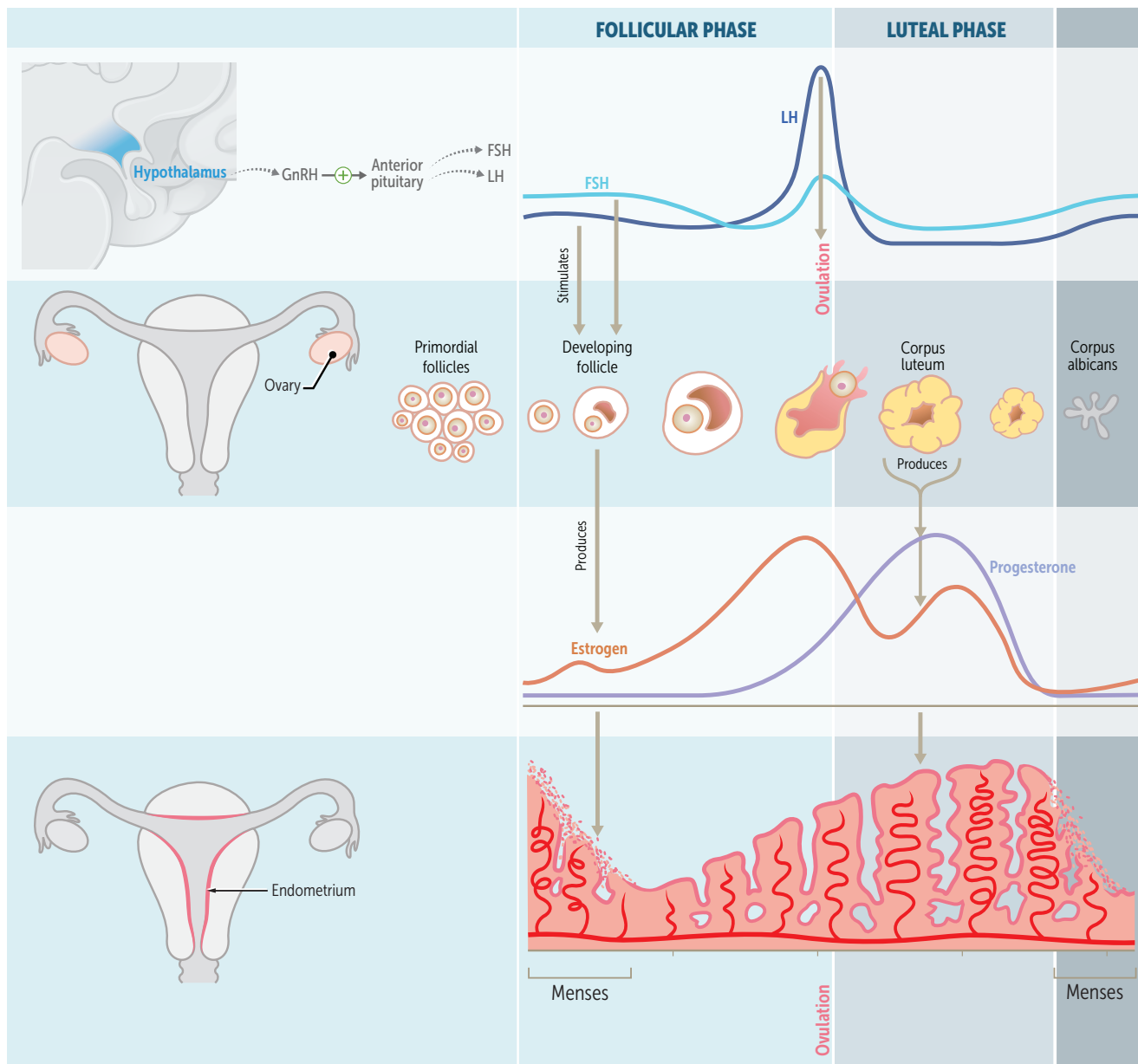
Follicular phase can vary in length. Luteal phase is 14 days. Ovulation day + 14 days = menstruation.

Follicular growth is fastest during 2nd week of the follicular phase.

Estrogen stimulates endometrial proliferation.

Progesterone maintains endometrium to support implantation.

↓ progesterone → ↓ fertility.



Dysmenorrhea

Pain with menses; often associated with endometriosis.

Oligomenorrhea

> 35-day cycle.

Polymenorrhea

< 21-day cycle.

Metrorrhagia

Frequent or irregular menstruation.

Menorrhagia

Heavy menstrual bleeding; > 80 mL blood loss or > 7 days of menses.

Menometrorrhagia

Heavy, irregular menstruation.

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.

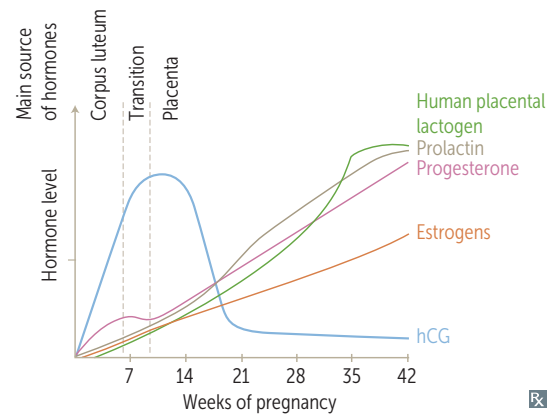
Syncytiotrophoblasts secrete hCG, which is detectable in blood 1 week after conception and on home test in urine 2 weeks after conception.

Gestational age—calculated from date of last menstrual period.

Embryonic age—calculated from date of conception (gestational age minus 2 weeks).

Physiologic adaptations in pregnancy:

- ↑ cardiac output (↑ preload, ↓ afterload, ↑ HR → ↑ placental and renal perfusion)
- Anemia (↑↑ plasma, ↑ RBCs → ↓ viscosity)
- Hypercoagulability (to ↓ blood loss at delivery)
- Hyperventilation (eliminate fetal CO₂)



Placental hormone secretion generally increases over the course of pregnancy, but hCG peaks at 8–10 weeks.

hCG

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 α subunit as LH, FSH, TSH (states of ↑ hCG can cause hyperthyroidism). β subunit is unique (pregnancy tests detect β subunit). hCG is ↑ in multiple gestations, hydatidiform moles, choriocarcinomas, and Down syndrome; hCG is ↓ in ectopic/failing pregnancy, Edward syndrome, and Patau syndrome.

Apgar score

	Score 2	Score 1	Score 0
A pppearance	 Pink	 Extremities blue	 Pale or blue
P ulse	> 100 bpm	< 100 bpm	No pulse
G rimace	Cries and pulls away	Grimaces or weak cry	No response to stimulation
A ctivity	 Active movement	 Arms, legs flexed	 No movement
R espiration	Strong cry	Slow, irregular	No breathing

Assessment of newborn vital signs following labor via a 10-point scale evaluated at 1 minute and 5 minutes. **A**pgar score is based on **A**pppearance, **P**ulse, **G**rimace, **A**ctivity, and **R**espiration. Apgar scores < 7 require further evaluation. If Apgar score remains low at later time points, there is ↑ risk the child will develop long-term neurologic damage.

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. Other problems include impaired thermoregulation and immune function, hypoglycemia, polycythemia, and impaired neurocognitive/emotional development. Complications include infections, respiratory distress syndrome, necrotizing enterocolitis, intraventricular hemorrhage, and persistent fetal circulation.

Lactation

After labor, the ↓ in progesterone and estrogen disinhibits lactation. Suckling is required to maintain milk production, 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 ↓ risk for child to develop asthma, allergies, diabetes mellitus, and obesity. Exclusively breastfed infants require vitamin D 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**: **H**ot flashes, **A**trophy of the **V**agina, **O**steoporosis, **C**oronary artery disease, **S**leep disturbances.
 Menopause before age 40 suggests 1° ovarian insufficiency (premature ovarian failure).

Androgens

Testosterone, dihydrotestosterone (DHT), androstenedione.

SOURCE

DHT and testosterone (testis), **AnD**rostenedione (**AD**renal)

Potency: DHT > testosterone > androstenedione.

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

5 α -reductase, which is inhibited by finasteride. In the male, androgens are converted to estrogen by cytochrome P-450 aromatase (primarily in adipose tissue and testis).

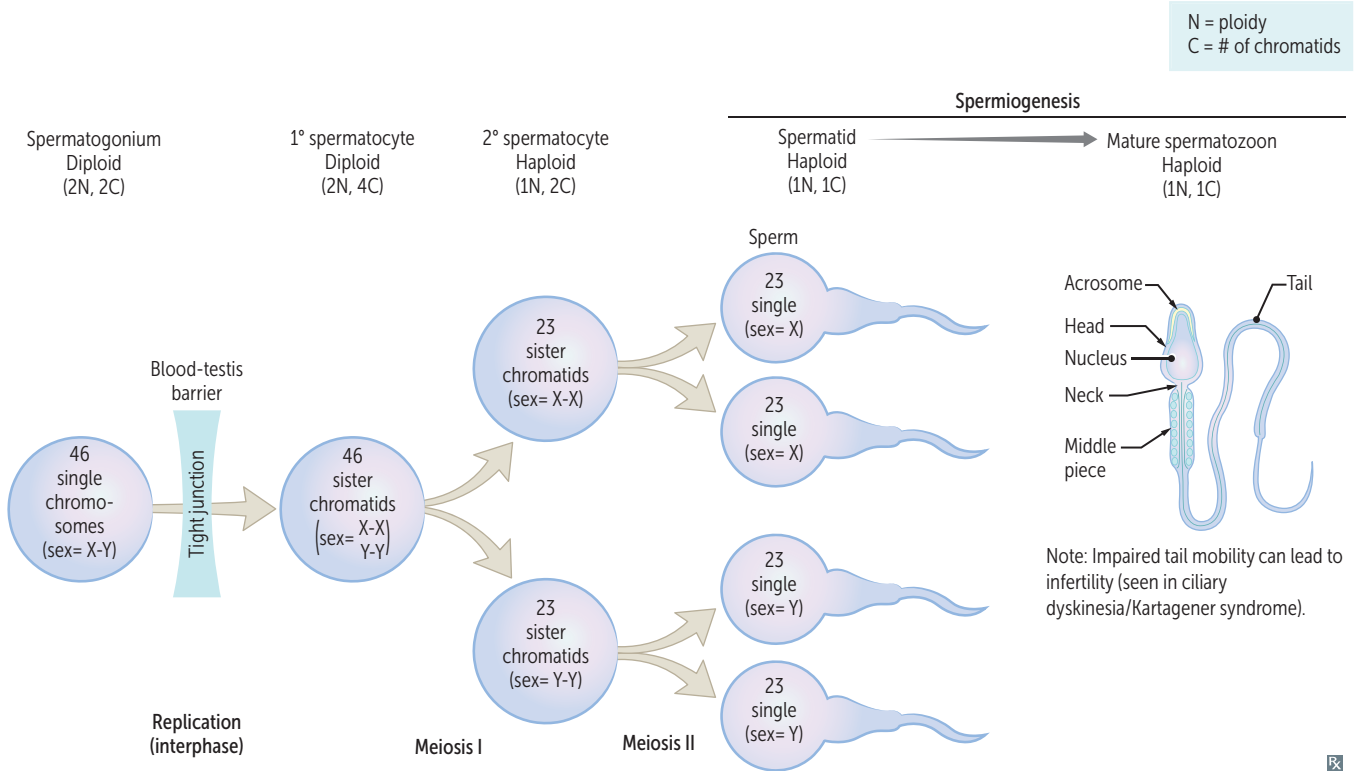
Aromatase is the key enzyme in conversion of androgens to estrogen.

Exogenous testosterone → inhibition of hypothalamic–pituitary–gonadal axis → ↓ intratesticular testosterone → ↓ testicular size → azoospermia.

Spermatogenesis

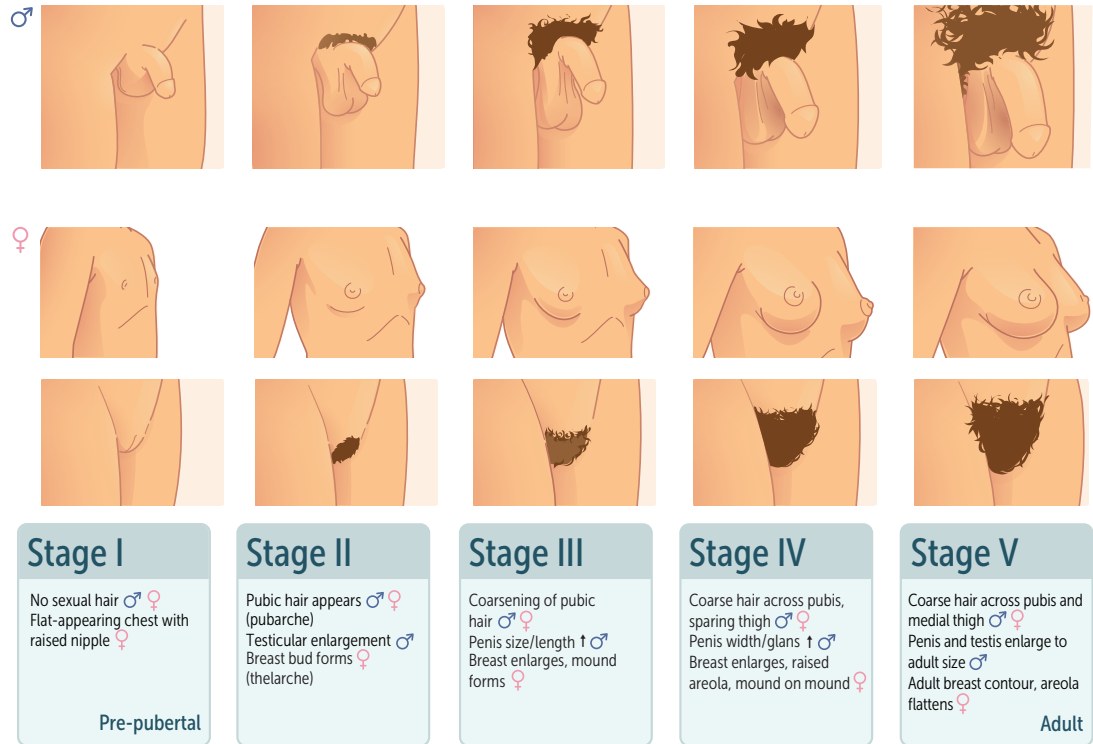
Spermatogenesis begins at puberty with spermatogonia. Full development takes 2 months. Occurs in seminiferous tubules. Produces spermatids that undergo spermiogenesis (loss of cytoplasmic contents, gain of acrosomal cap) to form mature spermatozoon.

“**Gonium**” is **going** to be a sperm; “**Zoon**” is “**Zooming**” to egg.



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).



▶ 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

→ ↓ inhibin B → ↑ FSH.

Abnormal Leydig cell function → ↓ testosterone

→ ↑ LH → ↑ estrogen.

Turner syndrome [female] (45,XO)

Short stature (if untreated), ovarian dysgenesis (streak ovary), shield chest, bicuspid aortic valve, coarctation (femoral < brachial pulse), lymphatic defects (result in webbed neck or cystic hygroma; lymphedema in feet, hands), horseshoe kidney **B**.

Most common cause of 1° amenorrhea. No Barr body.

Menopause before menarche.

↓ estrogen leads to ↑ LH, FSH.

Sometimes due to mitotic error → mosaicism (eg, 45,XO/46,XX).

Pregnancy is possible in some cases (IVF, exogenous estradiol-17β and progesterone).

Double Y males (XYY)

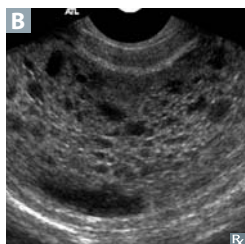
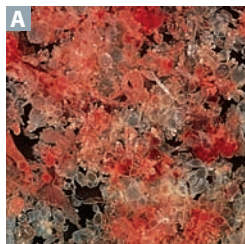
Phenotypically normal (usually undiagnosed), very tall. Normal fertility. May be associated with severe acne, learning disability, autism spectrum disorders.

Ovotesticular disorder of sex development

46,XX > 46,XY.

Both ovarian and testicular tissue present (ovotestis); ambiguous genitalia. Previously called true hermaphroditism.

Diagnosing disorders of sex hormones	Testosterone	LH	Diagnosis
	↑	↑	Defective androgen receptor
	↑	↓	Testosterone-secreting tumor, exogenous steroids
	↓	↑	1° hypogonadism
	↓	↓	Hypogonadotropic hypogonadism
Other disorders of sex development	Disagreement between the phenotypic (external genitalia) and gonadal (testes vs ovaries) sex. Include 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).		
Placental aromatase deficiency	Inability to synthesize estrogens from androgens. Masculinization of female (46,XX) infants (ambiguous genitalia), ↑ serum testosterone and androstenedione. Can present with maternal virilization during pregnancy (fetal androgens cross the placenta).		
Androgen insensitivity syndrome (46,XY)	Defect in androgen receptor resulting in normal-appearing female; female external genitalia with scant sexual hair, rudimentary vagina; uterus and fallopian tubes absent. 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). 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 GnRH cells and formation of olfactory bulb; ↓ synthesis of GnRH in the hypothalamus; anosmia; ↓ GnRH, FSH, LH, testosterone. Infertility (low sperm count in males; amenorrhea in females).		

Hydatidiform mole

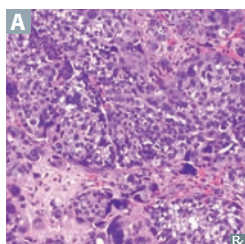
Cystic swelling of chorionic villi and proliferation of chorionic epithelium (only trophoblast).

Presents with vaginal bleeding, 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 β -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
FETAL PARTS	No	Yes (partial = fetal parts)
UTERINE SIZE	↑	—
hCG	↑↑↑↑	↑
IMAGING	“Honeycombed” uterus or “clusters of grapes” A , “snowstorm” on ultrasound B	Fetal parts
RISK OF MALIGNANCY (GESTATIONAL TROPHOBLASTIC NEOPLASIA)	15–20%	< 5%
RISK OF CHORIOCARCINOMA	2%	Rare

Choriocarcinoma

Rare; can develop during or after pregnancy in mother or baby. Malignancy of trophoblastic tissue

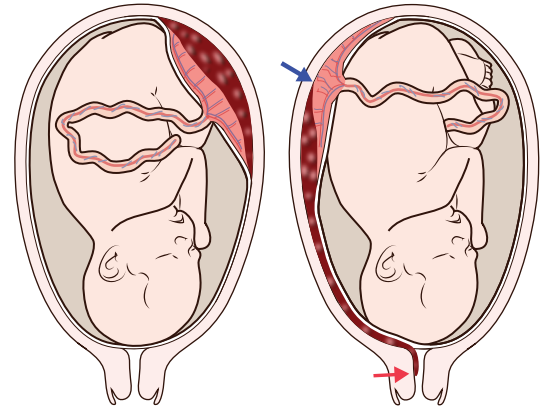
A (cytotrophoblasts, syncytiotrophoblasts); **no** chorionic villi present. ↑ frequency of bilateral/multiple theca-lutein cysts. Presents with abnormal ↑ β -hCG, shortness of breath, hemoptysis. Hematogenous spread to lungs.

Pregnancy complications

Placental **abruption (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, maternal shock, fetal distress. Life threatening for mother and fetus.



Complete abruption with concealed hemorrhage

Partial abruption with apparent hemorrhage

Placenta accreta/increta/percreta

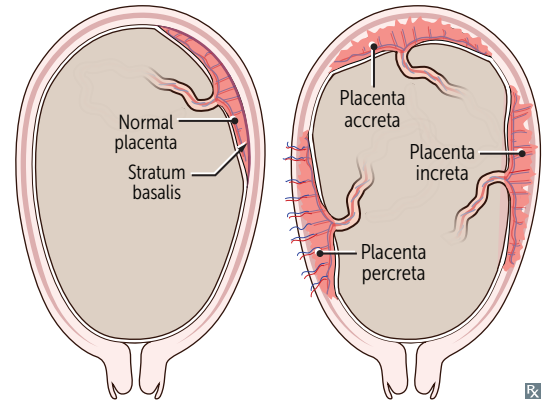
Defective decidual layer → abnormal attachment and separation after delivery. Risk factors: prior C-section, inflammation, placenta previa. Three types distinguishable by the depth of penetration:

Placenta accreta—placenta **attaches** to myometrium without penetrating it; most common type.

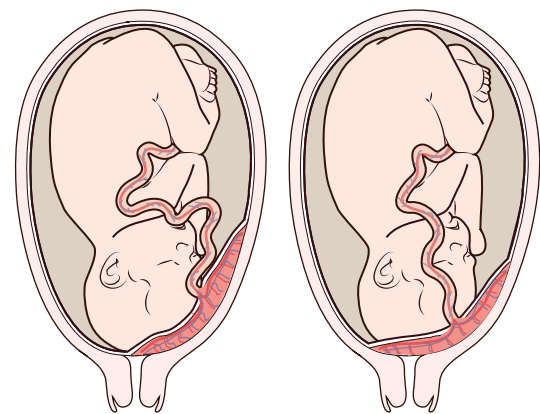
Placenta increta—placenta penetrates **into** myometrium.

Placenta percreta—placenta penetrates (“**perforates**”) through myometrium and into uterine serosa (invades entire uterine wall); can result in placental attachment to rectum or bladder.

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 to lower uterine segment over (or < 2 cm from) internal cervical os. Risk factors: multiparity, prior C-section. Associated with painless third-trimester bleeding.

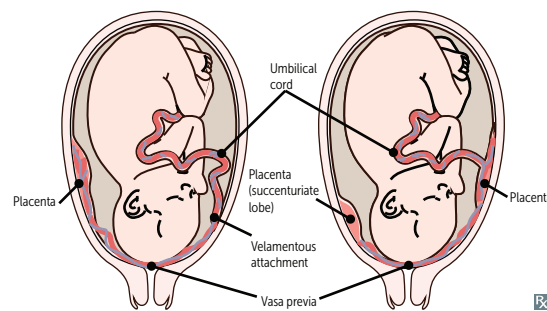


Partial placenta previa

Complete placenta previa

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: **T**one (uterine atony; most common), **T**rauma (lacerations, incisions, uterine rupture), **T**hrombin (coagulopathy), **T**issue (retained products of conception).

Ectopic pregnancy

Most often in ampulla of fallopian tube (A shows 10-mm embryo in oviduct at 7 weeks of gestation). Suspect with history of amenorrhea, lower-than-expected rise in hCG based on dates, and sudden lower abdominal pain; confirm with ultrasound. Often clinically mistaken for appendicitis.

Pain +/- bleeding.

Risk factors:

- Prior ectopic pregnancy
- History of infertility
- Salpingitis (PID)
- Ruptured appendix
- Prior tubal surgery

Amniotic fluid abnormalities**Polyhydramnios**

Too much amniotic fluid; 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.

Hypertension in pregnancy

Gestational hypertension (pregnancy-induced hypertension)	BP > 140/90 mm Hg after 20th week of gestation. No pre-existing hypertension. No proteinuria or end-organ damage.	Treatment: antihypertensives (H ydralazine, α-M ethyldopa, L abetalol, N ifedipine), deliver at 37–39 weeks. H ypertensive M oms L ove N ifedipine.
Preeclampsia	New-onset hypertension with either proteinuria or end-organ dysfunction after 20th week of gestation (< 20 weeks suggests molar pregnancy). May proceed to eclampsia (+ seizures) and/or HELLP syndrome. Caused by abnormal placental spiral arteries → endothelial dysfunction, vasoconstriction, ischemia. Incidence ↑ in patients with pre-existing hypertension, diabetes, chronic renal disease, autoimmune disorders. Complications: placental abruption, coagulopathy, renal failure, uteroplacental insufficiency, eclampsia.	Treatment: antihypertensives, IV magnesium sulfate (to prevent seizure); definitive is delivery of fetus.
Eclampsia	Preeclampsia + maternal seizures. Maternal death due to stroke, intracranial hemorrhage, or ARDS.	Treatment: IV magnesium sulfate, antihypertensives, immediate delivery.
HELLP syndrome	H emolysis, E levated L iver enzymes, L ow P latelets. A manifestation of severe preeclampsia. Blood smear shows schistocytes. Can lead to hepatic subcapsular hematomas → rupture → severe hypotension.	Treatment: immediate delivery.
Gynecologic tumor epidemiology	Incidence (US)—endometrial > ovarian > cervical; cervical cancer is more common worldwide due to lack of screening or HPV vaccination. Worst prognosis—ovarian > endometrial > cervical.	

Vaginal tumors**Squamous cell carcinoma (SCC)**

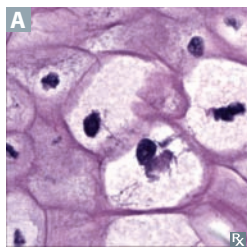
Usually 2° to cervical SCC; 1° vaginal carcinoma rare.

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.

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 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 *p53* suppressor gene) and E7 gene product (inhibits *RB* suppressor gene). 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 (#1), smoking, starting sexual intercourse at young age, HIV infection.

Invasive carcinoma

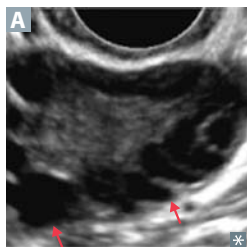
Often squamous cell carcinoma. Pap smear can catch cervical dysplasia (koilocytes **A**) before it progresses to invasive carcinoma. Diagnose via colposcopy and biopsy. Lateral invasion can block ureters → renal failure.

Premature ovarian failure

Premature atresia of ovarian follicles in women of reproductive age. 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, premature ovarian failure, hyperprolactinemia, thyroid disorders, eating disorders, competitive athletics, Cushing syndrome, adrenal insufficiency.

Polycystic ovarian syndrome (Stein-Leventhal 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 subfertility in women. Enlarged, bilateral cystic ovaries **A**; presents with amenorrhea/oligomenorrhea, hirsutism, acne, ↓ fertility. Associated with obesity. ↑ risk of endometrial cancer 2° to unopposed estrogen from repeated anovulatory cycles.

Treatment: weight reduction, OCPs, clomiphene citrate, ketoconazole, spironolactone.

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. Can be benign or malignant. Arise from surface epithelium, germ cells, or sex cord stromal tissue. Majority of malignant tumors are epithelial (serous cystadenocarcinoma most common). Risk ↑ with advanced age, infertility, endometriosis, PCOS, genetic predisposition (*BRCA-1* or *BRCA-2* mutation, Lynch syndrome, strong family history). Risk ↓ with previous pregnancy, history of breastfeeding, OCPs, tubal ligation. Presents with adnexal mass, abdominal distension, bowel obstruction, pleural effusion. Monitor response to therapy/relapse by measuring CA 125 levels (not good for screening).

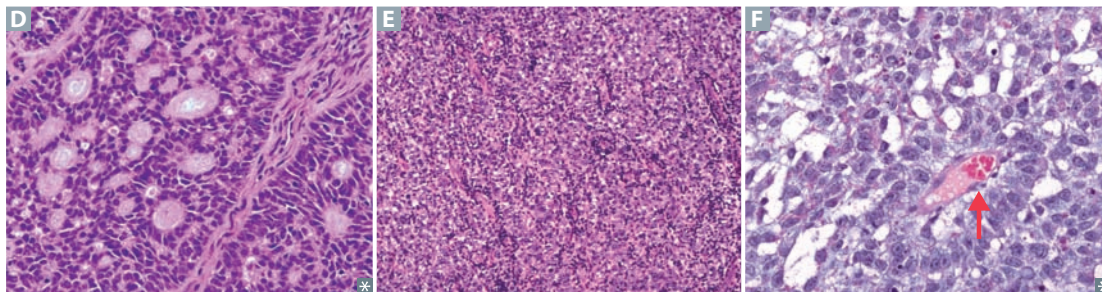
Benign ovarian neoplasms

Serous cystadenoma	Most common ovarian neoplasm. Lined with fallopian tube–like epithelium. Often bilateral.
Mucinous cystadenoma	Multiloculated, large. Lined by mucus-secreting epithelium A .
Endometrioma	Endometriosis (ectopic endometrial tissue) within ovary with cyst formation. Presents with pelvic pain, dysmenorrhea, dyspareunia; symptoms may vary with menstrual cycle. “Chocolate cyst”—endometrioma filled with dark, reddish-brown blood. Complex mass on ultrasound.
Mature cystic teratoma (dermoid cyst)	Germ cell tumor, most common ovarian tumor in females 10–30 years old. Cystic mass containing elements from all 3 germ layers (eg, teeth, hair, sebum) B . Can present with pain 2° to ovarian enlargement or torsion. A monodermal form with thyroid tissue (struma ovarii) uncommonly presents with hyperthyroidism C .
Brenner tumor	Looks like bladder. Solid tumor that is pale yellow-tan and appears encapsulated. “Coffee bean” nuclei on H&E stain.
Fibromas	Bundles of spindle-shaped fibroblasts. Meigs syndrome —triad of ovarian fibroma, ascites, hydrothorax. “Pulling” sensation in groin.
Thecoma	Like granulosa cell tumors, may produce estrogen. Usually presents as abnormal uterine bleeding in a postmenopausal woman.



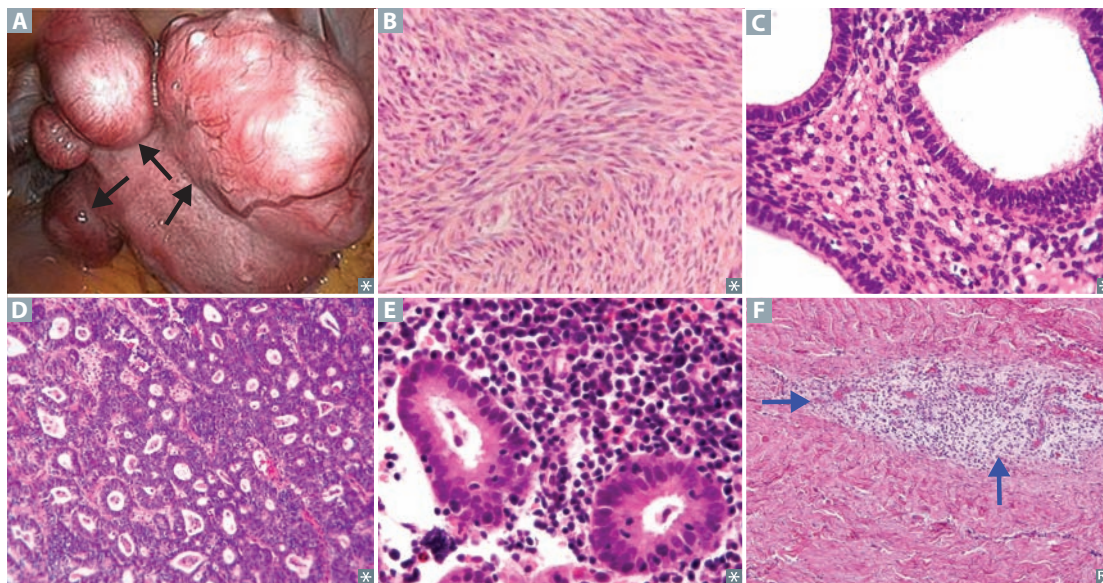
Ovarian neoplasms (continued)**Malignant ovarian neoplasms**

Granulosa cell tumor	Most common malignant stromal tumor. Predominantly women in their 50s. Often produces estrogen and/or progesterone and presents with postmenopausal bleeding, sexual precocity (in pre-adolescents), breast tenderness. Histology shows Call-Exner bodies D (granulosa cells arranged haphazardly around collections of eosinophilic fluid, resembling primordial follicles).
Serous cystadenocarcinoma	Most common malignant ovarian neoplasm, frequently bilateral. Psammoma bodies.
Mucinous cystadenocarcinoma	Pseudomyxoma peritonei—intraperitoneal accumulation of mucinous material from ovarian or appendiceal tumor.
Immature teratoma	Aggressive, contains fetal tissue, neuroectoderm. Commonly diagnosed after menopause. Typically represented by immature/embryonic-like neural tissue.
Dysgerminoma	Most common in adolescents. Equivalent to male seminoma but rarer. 1% of all ovarian tumors; 30% of germ cell tumors. Sheets of uniform “fried egg” cells E . hCG, LDH = tumor markers.
Yolk sac (endodermal sinus) tumor	Aggressive, in ovaries or testes (boys) and sacrococcygeal area in young children. Most common tumor in male infants. Yellow, friable (hemorrhagic), solid mass. 50% have Schiller-Duval bodies (resemble glomeruli) F . AFP = tumor marker.
Krukenberg tumor	GI malignancy that metastasizes to ovaries → mucin-secreting signet cell adenocarcinoma.

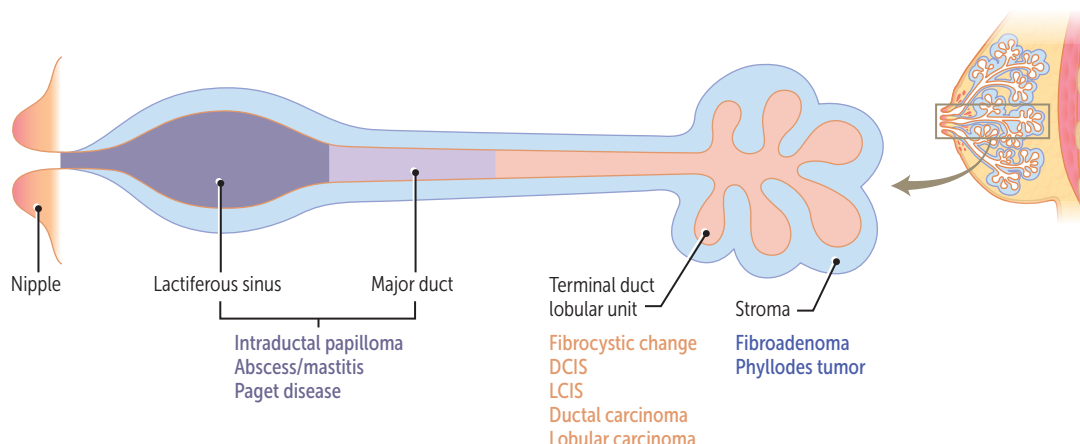


Endometrial conditions

Polyp	Well-circumscribed collection of endometrial tissue within uterine wall. May contain smooth muscle cells. Can extend into endometrial cavity in the form of a polyp. May be asymptomatic or present with painless abnormal uterine bleeding.
Adenomyosis	Extension of endometrial tissue (glandular) into uterine myometrium. Caused by hyperplasia of basal layer of endometrium. Presents with dysmenorrhea, menorrhagia, uniformly enlarged, soft, globular uterus. Treatment: GnRH agonists, hysterectomy.
Leiomyoma (fibroid)	Most common tumor in females. Often presents with multiple discrete tumors A . ↑ 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 old. May be asymptomatic, cause abnormal uterine bleeding, or result in miscarriage. Severe bleeding may lead to iron deficiency anemia. Whorled pattern of smooth muscle bundles with well-demarcated borders B .
Endometrial hyperplasia	Abnormal endometrial gland proliferation C usually caused by excess estrogen stimulation. ↑ risk for endometrial carcinoma; nuclear atypia is greater risk factor than complex (vs simple) architecture. Presents as postmenopausal vaginal bleeding. Risk factors include anovulatory cycles, hormone replacement therapy, polycystic ovarian syndrome, granulosa cell tumor.
Endometrial carcinoma	Most common gynecologic malignancy D . Peak occurrence at 55–65 years old. Presents with vaginal bleeding. Typically preceded by endometrial hyperplasia. Risk factors include prolonged use of estrogen without progestins, obesity, diabetes, hypertension, nulliparity, late menopause, Lynch syndrome.
Endometritis	Inflammation of endometrium E associated with retained products of conception following delivery, miscarriage, abortion, or with foreign body (eg, IUD). Retained material in uterus promotes infection by bacterial flora from vagina or intestinal tract. Treatment: gentamicin + clindamycin +/- ampicillin.
Endometriosis	Non-neoplastic endometrial glands/stroma outside endometrial cavity F . Can be found anywhere; most common sites are ovary (frequently bilateral), pelvis, peritoneum. In ovary, appears as endometrioma (blood-filled “chocolate cyst”). 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.



Breast pathology



Benign breast disease

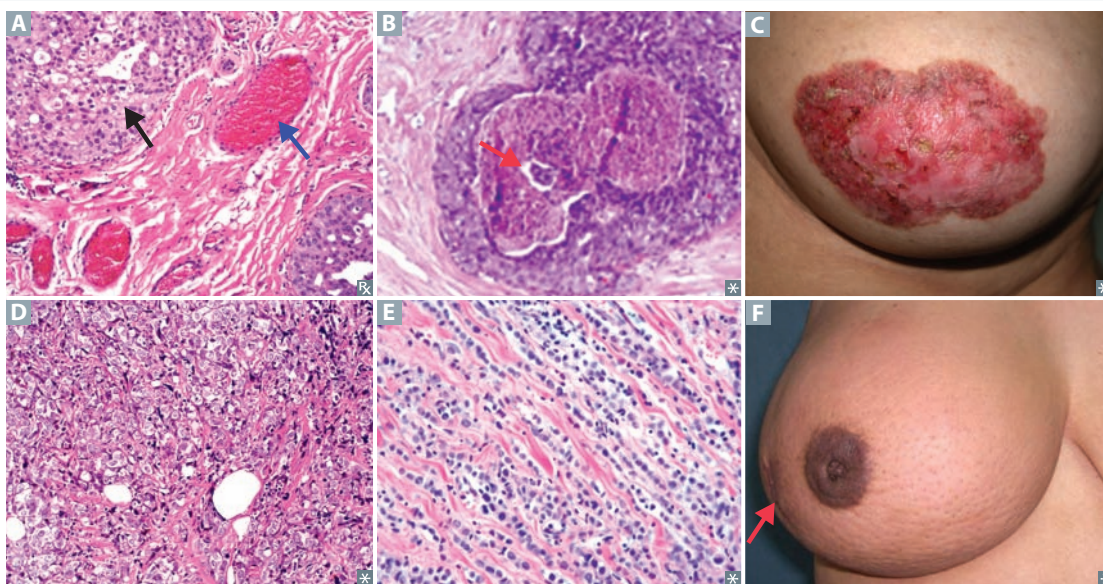
Fibroadenoma	Most common in women under 35 years. Small, well-defined, mobile mass. ↑ size and tenderness with ↑ estrogen (eg, pregnancy, prior to menstruation). Risk of cancer is usually not increased.
Fibrocystic changes	Most common in premenopausal women > 35 years. Presents with premenstrual breast 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.
Sclerosing adenosis	↑ acini and stromal fibrosis, associated with calcifications. Slight (1.5–2×) ↑ risk for cancer.
Intraductal papilloma	Small papillary tumor within lactiferous ducts, typically beneath areola. Most common cause of nipple discharge (serous or bloody). Slight (1.5–2×) ↑ risk for cancer.
Epithelial hyperplasia	↑ cells in terminal ductal or lobular epithelium. ↑ risk of carcinoma with atypical cells.
Phyllodes tumor	Large mass of connective tissue and cysts with “leaf-like” lobulations. Most common in 5th decade. Some may become malignant.
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	During breastfeeding, ↑ risk of bacterial infection through cracks in nipple. <i>S aureus</i> is most common pathogen. Treat with antibiotics and continue breastfeeding.
Gynecomastia	Breast enlargement in males due to ↑ estrogen compared with androgen activity. Physiologic (not pathologic) 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, Ketoconazole: “Some Hormones Create Knockers”).

Malignant breast tumors

Commonly postmenopausal. Usually arise from terminal duct lobular unit. Overexpression of estrogen/progesterone receptors or *c-erbB2* (HER-2, an EGF receptor) is common; triple negative (ER \ominus , PR \ominus , and Her2/Neu \ominus) more aggressive; type affects therapy and prognosis. Axillary lymph node involvement indicating metastasis is the most important prognostic factor in early-stage disease. Most often located in upper-outer quadrant of breast.

Risk factors: \uparrow estrogen exposure, \uparrow total number of menstrual cycles, older age at 1st live birth, obesity (\uparrow estrogen exposure as adipose tissue converts androstenedione to estrone), *BRCA1* and *BRCA2* gene mutations, African American ethnicity (\uparrow risk for triple \ominus breast cancer).

TYPE	CHARACTERISTICS	NOTES
Noninvasive		
Ductal carcinoma in situ	Fills ductal lumen (black arrow in A 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.
Comedocarcinoma	Ductal, central necrosis (arrow in B). Subtype of DCIS.	
Paget disease	Results from underlying DCIS or invasive breast cancer. Eczematous patches on nipple C . Paget cells = intraepithelial adenocarcinoma cells.	
Invasive		
Invasive ductal carcinoma	Firm, fibrous, “rock-hard” mass with sharp margins and small, glandular, duct-like cells D . Grossly, see classic “stellate” infiltration.	Most common (~ 75% of all breast cancers).
Invasive lobular carcinoma	Orderly row of cells (“Indian file” E), due to \downarrow E-cadherin expression.	Often bilateral with multiple lesions in the same location.
Medullary carcinoma	Fleshy, cellular, lymphocytic infiltrate.	Good prognosis.
Inflammatory breast cancer	Dermal lymphatic invasion by breast carcinoma. Peau d’orange (breast skin resembles orange peel F); neoplastic cells block lymphatic drainage.	Poor prognosis (50% survival at 5 years). Often mistaken for mastitis or Paget disease.

Malignant breast tumors (continued)**Penile pathology****Peyronie disease**

Abnormal curvature of penis due to fibrous plaque within tunica albuginea. Associated with erectile dysfunction. Can cause pain, anxiety. Consider surgical repair once curvature stabilizes. Distinct from penile fracture (rupture of corpora cavernosa due to forced bending).

Ischemic priapism

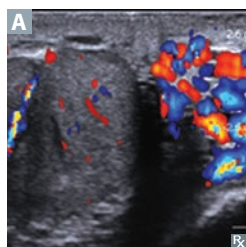
Painful sustained erection lasting > 4 hours. Associated with sickle cell disease (sickled RBCs get trapped in vascular channels), medications (eg, sildenafil, trazodone). Treat immediately with corporal aspiration, intracavernosal phenylephrine, or surgical decompression to prevent ischemia.

Squamous cell carcinoma

More common in Asia, Africa, South America. Precursor in situ lesions: Bowen disease (in penile shaft, presents as leukoplakia), erythroplasia of Queyrat (cancer of glans, presents as erythroplakia), Bowenoid papulosis (carcinoma in situ of unclear malignant potential, presenting as reddish papules). Associated with HPV and lack of circumcision.

Cryptorchidism

Undescended testis (one or both); impaired spermatogenesis (since sperm develop best at temperatures < 37°C); can have normal testosterone levels (Leydig cells are 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.

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 (distension on inspection and “bag of worms” on palpation) or ultrasound with Doppler **A**; does not transilluminate.

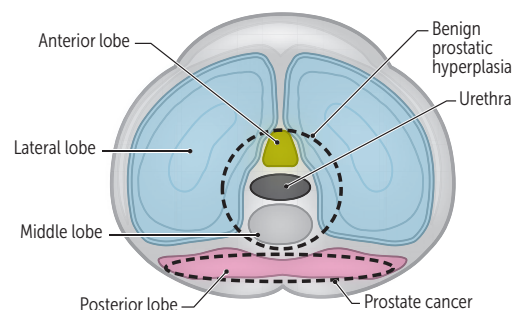
Treatment: varicocelectomy, embolization.

Extragenital germ cell tumors	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 in infants, due to incomplete obliteration of processus vaginalis.	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 germ cell tumors	~ 95% of all testicular tumors. Most often occur in young men. Risk factors: cryptorchidism, Klinefelter syndrome. Can present as a mixed germ cell tumor. Testicular mass that does not transilluminate.	
Seminoma	Malignant; painless, homogenous testicular enlargement; most common testicular tumor. Does not occur in infancy. Large cells in lobules with watery cytoplasm and “fried egg” appearance. ↑ placental ALP. Radiosensitive. Late metastasis, excellent prognosis.	
Yolk sac (endodermal sinus) tumor	Yellow, mucinous. Aggressive malignancy of testes, 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, ↑ hCG. Disordered syncytiotrophoblastic and cytotrophoblastic elements. Hematogenous metastases to lungs and brain. May produce gynecomastia, symptoms of hyperthyroidism (hCG is structurally similar to LH, FSH, TSH).	
Teratoma	Unlike in females, mature teratoma in adult males may be malignant. Benign in children.	
Embryonal carcinoma	Malignant, hemorrhagic mass with necrosis; painful; worse prognosis than seminoma. Often glandular/papillary morphology. “Pure” embryonal carcinoma is rare; most commonly mixed with other tumor types. May be associated with ↑ hCG and normal AFP levels when pure (↑ AFP when mixed).	
Testicular non-germ cell tumors	5% of all testicular tumors. Mostly benign.	
Leydig cell	Golden brown color; contains Reinke crystals (eosinophilic cytoplasmic inclusions). Produce androgens or estrogens → gynecomastia in men, precocious puberty in boys.	
Sertoli cell	Androblastoma from sex cord stroma.	
Testicular lymphoma	Most common testicular cancer in older men. Not a 1° cancer; arises from metastatic lymphoma to testes. Aggressive.	

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 stream, dysuria. May lead to distention and hypertrophy of bladder, hydronephrosis, UTIs. ↑ free prostate-specific antigen (PSA).

Treatment: α_1 -antagonists (terazosin, tamsulosin), which cause relaxation of smooth muscle; 5α -reductase inhibitors (eg, finasteride); tadalafil.

**Prostatitis**

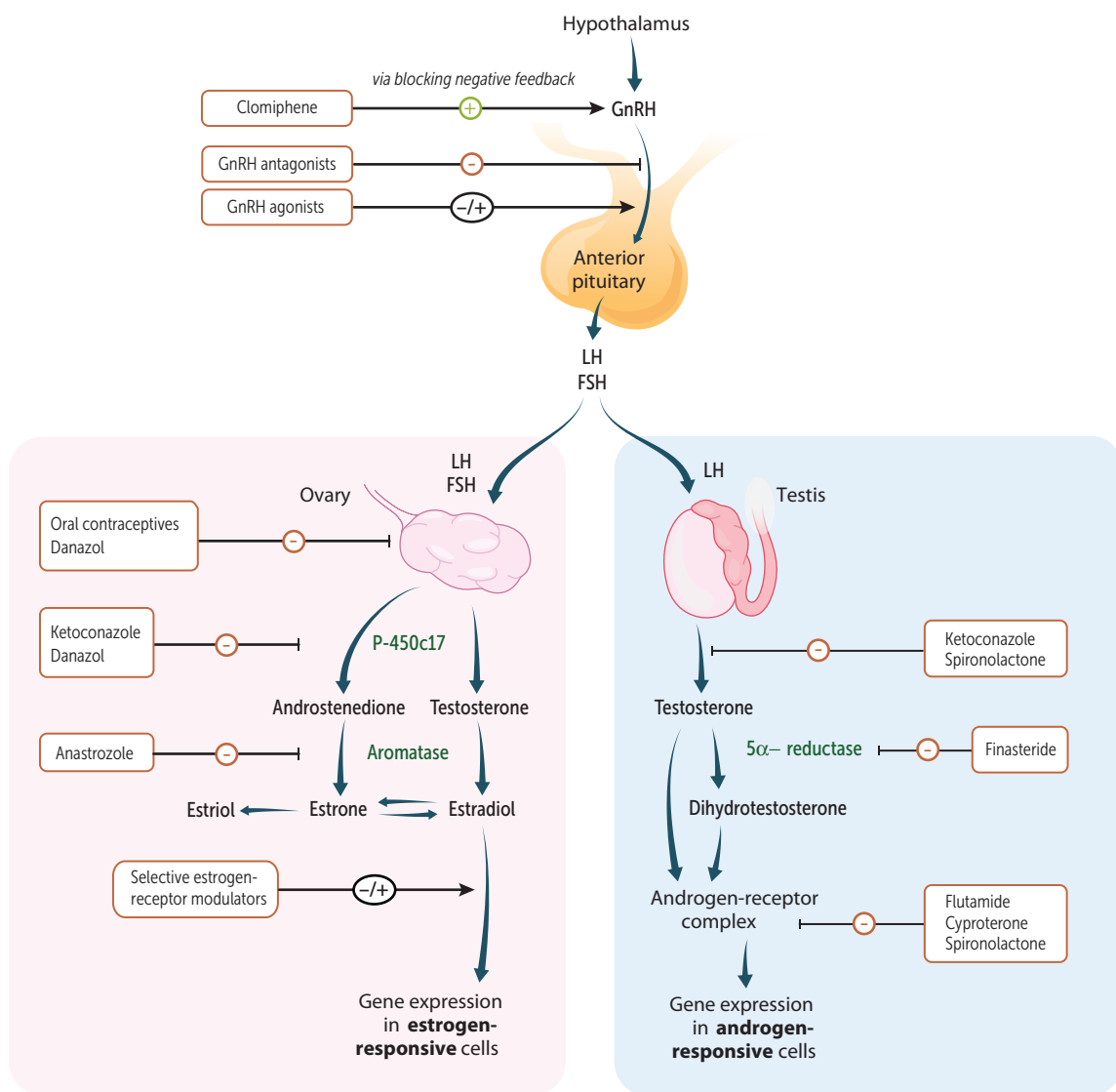
Dysuria, frequency, urgency, low back pain. Warm, tender, enlarged prostate. Acute: bacterial (eg, *E coli*); chronic: bacterial or abacterial.

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.

▶ REPRODUCTIVE—PHARMACOLOGY

Control of reproductive hormones



Leuprolide

MECHANISM	GnRH analog with agonist properties when used in pulsatile fashion; antagonist properties when used in continuous fashion (downregulates GnRH receptor in pituitary → ↓ FSH/LH).	Leuprolide can be used in lieu of GnRH.
CLINICAL USE	Uterine fibroids, endometriosis, precocious puberty, prostate cancer, infertility.	

Estrogens

	Ethinyl estradiol, DES, mestranol.
MECHANISM	Bind estrogen receptors.
CLINICAL USE	Hypogonadism or ovarian failure, menstrual abnormalities, hormone replacement therapy in postmenopausal women; use in men with androgen-dependent prostate cancer.
ADVERSE EFFECTS	↑ risk of endometrial cancer, 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.

Selective estrogen receptor 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 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 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	ER ⊕ breast cancer in postmenopausal women.

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, so progesterone is added.
Possible increased cardiovascular risk.

Progestins	Levonorgestrel, medroxyprogesterone, etonogestrel, norethindrone, megestrol, and many others when combined with estrogen.
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 contraception	<p>Progestins and ethinyl estradiol; forms include pill, patch, vaginal ring.</p> <p>Estrogen and progestins inhibit LH/FSH and thus prevent estrogen surge. No estrogen surge → no LH surge → no ovulation.</p> <p>Progestins cause thickening of cervical mucus, thereby limiting access of sperm to uterus.</p> <p>Progestins also inhibit endometrial proliferation → endometrium is less suitable to the implantation of an embryo.</p> <p>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.</p>
Copper intrauterine device	
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).
Terbutaline, ritodrine	β ₂ -agonists that relax the uterus; used to ↓ contraction frequency in women during labor.
Danazol	
MECHANISM	Synthetic androgen that acts as partial agonist at androgen receptors.
CLINICAL USE	Endometriosis, hereditary angioedema.
ADVERSE EFFECTS	Weight gain, edema, acne, hirsutism, masculinization, ↓ HDL levels, hepatotoxicity.

Testosterone, methyltestosterone

MECHANISM	Agonists at androgen receptors.
CLINICAL USE	Treat hypogonadism and promote development of 2° sex characteristics; stimulate anabolism to promote recovery after burn or injury.
ADVERSE EFFECTS	Causes masculinization in females; ↓ intratesticular testosterone in males by inhibiting release of LH (via negative feedback) → gonadal atrophy. Premature closure of epiphyseal plates. ↑ LDL, ↓ HDL.

Antiandrogens

Testosterone $\xrightarrow{5\alpha\text{-reductase}}$ DHT (more potent).

Finasteride	5 α -reductase inhibitor (↓ conversion of testosterone to DHT). Used for BPH and male-pattern baldness.	
Flutamide	Nonsteroidal competitive inhibitor at androgen receptors. Used for prostate carcinoma.	
Ketoconazole	Inhibits steroid synthesis (inhibits 17,20-desmolase).	Used for polycystic ovarian syndrome to reduce androgenic symptoms. Both have side effects of gynecomastia and amenorrhea.
Spirolonactone	Inhibits steroid binding, 17 α -hydroxylase, and 17,20-desmolase.	

Tamsulosin

α_1 -antagonist used to treat BPH by inhibiting smooth muscle contraction. Selective for $\alpha_{1A,D}$ receptors (found on prostate) vs vascular α_{1B} receptors.

Phosphodiesterase type 5 inhibitors

Sildenafil, vardenafil, tadalafil.

MECHANISM	Inhibit PDE-5 → ↑ cGMP → prolonged smooth muscle relaxation in response to NO → ↑ blood flow in corpus cavernosum of penis, ↓ pulmonary vascular resistance.	Sildenafil, vardenafil, and tadalafil fill the penis.
CLINICAL USE	Erectile dysfunction, pulmonary hypertension, BPH (tadalafil only).	
ADVERSE EFFECTS	Headache, flushing, dyspepsia, cyanopia (blue-tinted vision). Risk of life-threatening hypotension in patients taking nitrates.	“Hot and sweaty,” but then Headache, Heartburn, Hypotension.

Minoxidil

MECHANISM	Direct arteriolar vasodilator.
CLINICAL USE	Androgenetic alopecia; severe refractory hypertension.

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

“Mars is essentially in the same orbit. Somewhat the same distance from the Sun, which is very important. We have seen pictures where there are canals, we believe, and water. If there is water, that means there is oxygen. If there is oxygen, that means we can breathe.”

—Former Vice President Dan Quayle

“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.”

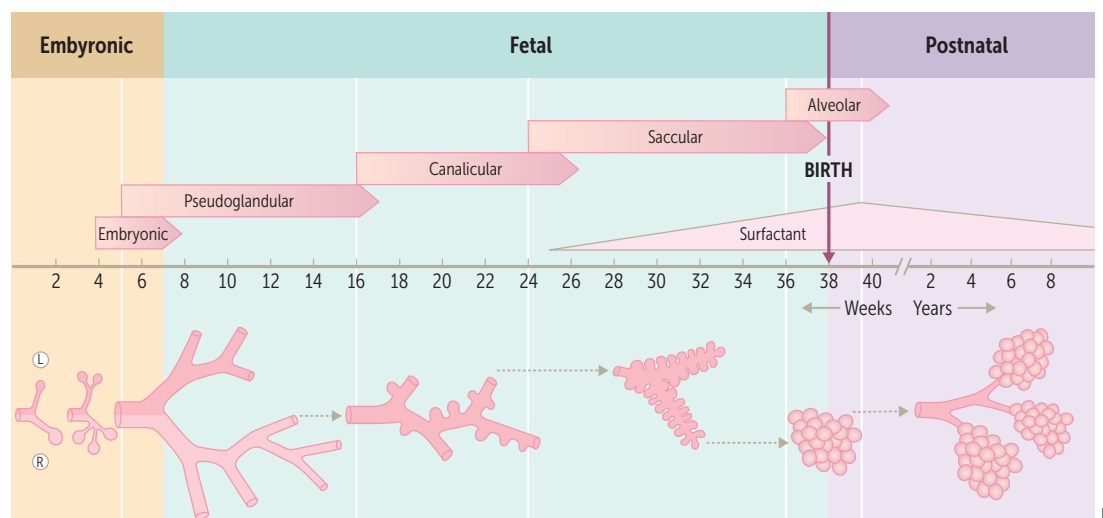
—Hitch

▶ Embryology	606
▶ Anatomy	608
▶ Physiology	610
▶ Pathology	616
▶ Pharmacology	627

▶ RESPIRATORY—EMBRYOLOGY

Lung development Occurs in five periods. Initial development includes development of lung bud from distal end of respiratory diverticulum during week 4. Lung bud divides into two bronchial buds that branch off into bronchi.

STAGE	IMPORTANT TERMS	NOTES
Embryonic (weeks 4–7)	Lung bud → trachea → mainstem bronchi → secondary (lobar) bronchi → tertiary (segmental) bronchi.	Errors at this stage can lead to TE fistula.
Pseudoglandular (weeks 5–16)	Endodermal tubules → terminal bronchioles. Surrounded by modest capillary network.	Respiration impossible, incompatible with life.
Canalicular (weeks 16–26)	Terminal bronchioles → respiratory bronchioles → alveolar ducts. Surrounded by prominent capillary network.	Airways increase in diameter. Respiration capable at 25 weeks.
Saccular (weeks 26–birth)	Alveolar ducts → terminal sacs. Terminal sacs separated by 1° septae. Pneumocytes develop.	
Alveolar (weeks 32–8 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.

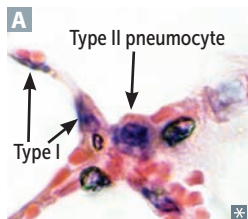
**Congenital lung malformations**

Pulmonary hypoplasia Poorly developed bronchial tree with abnormal histology usually involving right lung. Associated with congenital diaphragmatic hernia, bilateral renal agenesis (Potter sequence [syndrome]).

Bronchogenic cysts Caused by abnormal budding of the foregut and dilation of terminal or large bronchi. Discrete, round, sharply defined and air-filled densities on CXR. Drain poorly and cause chronic infections.

Pneumocytes**Type I cells**

97% of alveolar surfaces. Line the alveoli.
Squamous; thin for optimal gas diffusion.

Type II cells

Secrete pulmonary surfactant → ↓ alveolar surface tension, prevents alveolar collapse, ↓ lung recoil, and ↑ compliance. Cuboidal and clustered **A**. Also serve as precursors to type I cells and other type II cells. Type II cells proliferate during lung damage.

Club cells

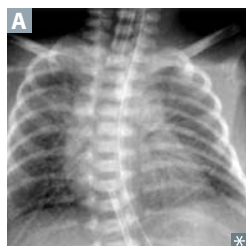
Nonciliated; low-columnar/cuboidal with secretory granules. Secrete component of surfactant; degrade toxins; act as reserve cells.

$$\text{Collapsing pressure (P)} = \frac{2 \text{ (surface tension)}}{\text{radius}}$$

Alveoli have ↑ tendency to collapse on expiration as radius ↓ (law of Laplace).

Pulmonary surfactant is a complex mix of lecithins, the most important of which is dipalmitoylphosphatidylcholine.

Surfactant synthesis begins around week 26 of gestation, but mature levels are not achieved until around week 35.

Neonatal respiratory distress syndrome

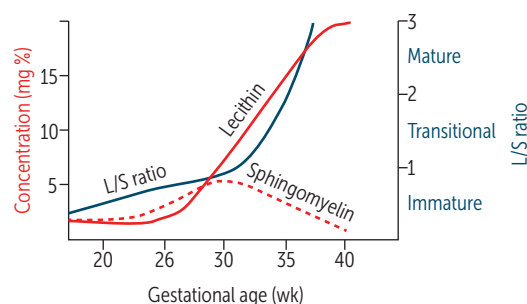
Surfactant deficiency → ↑ surface tension → alveolar collapse (“ground-glass” appearance of lung fields) **A**. Screening tests for fetal lung maturity: lecithin-sphingomyelin (L/S) ratio in amniotic fluid (> 2 is healthy; < 1.5 predictive of NRDS), foam stability index test, surfactant-albumin ratio. Persistently low O₂ tension → risk of PDA.

Risk factors: prematurity, maternal diabetes (due to ↑ fetal insulin), C-section delivery (↓ release of fetal glucocorticoids).

Complications: metabolic acidosis, PDA, necrotizing enterocolitis.

Treatment: maternal steroids before birth; artificial surfactant for infant.

Therapeutic supplemental O₂ can result in **R**etinopathy of prematurity, **I**ntraventricular hemorrhage, **B**ronchopulmonary dysplasia (**RIB**).



► RESPIRATORY—ANATOMY

Respiratory tree**Conducting zone**

Large airways consist of nose, pharynx, larynx, trachea, and 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 end of bronchi.

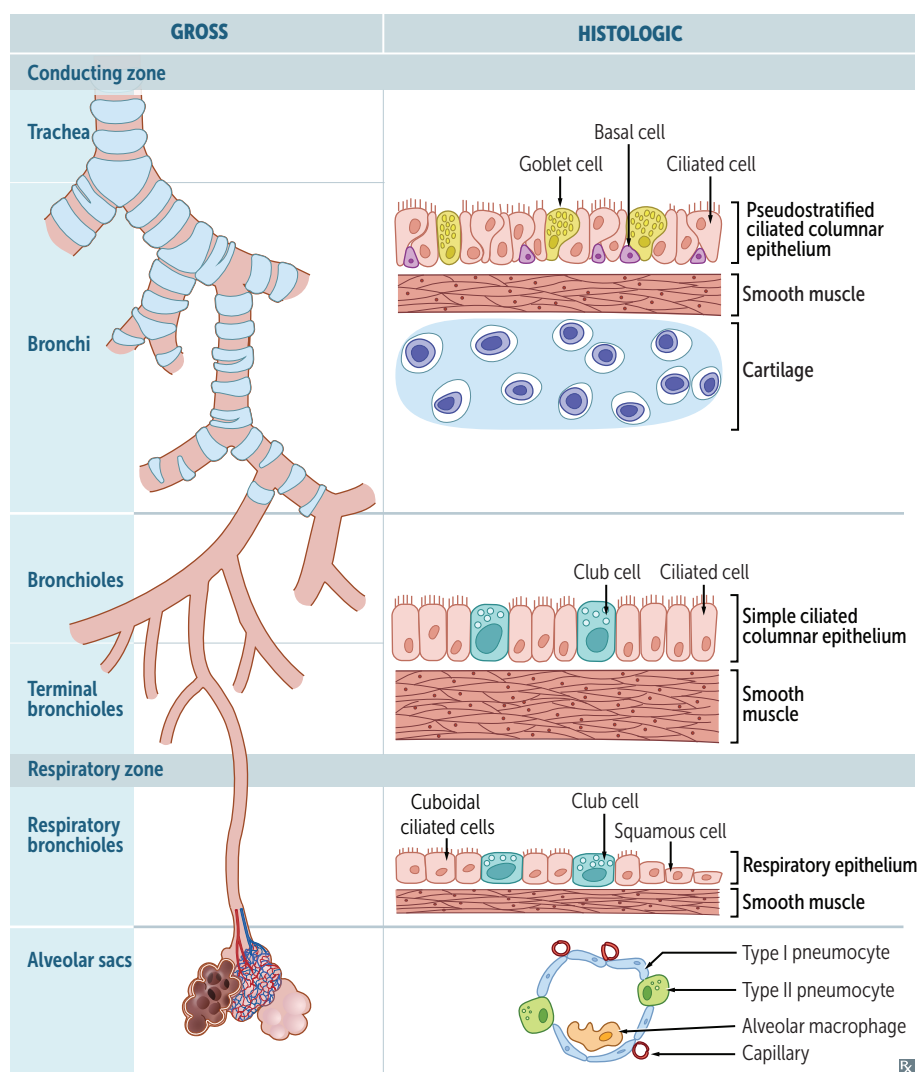
Pseudostratified ciliated columnar cells primarily make up epithelium of bronchus and extend to beginning of terminal bronchioles, then transition to cuboidal cells. Clear mucus and debris from lungs (mucociliary escalator).

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.



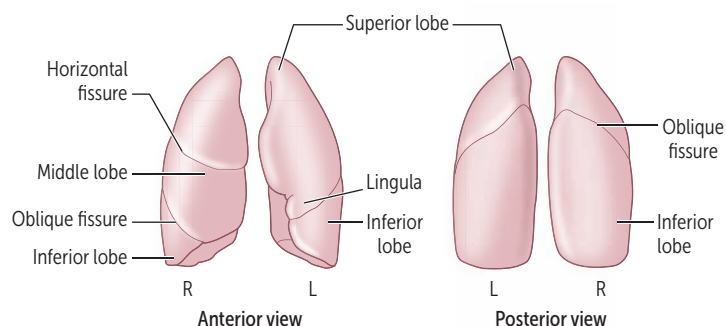
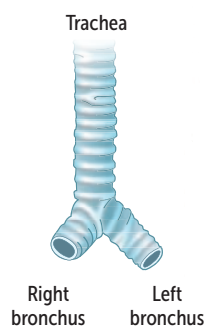
Lung relations

Right lung has 3 lobes; Left has **L**ess **L**obes (2) and **L**ingula (homolog of right middle lobe). Right lung is more common site for inhaled foreign body because the right main stem bronchus is wider and more vertical than the left.

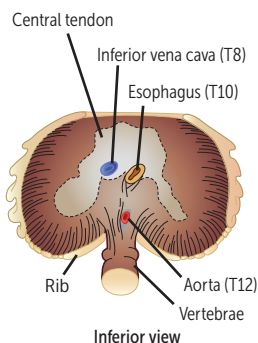
Instead of a middle lobe, the left lung has a space occupied by the heart. The relation of the pulmonary artery to the bronchus at each lung hilum is described by **RALS**—**R**ight **A**nterior; **L**eft **S**uperior.

If you aspirate a peanut:

- While upright—enters inferior segment of right inferior lobe.
- While supine—enters superior segment of right inferior lobe.



Diaphragm structures



Structures perforating diaphragm:

- At T8: IVC
- 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
- T10:** “oesophagus”
- T12:** aortic hiatus

I (IVC) **ate** (8) **ten** (10) **eggs** (esophagus) **at** (aorta) **twelve** (12).

C3, 4, 5 keeps the diaphragm **alive**.

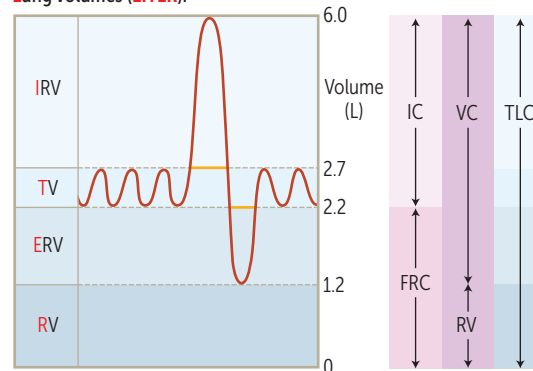
Other bifurcations:

- The common carotid **bifourcates** at **C4**.
- The trachea **bifourcates** at **T4**.
- The abdominal aorta **bifourcates** at **L4**.

► RESPIRATORY—PHYSIOLOGY

Lung volumes

Inspiratory reserve volume	Air that can still be breathed in after normal inspiration
Tidal volume	Air that moves into lung with each quiet inspiration, typically 500 mL
Expiratory reserve volume	Air that can still be breathed out after normal expiration
Residual volume	Air in lung after maximal inspiration; cannot be measured on spirometry
Inspiratory capacity	IRV + TV
Functional residual capacity	RV + ERV Volume of gas in lungs after normal expiration; includes RV, cannot be measured on spirometry
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; includes RV, cannot be measured by spirometry

Lung volumes (LITER):

A capacity is a sum of ≥ 2 physiologic volumes.

Determination of physiologic dead space

$$V_D = V_T \times \frac{P_{aCO_2} - P_{ECo_2}}{P_{aCO_2}}$$

V_D = 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.

P_{aCO_2} = arterial PCO_2 .

P_{ECo_2} = expired air PCO_2 .

T_aCO₂, **P**_aCO₂, **P**_ECO₂, **P**_aCO₂ (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.

Pathologic dead space—when part of the respiratory zone becomes unable to perform gas exchange. Ventilated but not perfused.

Ventilation

Minute ventilation (V_E)	Total volume of gas entering lungs per minute $V_E = V_T \times RR$	Normal values: Respiratory rate (RR) = 12–20 breaths/min
Alveolar ventilation (V_A)	Volume of gas per unit time that reaches alveoli $V_A = (V_T - V_D) \times RR$	$V_T = 500$ mL/breath $V_D = 150$ mL/breath

Lung and chest wall

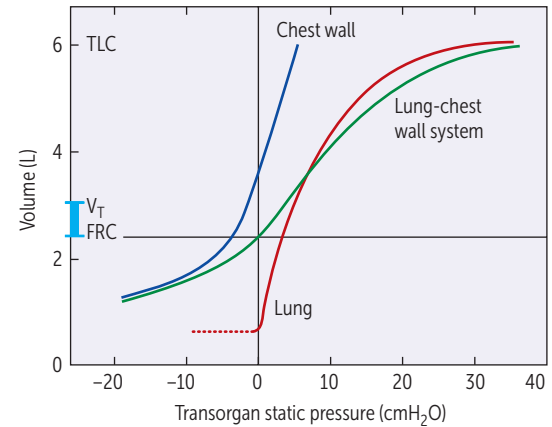
Elastic recoil—tendency for lungs to collapse inward and chest wall to spring outward. At FRC, inward pull of lung is balanced by outward pull of chest wall, and system pressure is atmospheric.

Elastic properties of both chest wall and lungs determine their combined volume.

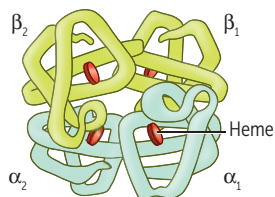
At FRC, airway and alveolar pressures are 0, and intrapleural pressure is negative (prevents pneumothorax). PVR is at minimum.

Compliance—change in lung volume for a change in pressure; expressed as $\Delta V/\Delta P$ and is inversely proportional to wall stiffness. High compliance = lung easier to fill, lower compliance = lung harder to fill. ↓ in pulmonary fibrosis, pneumonia, pulmonary edema; ↑ in emphysema, normal aging. Surfactant increases compliance.

Hysteresis—lung inflation curve follows a different curve than the lung deflation curve due to need to overcome surface tension forces in inflation.



Compliant lungs **comply** (cooperate) and fill easily with air.

Hemoglobin

Hemoglobin (Hb) is composed of 4 polypeptide subunits (2 α and 2 β) and exists in 2 forms:

- T (taut; deoxygenated) form has low affinity for O_2 , thus promoting release/unloading of O_2 .
- R (relaxed; oxygenated) form has high affinity for O_2 (300 \times). Hb exhibits positive cooperativity and negative allostery.

↑ Cl^- , H^+ , CO_2 , 2,3-BPG, and temperature favor taut form over relaxed form (shifts dissociation curve right \rightarrow ↑ O_2 unloading).

Fetal Hb (2 α and 2 γ subunits) has a higher affinity for O_2 than adult Hb, driving diffusion of oxygen across the placenta from mother to fetus. ↑ O_2 affinity results from ↓ affinity of HbF for 2,3-BPG.

Taut in **T**issues.

Relaxed in **R**espiratory area.

Hemoglobin acts as buffer for H^+ ions.

Hemoglobin modifications

Methemoglobin

Oxidized form of Hb (ferric, Fe^{3+}) that does not bind O_2 as readily, but has \uparrow affinity for cyanide.

Iron in Hb is normally in a reduced state (ferrous, Fe^{2+}).

Methemoglobinemia may present with cyanosis and chocolate-colored blood.

Induced methemoglobinemia (using nitrites, followed by thiosulfate) may be used to treat cyanide poisoning.

Methemoglobinemia can be treated with **methylene blue** and **vitamin C**.

Nitrites (eg, from dietary intake or polluted/high altitude H_2O) and benzocaine cause poisoning by oxidizing Fe^{2+} to Fe^{3+} .

Fe^{2+} binds O_2 .

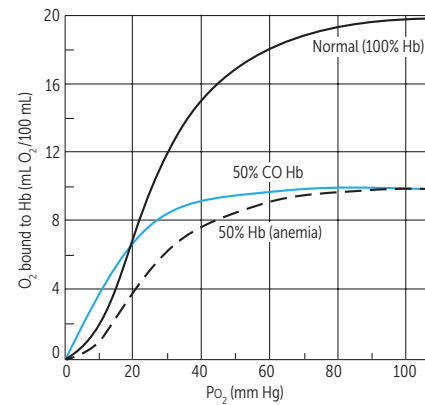
Carboxyhemoglobin

Form of Hb bound to CO in place of O_2 .

Causes \downarrow oxygen-binding capacity with left shift in oxygen-hemoglobin dissociation curve. \downarrow O_2 unloading in tissues.

CO binds competitively to Hb and with 200 \times greater affinity than O_2 .

Treat with 100% O_2 and hyperbaric O_2 .



Oxygen-hemoglobin dissociation curve

Sigmoidal shape due to positive cooperativity (ie, tetrameric Hb molecule can bind 4 O_2 molecules and has higher affinity for each subsequent O_2 molecule bound). Myoglobin is monomeric and thus does not show positive cooperativity; curve lacks sigmoidal appearance.

When curve shifts to the right, \downarrow affinity of Hb for O_2 (facilitates unloading of O_2 to tissue).

An \uparrow in all factors (including H^+) causes a shift of the curve to the right.

A \downarrow in all factors (including H^+) causes a left shift \rightarrow \downarrow O_2 unloading \rightarrow renal hypoxia \rightarrow \uparrow EPO synthesis \rightarrow compensatory erythrocytosis. **Lower = Left**.

Fetal Hb has higher affinity for O_2 than adult Hb, so its dissociation curve is shifted left.

Right shift—ACE BATs right handed:

Acid

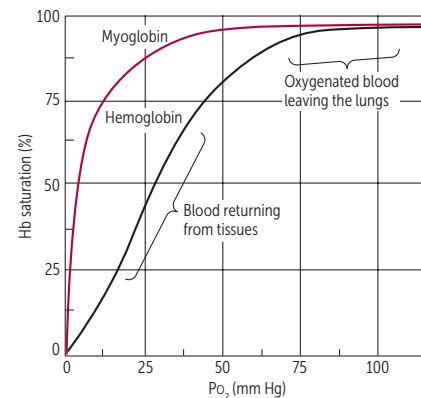
C O_2

Exercise

2,3-BPG

Altitude

Temperature



Oxygen content of blood

$$O_2 \text{ content} = (1.34 \times Hb \times SaO_2) + (0.003 \times PaO_2)$$

Hb = hemoglobin level
 SaO₂ = arterial O₂ saturation
 PaO₂ = partial pressure of O₂

Normally 1 g Hb can bind 1.34 mL O₂; normal Hb amount in blood is 15 g/dL.

O₂ binding capacity ≈ 20.1 mL O₂/dL blood.

With ↓ Hb there is ↓ O₂ content of arterial blood, but no change in O₂ saturation and PaO₂.

O₂ delivery to tissues = cardiac output × O₂ content of blood.

	Hb concentration	% O ₂ sat of Hb	Dissolved O ₂ (PaO ₂)	Total O ₂ content
CO poisoning	Normal	↓ (CO competes with O ₂)	Normal	↓
Anemia	↓	Normal	Normal	↓
Polycythemia	↑	Normal	Normal	↑

Pulmonary circulation

Normally a low-resistance, high-compliance system. PO₂ and PCO₂ exert opposite effects on pulmonary and systemic circulation. A ↓ in PAO₂ causes a hypoxic vasoconstriction that shifts blood away from poorly ventilated regions of lung to well-ventilated regions of lung.

Perfusion limited—O₂ (normal health), CO₂, N₂O. Gas equilibrates early along the length of the capillary. Diffusion can be ↑ only if blood flow ↑.

Diffusion limited—O₂ (emphysema, fibrosis), 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 (jugular venous distention, edema, hepatomegaly).

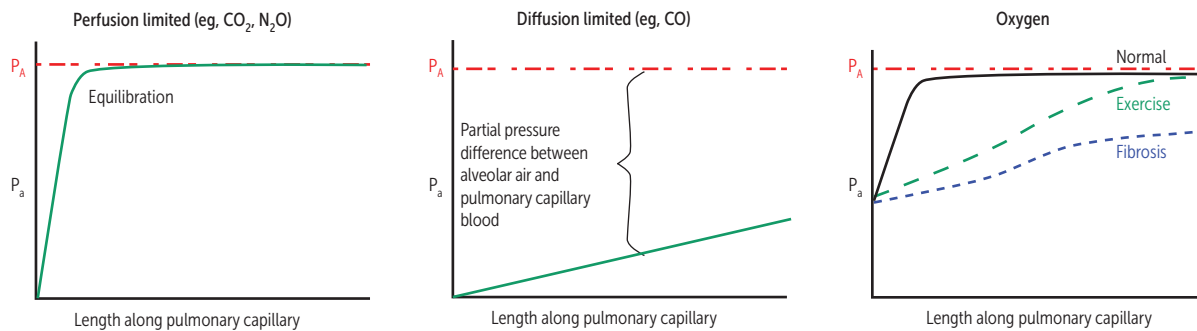
Diffusion: $\dot{V}_{\text{gas}} = A \times D_k \times \frac{P_1 - P_2}{T}$ where

A = area, T = alveolar wall thickness,

D_k(P₁ - P₂) ≈ difference in partial pressures:

- A ↓ in emphysema.
- T ↑ in pulmonary fibrosis.

DLCO is the extent to which oxygen passes from air sacs of lungs into blood.



P_a = partial pressure of gas in pulmonary capillary blood
 P_A = partial pressure of gas in alveolar air

Pulmonary vascular resistance

$$PVR = \frac{P_{\text{pulm artery}} - P_{\text{L atrium}}}{\text{cardiac output}}$$

Remember: $\Delta P = Q \times R$, so $R = \Delta P / Q$

$$R = 8\eta l / \pi r^4$$

R = resistance

$P_{\text{pulm artery}}$ = pressure in pulmonary artery

$P_{\text{L atrium}} \approx$ pulmonary capillary wedge pressure

η = viscosity of blood; l = vessel length;

r = vessel radius

Alveolar gas equation

$$PAO_2 = PIO_2 - \frac{PaCO_2}{R}$$

$$\approx 150 \text{ mm Hg}^a - \frac{PaCO_2}{0.8}$$

^aAt sea level breathing room air

PAO_2 = alveolar PO_2 (mm Hg)

PIO_2 = PO_2 in inspired air (mm Hg)

$PaCO_2$ = arterial PCO_2 (mm Hg)

R = respiratory quotient = CO_2 produced/ O_2 consumed

A-a gradient = $PAO_2 - PaO_2 = 10\text{--}15$ mm Hg

↑ A-a gradient may occur in hypoxemia; causes include shunting, \dot{V}/\dot{Q} mismatch, fibrosis (impairs diffusion)

Oxygen deprivation**Hypoxia (↓ O_2 delivery to tissue)**

↓ cardiac output
Hypoxemia
Anemia
CO poisoning

Hypoxemia (↓ PaO_2)

Normal A-a gradient

- High altitude
- Hypoventilation (eg, opioid use)

↑ A-a gradient

- \dot{V}/\dot{Q} mismatch
- Diffusion limitation (eg, fibrosis)
- Right-to-left shunt

Ischemia (loss of blood flow)

Impeded arterial flow
↓ venous drainage

 \dot{V}/\dot{Q} 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)
- \dot{V}/\dot{Q} at base of lung = 0.6 (wasted perfusion)

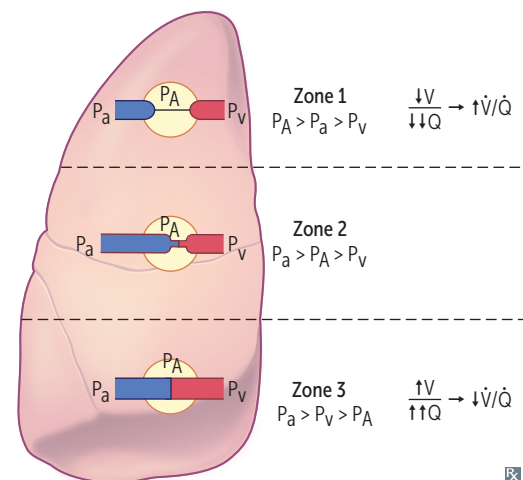
Both ventilation and perfusion are greater at the base of the lung than at the apex of the lung.

With exercise (↑ cardiac output), there is vasodilation of apical capillaries → \dot{V}/\dot{Q} ratio approaches 1.

Certain organisms that thrive in high O_2 (eg, TB) flourish in the apex.

$\dot{V}/\dot{Q} = 0$ = “airway” obstruction (shunt). In shunt, 100% O_2 does not improve PaO_2 (eg, foreign body aspiration).

$\dot{V}/\dot{Q} = \infty$ = blood flow obstruction (physiologic dead space). Assuming < 100% dead space, 100% O_2 improves PaO_2 (eg, pulmonary embolus).



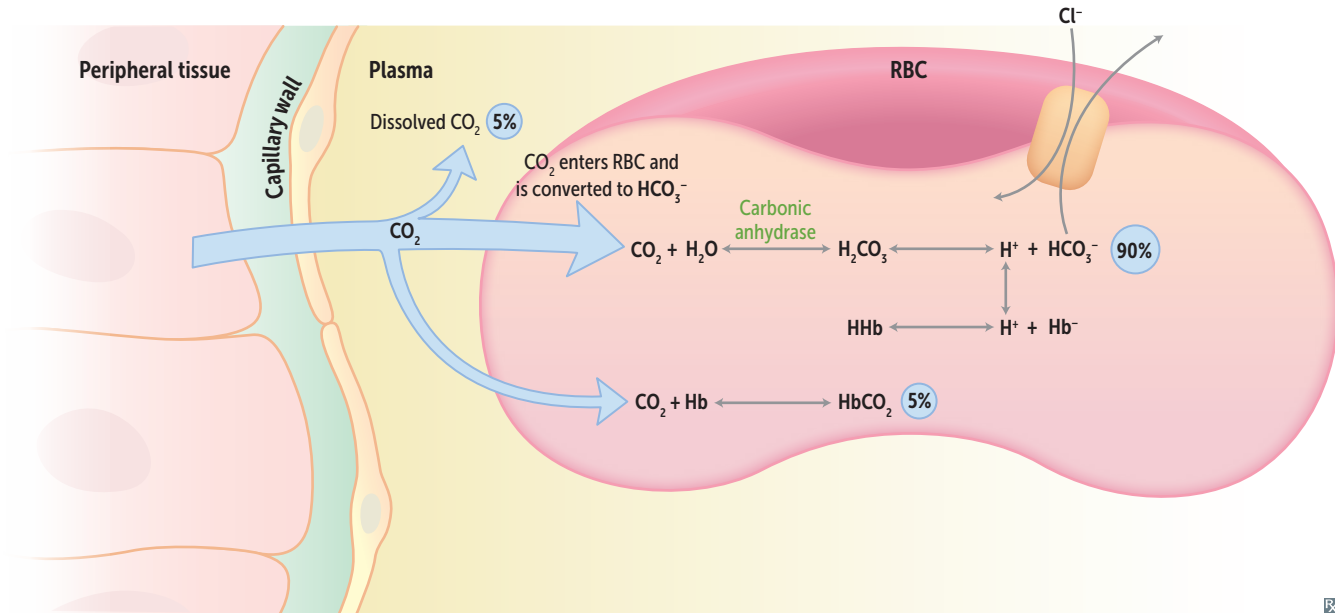
PK

CO₂ transport

CO₂ is transported from tissues to lungs in 3 forms:

- HCO₃⁻ (90%).
- Carbaminohemoglobin or HbCO₂ (5%). CO₂ bound to Hb at N-terminus of globin (not heme). CO₂ binding favors taut form (O₂ unloaded).
- Dissolved CO₂ (5%).

In lungs, oxygenation of Hb promotes dissociation of H⁺ from Hb. This shifts equilibrium toward CO₂ formation; therefore, CO₂ is released from RBCs (Haldane effect). In peripheral tissue, ↑ H⁺ from tissue metabolism shifts curve to right, unloading O₂ (Bohr effect). Majority of blood CO₂ is carried as HCO₃⁻ in the plasma.

**Response to high altitude**

↓ atmospheric oxygen (PO₂) → ↓ Pao₂ → ↑ ventilation → ↓ Paco₂ → respiratory alkalosis → altitude sickness.

Chronic ↑ in ventilation.

↑ erythropoietin → ↑ hematocrit and Hb (chronic hypoxia).

↑ 2,3-BPG (binds to Hb so that Hb releases more O₂).

Cellular changes (↑ mitochondria).

↑ renal excretion of HCO₃⁻ to compensate for respiratory alkalosis (can augment with acetazolamide).

Chronic hypoxic pulmonary vasoconstriction results in pulmonary hypertension and RVH.

Response to exercise

↑ CO₂ production.

↑ O₂ consumption.

↑ ventilation rate to meet O₂ demand.

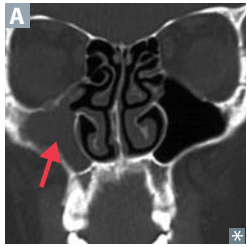
\dot{V}/\dot{Q} ratio from apex to base becomes more uniform.

↑ pulmonary blood flow due to ↑ cardiac output.

↓ pH during strenuous exercise (2° to lactic acidosis).

No change in Pao₂ and Paco₂, but ↑ in venous CO₂ content and ↓ in venous O₂ content.

▶ RESPIRATORY—PATHOLOGY

Rhinosinusitis

Obstruction of sinus drainage into nasal cavity → inflammation and pain over affected area (typically maxillary sinuses **A**, which drain into the middle meatus, in adults).

Most common acute cause is viral URI; may cause superimposed bacterial infection, most commonly *S pneumoniae*, *H influenzae*, *M catarrhalis*.

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).

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.

Deep venous thrombosis

Blood clot within a deep vein → swelling, redness **A**, warmth, pain. Predisposed by Virchow triad (**SHE**):

- **S**tasis (eg, post-op, long drive/flight)
- **H**ypercoagulability (eg, defect in coagulation cascade proteins, such as factor V Leiden)
- **E**ndothelial damage (exposed collagen triggers clotting cascade)

D-dimer lab test used clinically to rule out DVT (high sensitivity, low specificity).

Most pulmonary emboli arise from proximal deep veins of lower extremity.

Homan sign—dorsiflexion of foot → calf pain.

Use unfractionated heparin or low-molecular-weight heparins (eg, enoxaparin) for prophylaxis and acute management.

Use oral anticoagulants (eg, warfarin, rivaroxaban) for treatment (long-term prevention).

Imaging test of choice is compression ultrasound.

Pulmonary emboli

\dot{V}/\dot{Q} mismatch → hypoxemia → respiratory alkalosis. Sudden-onset dyspnea, chest pain, tachypnea, tachycardia. Large emboli or saddle embolus **A** may cause sudden death. 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 **B**.

Types: **F**at, **A**ir, **T**hrombus, **B**acteria, **A**mniotic fluid, **T**umor.

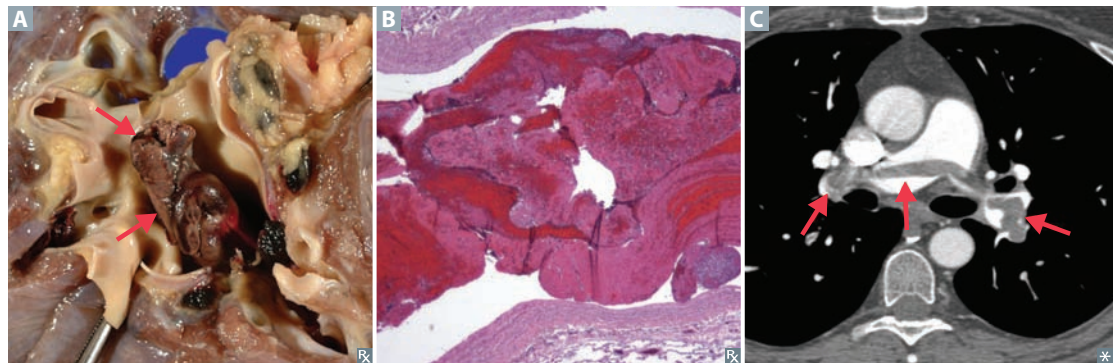
Fat emboli—associated with long bone fractures and liposuction; classic triad of hypoxemia, neurologic abnormalities, petechial rash.

Amniotic fluid emboli—can lead to DIC, especially postpartum.

Air emboli—nitrogen bubbles precipitate in ascending divers (caisson disease, decompression sickness); treat with hyperbaric O_2 ; or, can be iatrogenic 2° to invasive procedures (eg, central line placement).

CT pulmonary angiography is imaging test of choice for PE (look for filling defects) **C**.

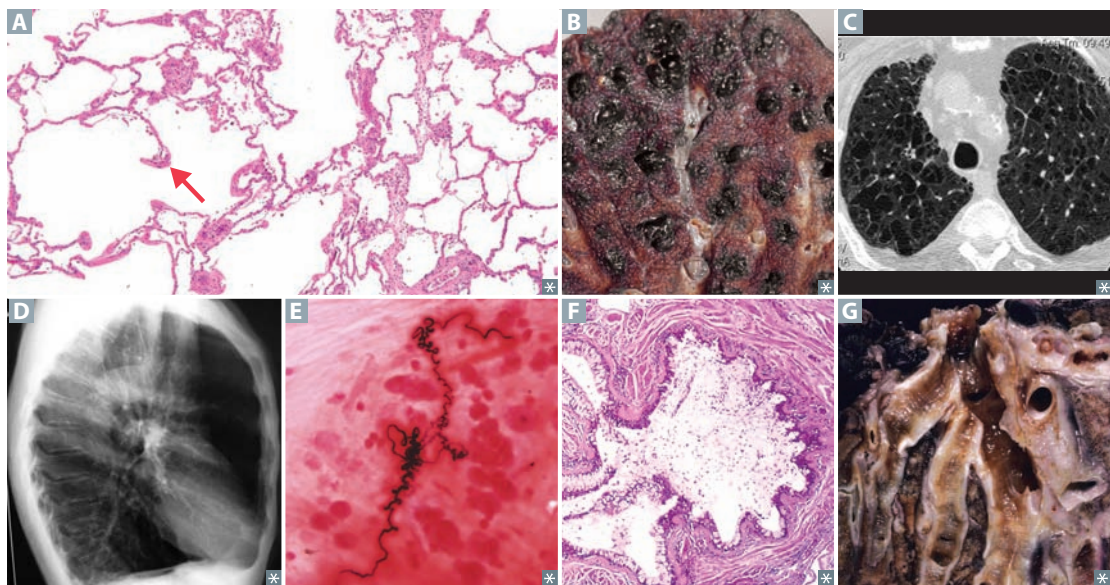
An embolus moves like a **FAT BAT**.



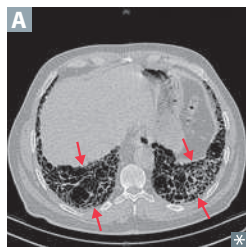
Obstructive lung diseases

Obstruction of air flow resulting in air trapping in lungs. Airways close prematurely at high lung volumes → ↑ RV and ↑ FRC, ↑ TLC. PFTs: ↓↓ FEV₁, ↓ FVC → ↓ FEV₁/FVC ratio (hallmark), \dot{V}/\dot{Q} mismatch. Chronic, hypoxic pulmonary vasoconstriction can lead to cor pulmonale.

TYPE	PATHOLOGY	OTHER
Chronic bronchitis ("blue bloater")	Hyperplasia of mucus-secreting glands in bronchi → Reid index (thickness of mucosal gland layer to thickness of wall between epithelium and cartilage) > 50%.	Productive cough for > 3 (not necessarily consecutive) months per year for > 2 consecutive years. Findings: wheezing, crackles, cyanosis (early-onset hypoxemia due to shunting), late-onset dyspnea, CO ₂ retention (hypercapnia), 2° polycythemia. Chronic complications: pulmonary hypertension, cor pulmonale.
Emphysema ("pink puffer")	Enlargement of air spaces, ↓ recoil, ↑ compliance, ↓ diffusing capacity for CO resulting from destruction of alveolar walls (arrow in A). Two types: <ul style="list-style-type: none"> ▪ Centriacinar—associated with smoking B C. Frequently in upper lobes. ▪ Panacinar—associated with α₁-antitrypsin deficiency. Frequently in lower lobes. 	↑ elastase activity → loss of elastic fibers → ↑ lung compliance. Exhalation through pursed lips to ↑ airway pressure and prevent airway collapse during respiration. Barrel-shaped chest D . X-ray shows ↑ AP diameter, flattened diaphragm, ↑ lung field lucency.
Asthma	Bronchial hyperresponsiveness causes reversible bronchoconstriction. Smooth muscle hypertrophy, Curschmann spirals E (shed epithelium forms whorled mucus plugs), and Charcot-Leyden crystals (eosinophilic, hexagonal, double-pointed, needle-like crystals formed from breakdown of eosinophils in sputum).	Can be triggered by viral URIs, allergens, stress. Clinical diagnosis can be supported by spirometry and methacholine challenge. Findings: cough, wheezing, tachypnea, dyspnea, hypoxemia, ↓ inspiratory/expiratory ratio, pulsus paradoxus, mucus plugging F . Peribronchial cuffing on CXR.
Bronchiectasis	Chronic necrotizing infection of bronchi → permanently dilated airways, purulent sputum, recurrent infections, hemoptysis, digital clubbing.	Associated with bronchial obstruction, poor ciliary motility (eg, smoking, Kartagener syndrome), cystic fibrosis G , allergic bronchopulmonary aspergillosis.



Restrictive lung diseases



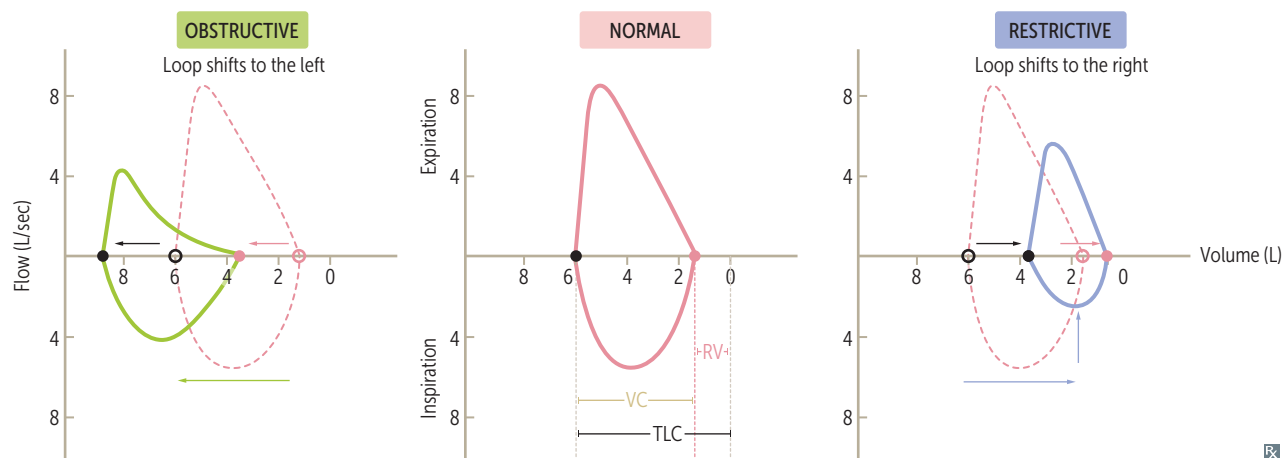
Restricted lung expansion causes ↓ lung volumes (↓ FVC and TLC). PFTs: FEV₁/FVC ratio ≥ 80%.

Types:

- Poor breathing mechanics (extrapulmonary, peripheral hypoventilation, normal A-a gradient):
 - Poor muscular effort—polio, myasthenia gravis, Guillain-Barré syndrome
 - Poor structural apparatus—scoliosis, morbid obesity
- Interstitial lung diseases (pulmonary ↓ diffusing capacity, ↑ A-a gradient):
 - Acute respiratory distress syndrome (ARDS)
 - Neonatal respiratory distress syndrome (NRDS; hyaline membrane disease)
 - Pneumoconioses (eg, anthracosis, silicosis, asbestosis)
 - Sarcoidosis: bilateral hilar lymphadenopathy, noncaseating granuloma; ↑ ACE and Ca²⁺
 - Idiopathic pulmonary fibrosis **A** (repeated cycles of lung injury and wound healing with ↑ collagen deposition, “honeycomb” lung appearance and digital clubbing)
 - Goodpasture syndrome
 - Granulomatosis with polyangiitis (Wegener)
 - Pulmonary Langerhans cell histiocytosis (eosinophilic granuloma)
 - Hypersensitivity pneumonitis
 - Drug toxicity (bleomycin, busulfan, amiodarone, methotrexate)

Flow volume loops

Obstructive lung volumes > normal (↑ TLC, ↑ FRC, ↑ RV); restrictive lung volumes < normal. In both obstructive and restrictive, FEV₁ and FVC are reduced. In obstructive, however, FEV₁ is more dramatically reduced compared to FVC, resulting in a ↓ FEV₁/FVC ratio.



Hypersensitivity pneumonitis

Mixed type III/IV hypersensitivity reaction to environmental antigen → dyspnea, cough, chest tightness, headache. Often seen in farmers and those exposed to birds.

Pneumoconioses

Coal workers' pneumoconiosis, silicosis, and asbestosis → ↑ risk of cor pulmonale, cancer, and Caplan syndrome (rheumatoid arthritis and pneumoconioses with intrapulmonary nodules).

Asbestosis

Associated with shipbuilding, roofing, plumbing. “Ivory white,” calcified, supradiaphragmatic and pleural plaques
A B are pathognomonic of asbestosis.
Risk of bronchogenic carcinoma > risk of mesothelioma.

Affects lower lobes.

Asbestos (ferruginous) bodies are golden-brown fusiform rods resembling dumbbells **C**, found in alveolar septum 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 on histology and therefore occasionally responsive to steroids.

Affects upper lobes.

Coal workers' pneumoconiosis

Prolonged coal dust exposure → macrophages laden with carbon → inflammation and fibrosis.
Also known as black lung disease.

Affects upper lobes.

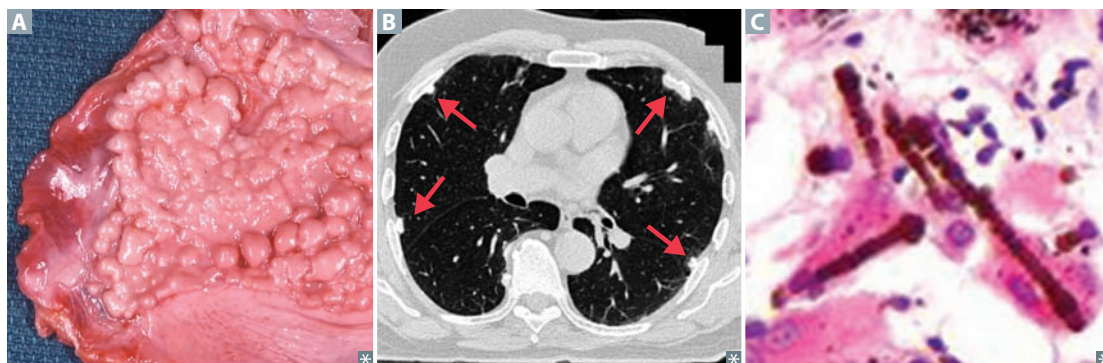
Anthracosis—asymptomatic condition found in many urban dwellers exposed to sooty air.

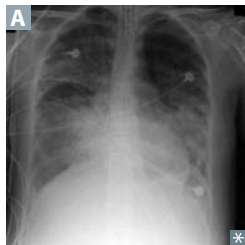
Silicosis

Associated with foundries, sandblasting, 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.

Affects upper lobes.

“Eggshell” calcification of hilar lymph nodes.
Asbestos is from the **roof** (was common in insulation), but affects the **base** (lower lobes).
Silica and coal are from the **base** (earth), but affect the **roof** (upper lobes).



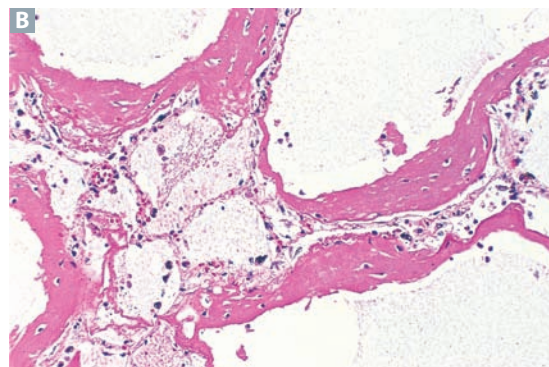
Acute respiratory distress syndrome

Clinical syndrome characterized by acute onset respiratory failure, bilateral lung opacities, \downarrow $\text{PaO}_2/\text{FiO}_2$, no evidence of HF/fluid overload.

SPARTAS: Sepsis, Pancreatitis, Pneumonia, Aspiration, uRemia, Trauma, Amniotic fluid embolism, Shock. Endothelial damage \rightarrow \uparrow alveolar capillary permeability \rightarrow protein-rich leakage into alveoli \rightarrow diffuse alveolar damage and noncardiogenic pulmonary edema (normal PCWP) **A**.

Results in formation of intra-alveolar hyaline membranes **B**. Initial damage due to release of neutrophilic substances toxic to alveolar wall, activation of coagulation cascade, and oxygen-derived free radicals.

Management: mechanical ventilation with low tidal volumes, address underlying cause.

**Sleep apnea**

Repeated cessation of breathing $>$ 10 seconds during sleep \rightarrow disrupted sleep \rightarrow daytime somnolence. Normal PaO_2 during the day.

Nocturnal hypoxia \rightarrow systemic/pulmonary hypertension, arrhythmias (atrial fibrillation/flutter), sudden death.

Hypoxia \rightarrow \uparrow EPO release \rightarrow \uparrow erythropoiesis.

Obstructive sleep apnea

Respiratory effort against airway obstruction. Associated with obesity, loud snoring. Caused by excess parapharyngeal tissue in adults, adenotonsillar hypertrophy in children. Treatment: weight loss, CPAP, surgery.

Central sleep apnea

No respiratory effort due to **CNS** injury/toxicity, HF, opioids.

Obesity hypoventilation syndrome

Obesity ($\text{BMI} \geq 30 \text{ kg/m}^2$) \rightarrow hypoventilation (\downarrow respiratory rate) \rightarrow \downarrow PaO_2 and \uparrow PaCO_2 during sleep; \uparrow PaCO_2 during waking hours (retention).

Pulmonary hypertension

Normal mean pulmonary artery pressure = 10–14 mm Hg; pulmonary hypertension \geq 25 mm Hg at rest. Results in arteriosclerosis, medial hypertrophy, intimal fibrosis of pulmonary arteries. Course: severe respiratory distress \rightarrow cyanosis and RVH \rightarrow death from decompensated cor pulmonale.

ETIOLOGIES

Pulmonary arterial hypertension

Idiopathic PAH.
Heritable PAH—often due to an inactivating mutation in *BMPR2* gene (normally inhibits vascular smooth muscle proliferation); poor prognosis.
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 (eg, mitral regurgitation).

Lung diseases or hypoxia

Destruction of lung parenchyma (eg, COPD), hypoxemic vasoconstriction (eg, obstructive sleep apnea, living in high altitude).

Chronic thromboembolic

Recurrent microthrombi \rightarrow \downarrow cross-sectional area of pulmonary vascular bed.

Multifactorial

Causes include hematologic, systemic, and metabolic disorders.

Lung—physical findings

ABNORMALITY	BREATH SOUNDS	PERCUSSION	FREMITUS	TRACHEAL DEVIATION
Pleural effusion	\downarrow	Dull	\downarrow	— or away from side of lesion (if large)
Atelectasis (bronchial obstruction)	\downarrow	Dull	\downarrow	Toward side of lesion
Simple pneumothorax	\downarrow	Hyperresonant	\downarrow	—
Tension pneumothorax	\downarrow	Hyperresonant	\downarrow	Away from side of lesion
Consolidation (lobar pneumonia, pulmonary edema)	Bronchial breath sounds; late inspiratory crackles	Dull	\uparrow	—

Pleural effusions

Excess accumulation of fluid between pleural layers **A** → restricted lung expansion during inspiration. Can be treated with thoracentesis to remove fluid **B**.

Transudate

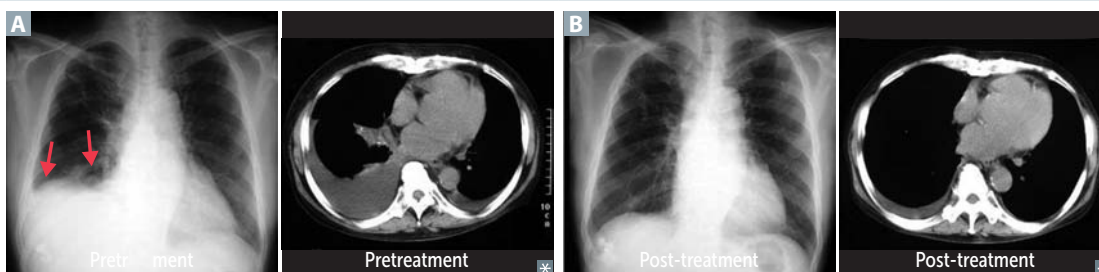
↓ protein content. Due to ↑ hydrostatic pressure (eg, HF) or ↓ oncotic pressure (eg, nephrotic syndrome, cirrhosis).

Exudate

↑ protein content, cloudy. Due to malignancy, pneumonia, collagen vascular disease, trauma (occurs in states of ↑ vascular permeability). Must be drained due to risk of infection.

Lymphatic

Also known as chylothorax. Due to thoracic duct injury from trauma or malignancy. Milky-appearing fluid; ↑ triglycerides.

**Pneumothorax**

Accumulation of air in pleural space **A**. Unilateral chest pain and dyspnea, unilateral chest expansion, ↓ tactile fremitus, hyperresonance, 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.

Secondary spontaneous pneumothorax

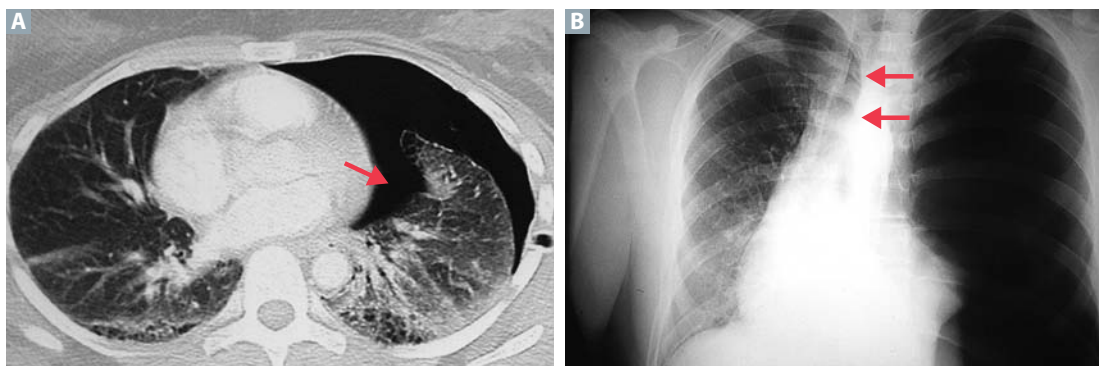
Due to diseased lung (eg, bullae in emphysema, infections), mechanical ventilation with use of high pressures → barotrauma.

Traumatic pneumothorax

Caused by blunt (eg, rib fracture) or penetrating (eg, gunshot) trauma.

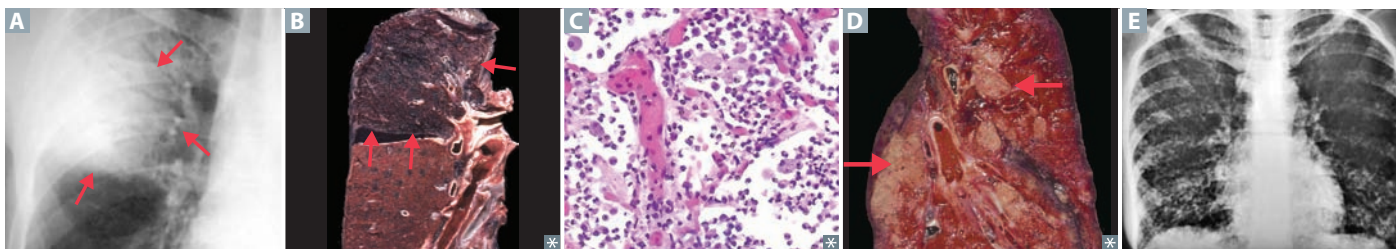
Tension pneumothorax

Can be any of the above. Air enters pleural space but cannot exit. Increasing trapped air → tension pneumothorax. Trachea deviates away from affected lung **B**. Needs immediate needle decompression and chest tube placement.

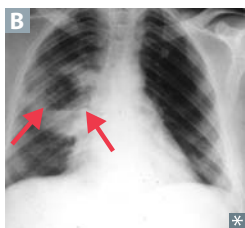


Pneumonia

TYPE	TYPICAL ORGANISMS	CHARACTERISTICS
Lobar	<i>S pneumoniae</i> most frequently, also <i>Legionella</i> , <i>Klebsiella</i>	Intra-alveolar exudate → consolidation A ; may involve entire lobe B or lung.
Bronchopneumonia	<i>S pneumoniae</i> , <i>S aureus</i> , <i>H influenzae</i> , <i>Klebsiella</i>	Acute inflammatory infiltrates C from bronchioles into adjacent alveoli; patchy distribution involving ≥ 1 lobe D .
Interstitial (atypical) pneumonia	<i>Mycoplasma</i> , <i>Chlamydia</i> , <i>Legionella</i> , viruses (RSV, CMV, influenza, adenovirus)	Diffuse patchy inflammation localized to interstitial areas at alveolar walls; diffuse distribution involving ≥ 1 lobe E . Generally follows a more indolent course (“walking” pneumonia).



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).

Treatment: clindamycin.

Air-fluid levels **B** often seen on CXR. Fluid levels common in cavities; presence suggests cavitation. Due to anaerobes (eg, *Bacteroides*, *Fusobacterium*, *Peptostreptococcus*) or *S aureus*. Lung abscess 2° to aspiration is most often found in right lung. Location depends on patient's position during aspiration:

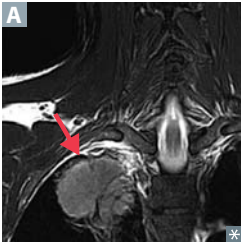
- Upright → basal segments of right lower lobe
- Supine → posterior segments of right upper lobe or superior segment of right lower lobe

Mesothelioma

Malignancy of the pleura associated with asbestosis. May result in hemorrhagic pleural effusion (exudative), pleural thickening.

Psammoma bodies seen on histology. Cytokeratin and calretinin ⊕ in almost all mesotheliomas, ⊖ in most carcinomas. Smoking not a risk factor.

Pancoast tumor (superior sulcus tumor)

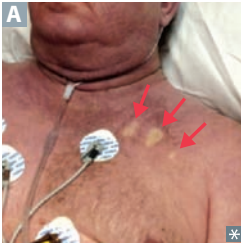


Carcinoma that occurs in the apex of lung **A** may cause Pancoast syndrome by invading cervical sympathetic chain.

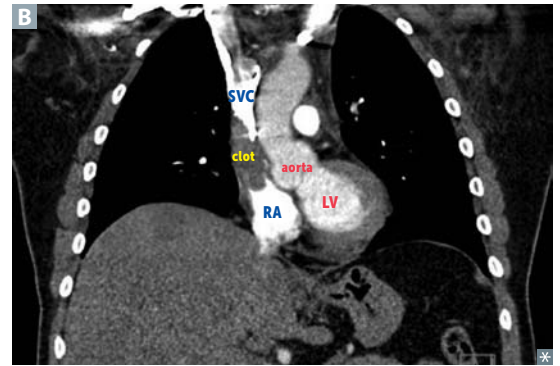
Compression of locoregional structures may cause array of findings:

- Recurrent laryngeal nerve → hoarseness
- Superior cervical ganglion → Horner syndrome (ipsilateral ptosis, miosis, anhidrosis)
- Superior vena cava → SVC syndrome
- Sensorimotor deficit

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, 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.



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: adrenals, brain, bone (pathologic fracture), liver (jaundice, hepatomegaly).

In the lung, metastases (usually multiple lesions) are more common than 1° neoplasms. Most often from breast, colon, prostate, and bladder cancer.

SPHERE of complications:

Superior vena cava syndrome

Pancoast tumor

Horner syndrome

Endocrine (paraneoplastic)

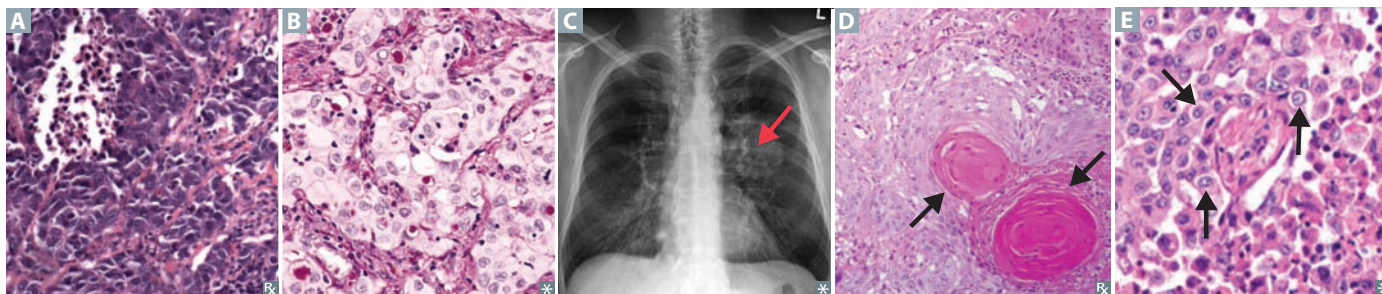
Recurrent laryngeal nerve compression (hoarseness)

Effusions (pleural or pericardial)

Risk factors include smoking, secondhand smoke, radon, asbestos, family history.

Squamous and **S**mall cell carcinomas are **S**entral (central) and often caused by **S**moking.

TYPE	LOCATION	CHARACTERISTICS	HISTOLOGY
Small cell			
Small cell (oat cell) carcinoma	Central	Undifferentiated → very aggressive. May produce ACTH (Cushing syndrome), SIADH , or Antibodies against presynaptic Ca^{2+} 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 ⊕.
Non-small cell			
Adenocarcinoma	Peripheral	Most common lung cancer in nonsmokers and overall (except for metastases). 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. Bronchial carcinoid and bronchioloalveolar cell carcinoma have lesser association with smoking.	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	C entral	Hilar mass arising from bronchus C ; C avitation; C igarettes; hyper C alcemia (produces PTHrP).	Keratin pearls D and intercellular bridges.
Large cell carcinoma	Peripheral	Highly anaplastic undifferentiated tumor; poor prognosis. Less responsive to chemotherapy; removed surgically.	Pleomorphic giant cells E . Can secrete β-hCG.
Bronchial carcinoid tumor	—	Excellent prognosis; metastasis rare. Symptoms due to mass effect or carcinoid syndrome (flushing, diarrhea, wheezing).	Nests of neuroendocrine cells; chromogranin A ⊕.



▶ RESPIRATORY—PHARMACOLOGY

Antihistamines	Reversible inhibitors of H ₁ histamine receptors.	
First generation	Diphenhydramine, dimenhydrinate, chlorpheniramine.	Names contain “-en/-ine” or “-en/-ate.”
CLINICAL USES	Allergy, motion sickness, sleep aid.	
ADVERSE EFFECTS	Sedation, antimuscarinic, anti- α -adrenergic.	
Second generation	Loratadine, fexofenadine, desloratadine, cetirizine.	Names usually end in “-adine.”
CLINICAL USES	Allergy.	
ADVERSE EFFECTS	Far less sedating than 1st generation because of ↓ entry into CNS.	

Expectorants

Guaifenesin	Expectorant—thins respiratory secretions; does not suppress cough reflex.	
N-acetylcysteine	Mucolytic—liquefies mucus in COPD patients by disrupting disulfide bonds. Also used as an antidote for acetaminophen overdose.	

Dextromethorphan Antitussive (antagonizes NMDA glutamate receptors). Synthetic codeine analog. Has mild opioid effect when used in excess. Naloxone can be given for overdose. Mild abuse potential. May cause serotonin syndrome if combined with other serotonergic agents.

Pseudoephedrine, phenylephrine

MECHANISM	α -adrenergic agonists, used as nasal decongestants.	
CLINICAL USE	Reduce hyperemia, edema, nasal congestion; open obstructed eustachian tubes. Pseudoephedrine also illicitly used to make methamphetamine.	
ADVERSE EFFECTS	Hypertension. Can also cause CNS stimulation/anxiety (pseudoephedrine).	

Pulmonary hypertension drugs

DRUG	MECHANISM	CLINICAL NOTES
BosENtan	Competitively antagonizes EN dothelin-1 receptors → ↓ pulmonary vascular resistance.	Hepatotoxic (monitor LFTs).
Sildenafil	Inhibits cGMP PDE-5 and prolongs vasodilatory effect of nitric oxide.	Also used to treat erectile dysfunction.
Epoprostenol, iloprost	PGI ₂ (prostacyclin) with direct vasodilatory effects on pulmonary and systemic arterial vascular beds. Inhibits platelet aggregation.	Side effects: flushing, jaw pain.

Asthma drugs

Bronchoconstriction is mediated by (1) inflammatory processes and (2) parasympathetic tone; therapy is directed at these 2 pathways.

 β_2 -agonists

Albuterol—relaxes bronchial smooth muscle (short acting β_2 -agonist). Used during acute exacerbation.

Salmeterol, formoterol—long-acting agents for prophylaxis. Adverse effects are tremor and arrhythmia.

Inhaled corticosteroids

Fluticasone, budesonide—inhibit the synthesis of virtually all cytokines. Inactivate NF- κ B, the transcription factor that induces production of TNF- α and other inflammatory agents. 1st-line therapy for chronic asthma.

Muscarinic antagonists

Ipratropium—competitively blocks muscarinic receptors, preventing bronchoconstriction. Also used for COPD. Tiotropium is long acting.

Antileukotrienes

Montelukast, zafirlukast—block leukotriene receptors (CysLT1). Especially good for aspirin-induced asthma.

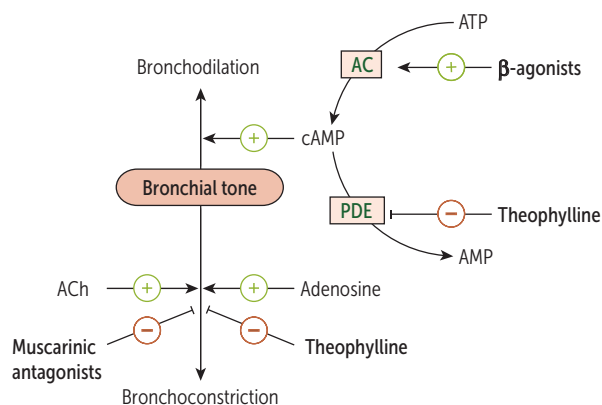
Zileuton—5-lipoxygenase pathway inhibitor. Blocks conversion of arachidonic acid to leukotrienes. Hepatotoxic.

Anti-IgE monoclonal therapy

Omalizumab—binds mostly unbound serum IgE and blocks binding to Fc ϵ RI. Used in allergic asthma with \uparrow IgE levels resistant to inhaled steroids and long-acting β_2 -agonists.

Methylxanthines

Theophylline—likely causes bronchodilation by inhibiting phosphodiesterase \rightarrow \uparrow cAMP levels due to \downarrow cAMP hydrolysis. Usage is limited because of narrow therapeutic index (cardiotoxicity, neurotoxicity); metabolized by cytochrome P-450. Blocks actions of adenosine.



Exposure to antigen
(dust, pollen, etc)

— Avoidance

Antigen and IgE on mast cells — Omalizumab

— Steroids

Mediators
(leukotrienes, histamine, etc)

β -agonists
Theophylline
Muscarinic
antagonists

— Steroids
Antileukotrienes

Early response:
bronchoconstriction

Late response:
inflammation

Symptoms

Bronchial
hyperreactivity

Methacholine

Muscarinic receptor (M_3) agonist. Used in bronchial challenge test to help diagnose asthma.

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 of diseases with their clinical findings, treatments, and pathophysiology. They serve as a quick review before the exam to tune your senses to commonly tested cases.

▶ Classic Presentations	630
▶ Classic Labs/ Findings	634
▶ Classic/Relevant Treatments	638
▶ Key Associations	641
▶ Equation Review	646

▶ CLASSIC PRESENTATIONS

CLINICAL PRESENTATION	DIAGNOSIS/DISEASE
Abdominal pain, ascites, hepatomegaly	Budd-Chiari syndrome (posthepatic venous thrombosis)
Abdominal pain, diarrhea, leukocytosis, recent antibiotic use	<i>Clostridium difficile</i> infection
Achilles tendon xanthoma	Familial hypercholesterolemia (↓ LDL receptor signaling)
Adrenal hemorrhage, hypotension, DIC	Waterhouse-Friderichsen syndrome (meningococemia)
Anaphylaxis following blood transfusion	IgA deficiency
Anterior “drawer sign” ⊕	Anterior cruciate ligament injury
Arachnodactyly, lens dislocation (upward), aortic dissection, hyperflexible joints	Marfan syndrome (fibrillin defect)
Athlete with polycythemia	2° to erythropoietin injection
Back pain, fever, night sweats	Pott disease (vertebral TB)
Bilateral acoustic schwannomas	Neurofibromatosis type 2
Bilateral hilar adenopathy, uveitis	Sarcoidosis (noncaseating granulomas)
Black eschar on face of patient with diabetic ketoacidosis	<i>Mucor</i> or <i>Rhizopus</i> fungal infection
Blue sclera	Osteogenesis imperfecta (type I collagen defect)
Bluish line on gingiva	Burton line (lead poisoning)
Bone pain, bone enlargement, arthritis	Paget disease of bone (↑ osteoblastic and osteoclastic activity)
Bounding pulses, wide pulse pressure, diastolic heart murmur, head bobbing	Aortic regurgitation
“Butterfly” facial rash and Raynaud phenomenon in a young female	Systemic lupus erythematosus
Café-au-lait spots, Lisch nodules (iris hamartoma), cutaneous neurofibromas, pheochromocytomas, optic gliomas	Neurofibromatosis type I
Café-au-lait spots (unilateral), polyostotic fibrous dysplasia, precocious puberty, multiple endocrine abnormalities	McCune-Albright syndrome (mosaic G-protein signaling mutation)
Calf pseudohypertrophy	Muscular dystrophy (most commonly Duchenne, due to X-linked recessive frameshift mutation of dystrophin gene)
Cervical lymphadenopathy, desquamating rash, coronary aneurysms, red conjunctivae and tongue, hand-foot changes	Kawasaki disease (treat with IVIG and aspirin)
“Cherry-red spots” on macula	Tay-Sachs (ganglioside accumulation) or Niemann-Pick (sphingomyelin accumulation), central retinal artery occlusion
Chest pain on exertion	Angina (stable: with moderate exertion; unstable: with minimal exertion or at rest)
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)
Chest pain with ST depressions on EKG	Unstable angina (⊖ troponins) or NSTEMI (⊕ troponins)
Child uses arms to stand up from squat	Duchenne muscular dystrophy (Gowers sign)
Child with fever later develops red rash on face that spreads to body	Erythema infectiosum/fifth disease (“slapped cheeks” appearance, caused by parvovirus B19)
Chorea, dementia, caudate degeneration	Huntington disease (autosomal dominant CAG repeat expansion)
Chorioretinitis, hydrocephalus, intracranial calcifications	Congenital toxoplasmosis

CLINICAL PRESENTATION	DIAGNOSIS/DISEASE
Chronic exercise intolerance with myalgia, fatigue, painful cramps, myoglobinuria	McArdle disease (skeletal muscle glycogen phosphorylase deficiency)
Cold intolerance	Hypothyroidism
Conjugate horizontal gaze palsy, horizontal diplopia	Internuclear ophthalmoplegia (damage to MLF; may be unilateral or bilateral)
Continuous “machine-like” heart murmur	PDA (close with indomethacin; keep open with PGE analogs)
Cutaneous/dermal edema due to connective tissue deposition	Myxedema (caused by hypothyroidism, Graves disease [pretibial])
Cutaneous flushing, diarrhea, bronchospasm	Carcinoid syndrome (right-sided cardiac valvular lesions, ↑ 5-HIAA)
Dark purple skin/mouth nodules in a patient with AIDS	Kaposi sarcoma, associated with HHV-8
Deep, labored breathing/hyperventilation	Diabetic ketoacidosis (Kussmaul respirations)
Dermatitis, dementia, diarrhea	Pellagra (niacin [vitamin B ₃] deficiency)
Dilated cardiomyopathy, edema, alcoholism or malnutrition	Wet beriberi (thiamine [vitamin B ₁] deficiency)
Dog or cat bite resulting in infection	<i>Pasteurella multocida</i> (cellulitis at inoculation site)
Dry eyes, dry mouth, arthritis	Sjögren syndrome (autoimmune destruction of exocrine glands)
Dysphagia (esophageal webs), glossitis, iron deficiency anemia	Plummer-Vinson syndrome (may progress to esophageal squamous cell carcinoma)
Elastic skin, hypermobility of joints, ↑ bleeding tendency	Ehlers-Danlos syndrome (type V collagen defect, type III collagen defect seen in vascular subtype of ED)
Enlarged, hard left supraclavicular node	Virchow node (abdominal metastasis)
Episodic vertigo, tinnitus, hearing loss	Meniere disease
Erythroderma, lymphadenopathy, hepatosplenomegaly, atypical T cells	Mycosis fungoides (cutaneous T-cell lymphoma) or Sézary syndrome (mycosis fungoides + malignant T cells in blood)
Facial muscle spasm upon tapping	Chvostek sign (hypocalcemia)
Fat, female, forty, and fertile	Cholelithiasis (gallstones)
Fever, chills, headache, myalgia following antibiotic treatment for syphilis	Jarisch-Herxheimer reaction (rapid lysis of spirochetes results in endotoxin release)
Fever, cough, conjunctivitis, coryza, diffuse rash	Measles
Fever, night sweats, weight loss	B symptoms (staging) of lymphoma
Fibrous plaques in soft tissue of penis with abnormal curvature	Peyronie disease (connective tissue disorder)
Golden brown rings around peripheral cornea	Wilson disease (Kayser-Fleischer rings due to copper accumulation)
Gout, intellectual disability, self-mutilating behavior in a boy	Lesch-Nyhan syndrome (HGPRT deficiency, X-linked recessive)
Hamartomatous GI polyps, hyperpigmentation of mouth/feet/hands/genitalia	Peutz-Jeghers syndrome (inherited, benign polyposis can cause bowel obstruction; ↑ cancer risk, mainly GI)
Hepatosplenomegaly, pancytopenia, osteoporosis, aseptic necrosis of femoral head, bone crises	Gaucher disease (glucocerebrosidase deficiency)

CLINICAL PRESENTATION	DIAGNOSIS/DISEASE
Hereditary nephritis, sensorineural hearing loss, cataracts	Alport syndrome (mutation in collagen IV)
Hyperphagia, hypersexuality, hyperorality, hyperdocility	Klüver-Bucy syndrome (bilateral amygdala lesion)
Hyperreflexia, hypertonia, Babinski sign present	UMN damage
Hyporeflexia, hypotonia, atrophy, fasciculations	LMN damage
Hypoxemia, polycythemia, hypercapnia	Chronic bronchitis (hyperplasia of mucous cells, “blue bloater”)
Indurated, ulcerated genital lesion	Nonpainful: chancre (1° syphilis, <i>Treponema pallidum</i>) Painful, with exudate: chancroid (<i>Haemophilus ducreyi</i>)
Infant with cleft lip/palate, microcephaly or holoprosencephaly, polydactyly, cutis aplasia	Patau syndrome (trisomy 13)
Infant with hypoglycemia, hepatomegaly	Cori disease (debranching enzyme deficiency) or Von Gierke disease (glucose-6-phosphatase deficiency, more severe)
Infant with microcephaly, rocker-bottom feet, clenched hands, and structural heart defect	Edwards syndrome (trisomy 18)
Jaundice, palpable distended non-tender gallbladder	Courvoisier sign (distal malignant obstruction of biliary tree)
Large rash with bull’s-eye appearance	Erythema chronicum migrans from <i>Ixodes</i> tick bite (Lyme disease: <i>Borrelia</i>)
Lucid interval after traumatic brain injury	Epidural hematoma (middle meningeal artery rupture)
Male child, recurrent infections, no mature B cells	Bruton disease (X-linked agammaglobulinemia)
Mucosal bleeding and prolonged bleeding time	Glanzmann thrombasthenia (defect in platelet aggregation due to lack of GpIIb/IIIa)
Muffled heart sounds, distended neck veins, hypotension	Beck triad of cardiac tamponade
Multiple colon polyps, osteomas/soft tissue tumors, impacted/supernumerary teeth	Gardner syndrome (subtype of FAP)
Myopathy (infantile hypertrophic cardiomyopathy), exercise intolerance	Pompe disease (lysosomal α -1,4-glucosidase deficiency)
Neonate with arm paralysis following difficult birth	Erb-Duchenne palsy (superior trunk [C5–C6] brachial plexus injury: “waiter’s tip”)
No lactation postpartum, absent menstruation, cold intolerance	Sheehan syndrome (pituitary infarction)
Nystagmus, intention tremor, scanning speech, bilateral internuclear ophthalmoplegia	Multiple sclerosis
Painful blue fingers/toes, hemolytic anemia	Cold agglutinin disease (autoimmune hemolytic anemia caused by <i>Mycoplasma pneumoniae</i> , infectious mononucleosis, CLL)
Painful fingers/toes changing color from blue to white to red with cold or stress	Raynaud phenomenon (vasospasm in extremities)
Painful, raised red lesions on pads of fingers/toes	Osler nodes (infective endocarditis, immune complex deposition)

CLINICAL PRESENTATION	DIAGNOSIS/DISEASE
Painless erythematous lesions on palms and soles	Janeway lesions (infective endocarditis, septic emboli/microabscesses)
Painless jaundice	Cancer of the pancreatic head obstructing bile duct
Palpable purpura on buttocks/legs, joint pain, abdominal pain (child), hematuria	Henoch-Schönlein purpura (IgA vasculitis affecting skin and kidneys)
Pancreatic, pituitary, parathyroid tumors	MEN 1 (autosomal dominant)
Periorbital and/or peripheral edema, proteinuria (> 3.5g/day), hypoalbuminemia, hypercholesterolemia	Nephrotic syndrome
Pink complexion, dyspnea, hyperventilation	Emphysema (“pink puffer,” centriacinar [smoking] or panacinar [α_1 -antitrypsin deficiency])
Polyuria, renal tubular acidosis type II, growth failure, electrolyte imbalances, hypophosphatemic rickets	Fanconi syndrome (multiple combined dysfunction of the proximal convoluted tubule)
Pruritic, purple, polygonal planar papules and plaques (6 P’s)	Lichen planus
Ptosis, miosis, anhidrosis	Horner syndrome (sympathetic chain lesion)
Pupil accommodates but doesn’t react	Neurosyphilis (Argyll Robertson pupil)
Rapidly progressive limb weakness that ascends following GI/upper respiratory infection	Guillain-Barré syndrome (acute inflammatory demyelinating polyradiculopathy subtype)
Rash on palms and soles	Coxsackie A, 2° syphilis, Rocky Mountain spotted fever
Recurrent cold (noninflamed) abscesses, unusual eczema, high serum IgE	Hyper-IgE syndrome (Job syndrome: neutrophil chemotaxis abnormality)
Red “currant jelly” sputum in alcoholic or diabetic patients	<i>Klebsiella pneumoniae</i> pneumonia
Red “currant jelly” stools	Acute mesenteric ischemia (adults), intussusception (children)
Red, itchy, swollen rash of nipple/areola	Paget disease of the breast (sign of underlying neoplasm)
Red urine in the morning, fragile RBCs	Paroxysmal nocturnal hemoglobinuria
Renal cell carcinoma (bilateral), hemangioblastomas, angiomatosis, pheochromocytoma	von Hippel-Lindau disease (dominant tumor suppressor gene mutation)
Resting tremor, rigidity, akinesia, postural instability, shuffling gait	Parkinson disease (loss of dopaminergic neurons in substantia nigra pars compacta)
Retinal hemorrhages with pale centers	Roth spots (bacterial endocarditis)
Severe jaundice in neonate	Crigler-Najjar syndrome (congenital unconjugated hyperbilirubinemia)
Severe RLQ pain with palpation of LLQ	Rovsing sign (acute appendicitis)
Severe RLQ pain with deep tenderness	McBurney sign (acute appendicitis)
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)
Single palmar crease	Down syndrome
Situs inversus, chronic sinusitis, bronchiectasis, infertility	Kartagener syndrome (dynein arm defect affecting cilia)
Skin hyperpigmentation, hypotension, fatigue	1° adrenocortical insufficiency (eg, Addison disease) causes ↑ ACTH and ↑ α -MSH production)
Slow, progressive muscle weakness in boys	Becker muscular dystrophy (X-linked missense mutation in dystrophin; less severe than Duchenne)

CLINICAL PRESENTATION	DIAGNOSIS/DISEASE
Small, irregular red spots on buccal/lingual mucosa with blue-white centers	Koplik spots (measles [rubeola] virus)
Smooth, moist, painless, wart-like white lesions on genitals	Condylomata lata (2° syphilis)
Splinter hemorrhages in fingernails	Bacterial endocarditis
“Strawberry tongue”	Scarlet fever, Kawasaki disease
Streak ovaries, congenital heart disease, horseshoe kidney, cystic hygroma at birth, short stature, webbed neck, lymphedema	Turner syndrome (45,XO)
Sudden swollen/painful big toe joint, tophi	Gout/podagra (hyperuricemia)
Swollen gums, mucosal bleeding, poor wound healing, petechiae	Scurvy (vitamin C deficiency: can't hydroxylate proline/lysine for collagen synthesis)
Swollen, hard, painful finger joints	Osteoarthritis (osteophytes on PIP [Bouchard nodes], DIP [Heberden nodes])
Systolic ejection murmur (crescendo-decrescendo)	Aortic stenosis
Telangiectasias, recurrent epistaxis, skin discoloration, arteriovenous malformations, GI bleeding, hematuria	Osler-Weber-Rendu syndrome
Thyroid and parathyroid tumors, pheochromocytoma	MEN 2A (autosomal dominant <i>RET</i> mutation)
Thyroid tumors, pheochromocytoma, ganglioneuromatosis	MEN 2B (autosomal dominant <i>RET</i> mutation)
Toe extension/fanning upon plantar scrape	Babinski sign (UMN lesion)
Unilateral facial drooping involving forehead	LMN facial nerve (CN VII) palsy; UMN lesions spare the forehead
Urethritis, conjunctivitis, arthritis in a male	Reactive arthritis associated with HLA-B27
Vascular birthmark (port-wine stain) of the face	Nevus flammeus (benign, but associated with Sturge-Weber syndrome)
Vomiting blood following gastroesophageal lacerations	Mallory-Weiss syndrome (alcoholic and bulimic patients)
Weight loss, diarrhea, arthritis, fever, adenopathy	Whipple disease (<i>Tropheryma whipplei</i>)
“Worst headache of my life”	Subarachnoid hemorrhage

▶ CLASSIC LABS/FINDINGS

LAB/DIAGNOSTIC FINDING	DIAGNOSIS/DISEASE
↑ AFP in amniotic fluid/maternal serum	Dating error, anencephaly, spina bifida (neural tube defects)
Anticentromere antibodies	Scleroderma (CREST)
Anti-desmoglein (anti-desmosome) antibodies	Pemphigus vulgaris (blistering)
Anti-glomerular basement membrane antibodies	Goodpasture syndrome (glomerulonephritis and hemoptysis)
Antihistone antibodies	Drug-induced SLE (eg, hydralazine, isoniazid, phenytoin, procainamide)
Anti-IgG antibodies	Rheumatoid arthritis (systemic inflammation, joint pannus, boutonnière deformity)
Antimitochondrial antibodies (AMAs)	1° biliary cirrhosis (female, cholestasis, portal hypertension)

LAB/DIAGNOSTIC FINDING	DIAGNOSIS/DISEASE
Antineutrophil cytoplasmic antibodies (ANCAs)	Microscopic polyangiitis and eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome) (MPO-ANCA/p-ANCA); granulomatosis with polyangiitis (Wegener; PR3-ANCA/c-ANCA)
Antinuclear antibodies (ANAs: anti-Smith and anti-dsDNA)	SLE (type III hypersensitivity)
Antiplatelet antibodies	Idiopathic thrombocytopenic purpura
Anti-topoisomerase antibodies	Diffuse systemic scleroderma
Anti-transglutaminase/anti-gliadin/anti-endomysial antibodies	Celiac disease (diarrhea, weight loss)
“Apple core” lesion on barium enema x-ray	Colorectal cancer (usually left-sided)
Atypical lymphocytes	EBV
Azurophilic peroxidase ⊕ granular inclusions in granulocytes and myeloblasts	Auer rods (AML, especially the promyelocytic [M3] type)
Bacitracin response	Sensitive: <i>S pyogenes</i> (group A); resistant: <i>S agalactiae</i> (group B)
“Bamboo spine” on x-ray	Ankylosing spondylitis (chronic inflammatory arthritis: HLA-B27)
Basophilic nuclear remnants in RBCs	Howell-Jolly bodies (due to splenectomy or nonfunctional spleen)
Basophilic stippling of RBCs	Lead poisoning or sideroblastic anemia
Bloody or yellow tap on lumbar puncture	Subarachnoid hemorrhage
“Boot-shaped” heart on x-ray	Tetralogy of Fallot (due to RVH)
Branching gram ⊕ rods with sulfur granules	<i>Actinomyces israelii</i>
Bronchogenic apical lung tumor on imaging	Pancoast tumor (can compress cervical sympathetic chain and cause Horner syndrome)
“Brown” tumor of bone	Hyperparathyroidism or osteitis fibrosa cystica (deposited hemosiderin from hemorrhage gives brown color)
Cardiomegaly with apical atrophy	Chagas disease (<i>Trypanosoma cruzi</i>)
Cellular crescents in Bowman capsule	Rapidly progressive crescentic glomerulonephritis
“Chocolate cyst” of ovary	Endometriosis (frequently involves both ovaries)
Circular grouping of dark tumor cells surrounding pale neurofibrils	Homer-Wright rosettes (neuroblastoma, medulloblastoma)
Colonies of mucoid <i>Pseudomonas</i> in lungs	Cystic fibrosis (autosomal recessive mutation in <i>CFTR</i> gene → fat-soluble vitamin deficiency and mucous plugs)
↓ AFP in amniotic fluid/maternal serum	Down syndrome or other chromosomal abnormalities
Degeneration of dorsal column fibers	Tabes dorsalis (3° syphilis), subacute combined degeneration (dorsal columns, lateral corticospinal, spinocerebellar tracts affected)
“Delta wave” on EKG, short PR interval, supraventricular tachycardia	Wolff-Parkinson-White syndrome (Bundle of Kent bypasses AV node)
Depigmentation of neurons in substantia nigra	Parkinson disease (basal ganglia disorder: rigidity, resting tremor, bradykinesia)
Desquamated epithelium casts in sputum	Curschmann spirals (bronchial asthma; can result in whorled mucous plugs)

LAB/DIAGNOSTIC FINDING	DIAGNOSIS/DISEASE
Disarrayed granulosa cells arranged around collections of eosinophilic fluid	Call-Exner bodies (granulosa cell tumor of the ovary)
Dysplastic squamous cervical cells with “raisinoid” nuclei and hyperchromasia	Koilocytes (HPV: predisposes to cervical cancer)
Electrical alternans (alternating amplitude on EKG)	Pericardial tamponade
Enlarged cells with intranuclear inclusion bodies	“Owl eye” appearance of CMV
Enlarged thyroid cells with ground-glass nuclei with central clearing	“Orphan Annie” eyes nuclei (papillary carcinoma of the thyroid)
Eosinophilic cytoplasmic inclusion in liver cell	Mallory body (alcoholic liver disease)
Eosinophilic cytoplasmic inclusion in neuron	Lewy body (Parkinson disease and Lewy body dementia)
Eosinophilic globule in liver	Councilman body (viral hepatitis, yellow fever), represents hepatocyte undergoing apoptosis
Eosinophilic inclusion bodies in cytoplasm of hippocampal and cerebellar neurons	Negri bodies of rabies
Extracellular amyloid deposition in gray matter of brain	Senile plaques (Alzheimer disease)
Giant B cells with bilobed nuclei with prominent inclusions (“owl’s eye”)	Reed-Sternberg cells (Hodgkin lymphoma)
Glomerulus-like structure surrounding vessel in germ cells	Schiller-Duval bodies (yolk sac tumor)
“Hair on end” (“Crew-cut”) appearance on x-ray	β-thalassemia, sickle cell disease (marrow expansion)
hCG elevated	Choriocarcinoma, hydatidiform mole (occurs with and without embryo, and multiple pregnancy)
Heart nodules (granulomatous)	Aschoff bodies (rheumatic fever)
Heterophile antibodies	Infectious mononucleosis (EBV)
Hexagonal, double-pointed, needle-like crystals in bronchial secretions	Bronchial asthma (Charcot-Leyden crystals: eosinophilic granules)
High level of D-dimers	DVT, PE, DIC
Hilar lymphadenopathy, peripheral granulomatous lesion in middle or lower lung lobes (can calcify)	Ghon complex (1° TB: <i>Mycobacterium bacilli</i>)
“Honeycomb lung” on x-ray or CT	Interstitial pulmonary fibrosis
Hypercoagulability (leading to migrating DVTs and vasculitis)	Trousseau syndrome (adenocarcinoma of pancreas or lung)
Hypersegmented neutrophils	Megaloblastic anemia (B ₁₂ deficiency: neurologic symptoms; folate deficiency: no neurologic symptoms)
Hypertension, hypokalemia, metabolic alkalosis	1° hyperaldosteronism (Conn syndrome)
Hypochromic, microcytic anemia	Iron deficiency anemia, lead poisoning, thalassemia (fetal hemoglobin sometimes present)
Intranuclear eosinophilic droplet-like bodies	Cowdry type A bodies (HSV or VZV)
Iron-containing nodules in alveolar septum	Ferruginous bodies (asbestosis: ↑ chance of mesothelioma)
Keratin pearls on a skin biopsy	Squamous cell carcinoma
Large granules in phagocytes, immunodeficiency	Chédiak-Higashi disease (congenital failure of phagolysosome formation)
“Lead pipe” appearance of colon on abdominal imaging	Ulcerative colitis (loss of haustra)
Linear appearance of IgG deposition on glomerular and alveolar basement membranes	Goodpasture syndrome

LAB/DIAGNOSTIC FINDING	DIAGNOSIS/DISEASE
Low serum ceruloplasmin	Wilson disease (hepatolenticular degeneration)
“Lumpy bumpy” appearance of glomeruli on immunofluorescence	Poststreptococcal glomerulonephritis (due to deposition of IgG, IgM, and C3)
Lytic (“punched-out”) bone lesions on x-ray	Multiple myeloma
Mammary gland (“blue domed”) cyst	Fibrocystic change of the breast
Monoclonal antibody spike	<ul style="list-style-type: none"> ▪ Multiple myeloma (usually IgG or IgA) ▪ Monoclonal gammopathy of undetermined significance (MGUS consequence of aging) ▪ Waldenström (M protein = IgM) macroglobulinemia ▪ Primary amyloidosis
Mucin-filled cell with peripheral nucleus	“Signet ring” (gastric carcinoma)
Narrowing of bowel lumen on barium x-ray	“String sign” (Crohn disease)
Necrotizing vasculitis (lungs) and necrotizing glomerulonephritis	Granulomatosis with polyangiitis (Wegener; PR3-ANCA/c-ANCA) and Goodpasture syndrome (anti-basement membrane antibodies)
Needle-shaped, ⊖ birefringent crystals	Gout (monosodium urate crystals)
Nodular hyaline deposits in glomeruli	Kimmelstiel-Wilson nodules (diabetic nephropathy)
Novobiocin response	Sensitive: <i>S epidermidis</i> ; resistant: <i>S saprophyticus</i>
“Nutmeg” appearance of liver	Chronic passive congestion of liver due to right heart failure or Budd-Chiari syndrome
“Onion skin” periosteal reaction	Ewing sarcoma (malignant small blue cell tumor)
Optochin response	Sensitive: <i>S pneumoniae</i> ; resistant: viridans streptococci (<i>S mutans</i> , <i>S sanguis</i>)
Podocyte fusion or “effacement” on electron microscopy	Minimal change disease (child with nephrotic syndrome)
Polished, “ivory-like” appearance of bone at cartilage erosion	Eburnation (osteoarthritis resulting in bony sclerosis)
Protein aggregates in neurons from hyperphosphorylation of tau protein	Neurofibrillary tangles (Alzheimer disease) and Pick bodies (Pick disease)
Psammoma bodies	Meningiomas, papillary thyroid carcinoma, mesothelioma, papillary serous carcinoma of the endometrium and ovary
Pseudopalisading tumor cells on brain biopsy	Glioblastoma multiforme
Raised periosteum (creating a “Codman triangle”)	Aggressive bone lesion (eg, osteosarcoma, Ewing sarcoma, osteomyelitis)
RBC casts in urine	Glomerulonephritis
Rectangular, crystal-like, cytoplasmic inclusions in Leydig cells	Reinke crystals (Leydig cell tumor)
Recurrent infections, eczema, thrombocytopenia	Wiskott-Aldrich syndrome
Renal epithelial casts in urine	Intrinsic renal failure (eg, ischemia or toxic injury)
Rhomboid crystals, ⊕ birefringent	Pseudogout (calcium pyrophosphate dihydrate crystals)
Rib notching (inferior surface, on x-ray)	Coarctation of the aorta
Ring-enhancing brain lesion on CT/MRI in AIDS	<i>Toxoplasma gondii</i> , CNS lymphoma
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)
Silver-staining spherical aggregation of tau proteins in neurons	Pick bodies (Pick disease: progressive dementia, changes in personality)

LAB/DIAGNOSTIC FINDING	DIAGNOSIS/DISEASE
“Soap bubble” in femur or tibia on x-ray	Giant cell tumor of bone (generally benign)
“Spikes” on basement membrane, “dome-like” subepithelial deposits	Membranous nephropathy (nephrotic syndrome)
Stacks of RBCs	Rouleaux formation (high ESR, multiple myeloma)
“Steeple” sign on frontal CXR	Croup (parainfluenza virus)
Stippled vaginal epithelial cells	“Clue cells” (<i>Gardnerella vaginalis</i>)
<i>Streptococcus bovis</i> bacteremia	Colon cancer
“Tennis racket”-shaped cytoplasmic organelles (EM) in Langerhans cells	Birbeck granules (Langerhans cell histiocytosis)
Thousands of polyps on colonoscopy	Familial adenomatous polyposis (autosomal dominant, mutation of APC gene)
Thrombi made of white/red layers	Lines of Zahn (arterial thrombus, layers of platelets/RBCs)
“Thumb sign” on lateral neck x-ray	Epiglottitis (<i>Haemophilus influenzae</i>)
Thyroid-like appearance of kidney	Chronic pyelonephritis (usually due to recurrent infections)
“Tram-track” appearance of capillary loops of glomerular basement membranes on light microscopy	Membranoproliferative glomerulonephritis
Triglyceride accumulation in liver cell vacuoles	Fatty liver disease (alcoholic or metabolic syndrome)
↑ uric acid levels	Gout, Lesch-Nyhan syndrome, tumor lysis syndrome, loop and thiazide diuretics
“Waxy” casts with very low urine flow	Chronic end-stage renal disease
WBC casts in urine	Acute pyelonephritis
WBCs that look “smudged”	CLL (almost always B cell)
“Wire loop” glomerular capillary appearance on light microscopy	Diffuse proliferative glomerulonephritis (usually seen with lupus)
Yellowish CSF	Xanthochromia (eg, due to subarachnoid hemorrhage)s

▶ CLASSIC/RELEVANT TREATMENTS

CONDITION	COMMON TREATMENT(S)
Absence seizures	Ethosuximide
Acute gout attack	NSAIDs, colchicine, glucocorticoids
Acute promyelocytic leukemia (M3)	All- <i>trans</i> retinoic acid
ADHD	Methylphenidate, CBT, atomoxetine, guanfacine, clonidine
Alcoholism	Disulfiram, acamprosate, naltrexone, supportive care
Alcohol withdrawal	Long-acting benzodiazepines
Anorexia	Nutrition, psychotherapy, mirtazapine
Arrhythmia in damaged cardiac tissue	Class IB antiarrhythmic (lidocaine, mexiletine)
Benign prostatic hyperplasia	α_1 -antagonists, 5 α -reductase inhibitors, PDE-5 inhibitors
Bipolar disorder	Mood stabilizers (eg, lithium, valproic acid, carbamazepine), atypical antipsychotics

CONDITION	COMMON TREATMENT(S)
Breast cancer in postmenopausal woman	Aromatase inhibitor (anastrozole)
Buerger disease	Smoking cessation
Bulimia nervosa	SSRIs
<i>Candida albicans</i>	Topical azoles (vaginitis); nystatin, fluconazole, caspofungin (oral/esophageal); fluconazole, caspofungin, amphotericin B (systemic)
Carcinoid syndrome	Octreotide
<i>Chlamydia trachomatis</i>	Doxycycline (+ ceftriaxone for gonorrhea coinfection), erythromycin eye drops (prophylaxis in infants)
Chronic gout	Xanthine oxidase inhibitors (eg, allopurinol, febuxostat); pegloticase; probenecid
Chronic hepatitis B or C	IFN- α (HBV and HCV); ribavirin, simeprevir, sofosbuvir (HCV)
Chronic myelogenous leukemia	Imatinib
<i>Clostridium botulinum</i>	Antitoxin
<i>Clostridium difficile</i>	Oral metronidazole; if refractory, oral vancomycin
<i>Clostridium tetani</i>	Antitoxin
CMV	Ganciclovir, foscarnet, cidofovir
Crohn disease	Corticosteroids, infliximab, azathioprine
<i>Cryptococcus neoformans</i>	Fluconazole (in AIDS patients)
Cyclophosphamide-induced hemorrhagic cystitis	Mesna
Depression	SSRIs (first-line)
Diabetes insipidus	Desmopressin (central); hydrochlorothiazide, indomethacin, amiloride (nephrogenic)
Diabetes mellitus type 1	Dietary intervention (low carbohydrate) + insulin replacement
Diabetes mellitus type 2	Dietary intervention, oral hypoglycemics, and insulin (if refractory)
Diabetic ketoacidosis	Fluids, insulin, K ⁺
Drug of choice for anticoagulation during pregnancy	Heparin
Enterococci	Vancomycin, aminopenicillins/cephalosporins
Erectile dysfunction	Sildenafil, tadalafil, vardenafil
ER \oplus breast cancer	Tamoxifen
Ethylene glycol/methanol intoxication	Fomepizole (alcohol dehydrogenase inhibitor)
<i>Haemophilus influenzae</i> (B)	Rifampin (prophylaxis)
Generalized anxiety disorder	SSRIs, SNRIs (first line); buspirone (second line)
Granulomatosis with polyangiitis (Wegener)	Cyclophosphamide, corticosteroids
Heparin reversal	Protamine sulfate
HER2/neu \oplus breast cancer	Trastuzumab
Hyperaldosteronism	Spironolactone

CONDITION	COMMON TREATMENT(S)
Hypercholesterolemia	Statin (first-line)
Hypertriglyceridemia	Fibrate
Immediate anticoagulation	Heparin
Infertility	Leuprolide, GnRH (pulsatile), clomiphene
Influenza	Oseltamivir, zanamivir
Kawasaki disease	IVIG, high-dose aspirin
<i>Legionella pneumophila</i>	Macrolides (eg, azithromycin)
Long-term anticoagulation	Warfarin, dabigatran, rivaroxaban and apixaban
Malaria	Chloroquine, mefloquine, atovaquone/proguanil (for blood schizont), primaquine (for liver hypnozoite)
Malignant hyperthermia	Dantrolene
Medical abortion	Mifepristone
Migraine	Abortive therapies (eg, sumatriptan, NSAIDs); prophylaxis (eg, propranolol, topiramate, CCBs, amitriptyline)
Multiple sclerosis	Disease-modifying therapies (eg, β -interferon, natalizumab); for acute flares, use IV steroids
<i>Mycobacterium tuberculosis</i>	RIPE (rifampin, isoniazid, pyrazinamide, ethambutol)
<i>Neisseria gonorrhoeae</i>	Ceftriaxone (add doxycycline to cover likely concurrent <i>C trachomatis</i>)
<i>Neisseria meningitidis</i>	Penicillin/ceftriaxone, rifampin (prophylaxis)
Neural tube defect prevention	Prenatal folic acid
Osteomalacia/rickets	Vitamin D supplementation
Osteoporosis	Calcium/vitamin D supplementation (prophylaxis); bisphosphonates, PTH analogs, SERMs, calcitonin, denosumab (treatment)
Patent ductus arteriosus	Close with indomethacin; keep open with PGE analogs
Pheochromocytoma	α -antagonists (eg, phenoxybenzamine)
<i>Pneumocystis jirovecii</i>	TMP-SMX (prophylaxis and treatment in immunosuppressed patients)
Prolactinoma	Cabergoline/bromocriptine (dopamine agonists)
Prostate adenocarcinoma/uterine fibroids	Leuprolide, GnRH (continuous)
Prostate adenocarcinoma	Flutamide
<i>Pseudomonas aeruginosa</i>	Antipseudomonal penicillins, aminoglycosides, carbapenems
Pulmonary arterial hypertension (idiopathic)	Sildenafil, bosentan, epoprostenol
<i>Rickettsia rickettsii</i>	Doxycycline, chloramphenicol
Schizophrenia (negative symptoms)	Atypical antipsychotics
Schizophrenia (positive symptoms)	Typical and atypical antipsychotics
SIADH	Fluid restriction, IV hypertonic saline, conivaptan/tolvaptan, demeclocycline

CONDITION	COMMON TREATMENT(S)
Sickle cell disease	Hydroxyurea (↑ fetal hemoglobin)
<i>Sporothrix schenckii</i>	Itraconazole, oral potassium iodide
Stable angina	Sublingual nitroglycerin
<i>Staphylococcus aureus</i>	MSSA: nafcillin, oxacillin, dicloxacillin (antistaphylococcal penicillins); MRSA: vancomycin, daptomycin, linezolid, ceftaroline
<i>Streptococcus bovis</i>	Penicillin prophylaxis; evaluation for colon cancer if linked to endocarditis
<i>Streptococcus pneumoniae</i>	Penicillin/cephalosporin (systemic infection, pneumonia), vancomycin (meningitis)
<i>Streptococcus pyogenes</i>	Penicillin prophylaxis
Temporal arteritis	High-dose steroids
Tonic-clonic seizures	Levetiracetam, phenytoin, valproate, carbamazepine
<i>Toxoplasma gondii</i>	Sulfadiazine + pyrimethamine
<i>Treponema pallidum</i>	Penicillin
<i>Trichomonas vaginalis</i>	Metronidazole (patient and partner)
Trigeminal neuralgia (tic douloureux)	Carbamazepine
Ulcerative colitis	5-ASA preparations (eg, mesalamine), 6-mercaptopurine, infliximab, colectomy
UTI prophylaxis	TMP-SMX
Warfarin reversal	Fresh frozen plasma (acute), vitamin K (non-acute)

▶ KEY ASSOCIATIONS

DISEASE/FINDING	MOST COMMON/IMPORTANT ASSOCIATIONS
Actinic (solar) keratosis	Precursor to squamous cell carcinoma
Acute gastric ulcer associated with CNS injury	Cushing ulcer (↑ intracranial pressure stimulates vagal gastric H ⁺ secretion)
Acute gastric ulcer associated with severe burns	Curling ulcer (greatly reduced plasma volume results in sloughing of gastric mucosa)
Age ranges for patient with ALL/CLL/AML/CML	ALL: child, CLL: adult > 60, AML: adult ~ 65, CML: adult 45–85
Alternating areas of transmural inflammation and normal colon	Skip lesions (Crohn disease)
Aortic aneurysm, abdominal	Atherosclerosis
Aortic aneurysm, ascending or arch	3° syphilis (syphilitic aortitis), vasa vasorum destruction
Aortic aneurysm, thoracic	Marfan syndrome (idiopathic cystic medial degeneration)
Aortic dissection	Hypertension
Atrophy of the mammillary bodies	Wernicke encephalopathy (thiamine deficiency causing ataxia, ophthalmoplegia, and confusion)

DISEASE/FINDING	MOST COMMON/IMPORTANT ASSOCIATIONS
Autosplenectomy (fibrosis and shrinkage)	Sickle cell disease (hemoglobin S)
Bacteria associated with gastritis, peptic ulcer disease, and gastric malignancies (eg, adenocarcinoma, MALToma)	<i>H pylori</i>
Bacterial meningitis (adults and elderly)	<i>S pneumoniae</i>
Bacterial meningitis (newborns and kids)	Group B streptococcus/ <i>E coli</i> (newborns), <i>S pneumoniae</i> / <i>N meningitidis</i> (kids/teens)
Bilateral ovarian metastases from gastric carcinoma	Krukenberg tumor (mucin-secreting signet ring cells)
Bleeding disorder with GpIb deficiency	Bernard-Soulier syndrome (defect in platelet adhesion to von Willebrand factor)
Brain tumor (adults)	Supratentorial: metastasis, astrocytoma (including glioblastoma multiforme), meningioma, schwannoma
Brain tumor (kids)	Infratentorial: medulloblastoma (cerebellum) or supratentorial: craniopharyngioma
Breast cancer	Invasive ductal carcinoma
Breast mass	Fibrocystic change, carcinoma (in postmenopausal women)
Breast tumor (benign, young woman)	Fibroadenoma
Cardiac 1° tumor (kids)	Rhabdomyoma, often seen in tuberous sclerosis
Cardiac manifestation of lupus	Marantic/thrombotic endocarditis (nonbacterial)
Cardiac tumor (adults)	Metastasis, myxoma (90% in left atrium; “ball and valve”)
Cerebellar tonsillar herniation	Chiari II malformation
Chronic arrhythmia	Atrial fibrillation (associated with high risk of emboli)
Chronic atrophic gastritis (autoimmune)	Predisposition to gastric carcinoma (can also cause pernicious anemia)
Clear cell adenocarcinoma of the vagina	DES exposure in utero
Congenital adrenal hyperplasia, hypotension	21-hydroxylase deficiency
Congenital cardiac anomaly	VSD
Congenital conjugated hyperbilirubinemia (black liver)	Dubin-Johnson syndrome (inability of hepatocytes to secrete conjugated bilirubin into bile)
Constrictive pericarditis	TB (developing world); idiopathic, viral illness (developed world)
Coronary artery involved in thrombosis	LAD > RCA > circumflex
Cretinism	Iodine deficit/congenital hypothyroidism
Cushing syndrome	<ul style="list-style-type: none"> ▪ Iatrogenic (from corticosteroid therapy) ▪ Adrenocortical adenoma (secretes excess cortisol) ▪ ACTH-secreting pituitary adenoma (Cushing disease) ▪ Paraneoplastic (due to ACTH secretion by tumors)
Cyanosis (early; less common)	Tetralogy of Fallot, transposition of great vessels, truncus arteriosus
Death in CML	Blast crisis
Death in SLE	Lupus nephropathy

DISEASE/FINDING	MOST COMMON/IMPORTANT ASSOCIATIONS
Dementia	Alzheimer disease, multiple infarcts (vascular dementia)
Demyelinating disease in young women	Multiple sclerosis
DIC	Severe sepsis, obstetric complications, cancer, burns, trauma, major surgery, acute pancreatitis, APL
Diverticulum in pharynx	Zenker diverticulum (diagnosed by barium swallow)
Ejection click	Aortic stenosis
Esophageal cancer	Squamous cell carcinoma (worldwide); adenocarcinoma (US)
Food poisoning (exotoxin mediated)	<i>S aureus</i> , <i>B cereus</i>
Gastric cancer	Adenocarcinoma
Glomerulonephritis (adults)	Berger disease (IgA nephropathy)
Gynecologic malignancy	Endometrial carcinoma (most common in US); cervical carcinoma (most common worldwide)
Heart murmur, congenital	Mitral valve prolapse
Heart valve in bacterial endocarditis	Mitral > aortic (rheumatic fever), tricuspid (IV drug abuse)
Helminth infection (US)	<i>Enterobius vermicularis</i> , <i>Ascaris lumbricoides</i>
Hematoma—epidural	Rupture of middle meningeal artery (trauma; lentiform shaped)
Hematoma—subdural	Rupture of bridging veins (crescent shaped)
Hemochromatosis	Multiple blood transfusions or hereditary <i>HFE</i> mutation (can result in heart failure, “bronze diabetes,” and ↑ risk of hepatocellular carcinoma)
Hepatocellular carcinoma	Cirrhotic liver (associated with hepatitis B and C and with alcoholism)
Hereditary bleeding disorder	von Willebrand disease
Hereditary harmless jaundice	Gilbert syndrome (benign congenital unconjugated hyperbilirubinemia)
HLA-B27	Psoriatic arthritis, ankylosing spondylitis, IBD-associated arthritis, reactive arthritis (formerly Reiter syndrome)
HLA-DR3	Diabetes mellitus type 1, SLE, Graves disease, Hashimoto thyroiditis, Addison disease
HLA-DR4	Diabetes mellitus type 1, rheumatoid arthritis, Addison disease
Holosystolic murmur	VSD, tricuspid regurgitation, mitral regurgitation
Hypercoagulability, endothelial damage, blood stasis	Virchow triad (↑ risk of thrombosis)
Hypertension, 2°	Renal artery stenosis, chronic kidney disease (eg, polycystic kidney disease, diabetic nephropathy), hyperaldosteronism
Hypoparathyroidism	Accidental excision during thyroidectomy
Hypopituitarism	Pituitary adenoma (usually benign tumor)
Infection 2° to blood transfusion	Hepatitis C
Infections in chronic granulomatous disease	<i>S aureus</i> , <i>E coli</i> , <i>Aspergillus</i> (catalase ⊕)

DISEASE/FINDING	MOST COMMON/IMPORTANT ASSOCIATIONS
Intellectual disability	Down syndrome, fragile X syndrome
Kidney stones	<ul style="list-style-type: none"> ▪ Calcium = radiopaque ▪ Struvite (ammonium) = radiopaque (formed by urease ⊕ organisms such as <i>Klebsiella</i>, <i>Proteus</i> species, and <i>S saprophyticus</i>) ▪ Uric acid = radiolucent ▪ Cystine = radiolucent
Late cyanotic shunt (uncorrected left to right becomes right to left)	Eisenmenger syndrome (caused by ASD, VSD, PDA; results in pulmonary hypertension/polycythemia)
Liver disease	Alcoholic cirrhosis
Lysosomal storage disease	Gaucher disease
Male cancer	Prostatic carcinoma
Malignancy associated with noninfectious fever	Hodgkin lymphoma
Malignancy (kids)	ALL, medulloblastoma (cerebellum)
Metastases to bone	Prostate, breast > lung > thyroid
Metastases to brain	Lung > breast > genitourinary > melanoma > GI
Metastases to liver	Colon >> stomach, pancreas
Microcytic anemia	Iron deficiency
Mitochondrial inheritance	Disease occurs in both males and females, inherited through females only
Mitral valve stenosis	Rheumatic heart disease
Mixed (UMN and LMN) motor neuron disease	Amyotrophic lateral sclerosis
Myocarditis	Coxsackie B
Nephrotic syndrome (adults)	Focal segmental glomerulosclerosis
Nephrotic syndrome (kids)	Minimal change disease
Neuron migration failure	Kallmann syndrome (hypogonadotropic hypogonadism and anosmia)
Nosocomial pneumonia	<i>S aureus</i> , <i>Pseudomonas</i> , other enteric gram ⊖ rods
Obstruction of male urinary tract	BPH
Opening snap	Mitral stenosis
Opportunistic infection in AIDS	<i>Pneumocystis jirovecii</i> pneumonia
Osteomyelitis	<i>S aureus</i> (most common overall)
Osteomyelitis in sickle cell disease	<i>Salmonella</i>
Osteomyelitis with IV drug use	<i>Pseudomonas</i> , <i>Candida</i> , <i>S aureus</i>
Ovarian tumor (benign, bilateral)	Serous cystadenoma
Ovarian tumor (malignant)	Serous cystadenocarcinoma
Pancreatitis (acute)	Gallstones, alcohol
Pancreatitis (chronic)	Alcohol (adults), cystic fibrosis (kids)
Pelvic inflammatory disease	<i>C trachomatis</i> , <i>N gonorrhoeae</i>
Philadelphia chromosome t(9;22) (<i>BCR-ABL</i>)	CML (may sometimes be associated with ALL/AML)
Pituitary tumor	Prolactinoma, somatotrophic adenoma

DISEASE/FINDING	MOST COMMON/IMPORTANT ASSOCIATIONS
1° amenorrhea	Turner syndrome (45,XO or 45,XO/46,XX mosaic)
1° bone tumor (adults)	Multiple myeloma
1° hyperaldosteronism	Adenoma of adrenal cortex
1° hyperparathyroidism	Adenomas, hyperplasia, carcinoma
1° liver cancer	Hepatocellular carcinoma (chronic hepatitis, cirrhosis, hemochromatosis, α_1 -antitrypsin deficiency, Wilson disease)
Pulmonary hypertension	Idiopathic, heritable, left heart disease (eg, HF), lung disease (eg, COPD), hypoxemic vasoconstriction (eg, OSA), thromboembolic (eg, PE)
Recurrent inflammation/thrombosis of small/medium vessels in extremities	Buerger disease (strongly associated with tobacco)
Refractory peptic ulcers and high gastrin levels	Zollinger-Ellison syndrome (gastrinoma of duodenum or pancreas), associated with MEN1
Renal tumor	Renal cell carcinoma: associated with von Hippel-Lindau and cigarette smoking; paraneoplastic syndromes (EPO, renin, PTHrP, ACTH)
Right heart failure due to a pulmonary cause	Cor pulmonale
S3 heart sound	↑ ventricular filling pressure (eg, mitral regurgitation, HF), common in dilated ventricles
S4 heart sound	Stiff/hypertrophic ventricle (aortic stenosis, restrictive cardiomyopathy)
2° hyperparathyroidism	Hypocalcemia of chronic kidney disease
Sexually transmitted disease	<i>C trachomatis</i> (usually coinfects with <i>N gonorrhoeae</i>)
SIADH	Small cell carcinoma of the lung
Site of diverticula	Sigmoid colon
Sites of atherosclerosis	Abdominal aorta > coronary artery > popliteal artery > carotid artery
t(14;18)	Follicular lymphomas (<i>BCL-2</i> activation, anti-apoptotic oncogene)
t(8;14)	Burkitt lymphoma (<i>c-myc</i> fusion, transcription factor oncogene)
t(9;22)	Philadelphia chromosome, CML (<i>BCR-ABL</i> activation, tyrosine kinase oncogene)
Temporal arteritis	Risk of ipsilateral blindness due to occlusion of ophthalmic artery; polymyalgia rheumatica
Testicular tumor	Seminoma (malignant, radiosensitive), ↑ placental ALP
Thyroid cancer	Papillary carcinoma (childhood irradiation)
Tumor in women	Leiomyoma (estrogen dependent, not precancerous)
Tumor of infancy	Strawberry hemangioma (grows rapidly and regresses spontaneously by childhood)
Tumor of the adrenal medulla (adults)	Pheochromocytoma (usually benign)
Tumor of the adrenal medulla (kids)	Neuroblastoma (malignant)
Type of Hodgkin lymphoma	Nodular sclerosing (vs mixed cellularity, lymphocytic predominance, lymphocytic depletion)

DISEASE/FINDING	MOST COMMON/IMPORTANT ASSOCIATIONS
Type of non-Hodgkin lymphoma	Diffuse large B-cell lymphoma
UTI	<i>E coli</i> , <i>Staphylococcus saprophyticus</i> (young women)
Vertebral compression fracture	Osteoporosis (type I: postmenopausal woman; type II: elderly man or woman)
Viral encephalitis affecting temporal lobe	HSV-1
Vitamin deficiency (US)	Folate (pregnant women are at high risk; body stores only 3- to 4-month supply; prevents neural tube defects)

▶ EQUATION REVIEW

TOPIC	EQUATION	PAGE
Sensitivity	$\text{Sensitivity} = \text{TP} / (\text{TP} + \text{FN})$	33
Specificity	$\text{Specificity} = \text{TN} / (\text{TN} + \text{FP})$	33
Positive predictive value	$\text{PPV} = \text{TP} / (\text{TP} + \text{FP})$	33
Negative predictive value	$\text{NPV} = \text{TN} / (\text{FN} + \text{TN})$	33
Odds ratio (for case-control studies)	$\text{OR} = \frac{a/c}{b/d} = \frac{ad}{bc}$	34
Relative risk	$\text{RR} = \frac{a/(a+b)}{c/(c+d)}$	34
Attributable risk	$\text{AR} = \frac{a}{a+b} - \frac{c}{c+d}$	34
Relative risk reduction	$\text{RRR} = 1 - \text{RR}$	34
Absolute risk reduction	$\text{ARR} = \frac{c}{c+d} - \frac{a}{a+b}$	34
Number needed to treat	$\text{NNT} = 1/\text{ARR}$	34
Number needed to harm	$\text{NNH} = 1/\text{AR}$	34
Hardy-Weinberg equilibrium	$p^2 + 2pq + q^2 = 1$ $p + q = 1$	69
Volume of distribution	$V_d = \frac{\text{amount of drug in the body}}{\text{plasma drug concentration}}$	237
Half-life	$t_{1/2} = \frac{0.693 \times V_d}{\text{CL}}$	237
Drug clearance	$\text{CL} = \frac{\text{rate of elimination of drug}}{\text{plasma drug concentration}} = V_d \times K_e$ (elimination constant)	237
Loading dose	$\text{LD} = \frac{C_p \times V_d}{F}$	237
Maintenance dose	$D = \frac{C_p \times \text{CL} \times \tau}{F}$	237

TOPIC	EQUATION	PAGE
Cardiac output	$CO = \frac{\text{rate of O}_2 \text{ consumption}}{\text{arterial O}_2 \text{ content} - \text{venous O}_2 \text{ content}}$	266
	$CO = \text{stroke volume} \times \text{heart rate}$	266
Mean arterial pressure	$MAP = \text{cardiac output} \times \text{total peripheral resistance}$	266
	$MAP = \frac{2}{3} \text{ diastolic} + \frac{1}{3} \text{ systolic}$	266
Stroke volume	$SV = EDV - ESV$	266
Ejection fraction	$EF = \frac{SV}{EDV} = \frac{EDV - ESV}{EDV}$	267
Resistance	$\text{Resistance} = \frac{\text{driving pressure } (\Delta P)}{\text{flow } (Q)} = \frac{8\eta \text{ (viscosity)} \times \text{length}}{\pi r^4}$	268
Capillary fluid exchange	$J_v = \text{net fluid flow} = K_f [(P_c - P_i) - \zeta(\pi_c - \pi_i)]$	281
Renal clearance	$C_x = U_x V / P_x$	533
Glomerular filtration rate	$GFR = U_{\text{inulin}} \times V / P_{\text{inulin}} = C_{\text{inulin}}$	534
	$GFR = K_f [(P_{GC} - P_{BS}) - (\pi_{GC} - \pi_{BS})]$	
Effective renal plasma flow	$eRPF = U_{PAH} \times \frac{V}{P_{PAH}} = C_{PAH}$	534
Renal blood flow	$RBF = \frac{RPF}{1 - Hct}$	534
Filtration fraction	$FF = \frac{GFR}{RPF}$	535
Henderson-Hasselbalch equation (for extracellular pH)	$pH = 6.1 + \log \frac{[HCO_3^-]}{0.03 P_{CO_2}}$	543
Winters formula	$P_{CO_2} = 1.5 [HCO_3^-] + 8 \pm 2$	543
Physiologic dead space	$V_D = V_T \times \frac{P_{aCO_2} - P_{eCO_2}}{P_{aCO_2}}$	610
Pulmonary vascular resistance	$PVR = \frac{P_{\text{pulm artery}} - P_{\text{L atrium}}}{\text{cardiac output}}$	614
Alveolar gas equation	$P_{AO_2} = P_{IO_2} - \frac{P_{aCO_2}}{R}$	614

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	650
▶ Question Banks	652
▶ Question Books	652
▶ Internet Sites	652
▶ Mobile Apps	652
▶ Comprehensive	653
▶ Anatomy, Embryology, and Neuroscience	653
▶ Behavioral Science	654
▶ Biochemistry	654
▶ Cell Biology and Histology	655
▶ Microbiology and Immunology	655
▶ Pathology	656
▶ Pharmacology	657
▶ Physiology	657

▶ 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.
B-	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 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

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 Web sites.

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 the senior 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

		AUTHOR	PUBLISHER	TYPE	PRICE
A⁺	<i>USMLEWorld Qbank</i>	USMLEWorld	www.usmleworld.com	Test/2200 q	\$129–\$399
A	<i>USMLE-Rx Qmax</i>	MedIQ Learning	www.usmle-rx.com	Test/2300 q	\$99–\$299
A⁻	<i>Kaplan Qbank</i>	Kaplan	www.kaplanmedical.com	Test/2200 q	\$99–\$199
B⁺	<i>USMLE Consult</i>	Elsevier	www.usmleconsult.com	Test/2500 q	\$75–\$395

Question Books

		AUTHOR	PUBLISHER	TYPE	PRICE
A⁻	<i>First Aid Q&A for the USMLE Step 1</i>	Le	McGraw-Hill, 2012, 784 pages	Test/1000 q	\$46.00
B⁺	<i>Kaplan USMLE Step 1 Qbook</i>	Kaplan	Kaplan, 2013, 456 pages	Test/850 q	\$44.99
B⁺	<i>PreTest Clinical Vignettes for the USMLE Step 1</i>	McGraw-Hill	McGraw-Hill, 2010, 318 pages	Test/322 q	\$39.00

Internet Sites

		AUTHOR	PUBLISHER	TYPE	PRICE
A	<i>First Aid Step 1 Express</i>		www.usmle-rx.com	Review/Test	\$99.00–\$249.00
B⁺	<i>Firecracker</i>	Firecracker Inc.	www.firecracker.me	Review/Test/1500 q	\$117–\$500
B⁺	<i>SketchyMedical</i>		www.SketchyMedical.com	Review	\$99–\$159
B⁺	<i>WebPath: The Internet Pathology Laboratory</i>		library.med.utah.edu/WebPath/	Review/Test/1300 q	Free
B	<i>Blue Histology</i>		www.lab.anhb.uwa.edu.au/mb140	Review/Test	Free
B	<i>Dr. Najeeb Lectures</i>		www.drnajeeblectures.com	Review	\$49
B	<i>Medical School Pathology</i>		www.medicalstudentpathology.com	Review	Free
B	<i>The Pathology Guy</i>	Friedlander	www.pathguy.com	Review	Free
B	<i>The Whole Brain Atlas</i>	Johnson	www.med.harvard.edu/aanlib/	Review	Free
B	<i>Radiopaedia.org</i>		www.radiopaedia.org	Cases/Test	Free
B⁻	<i>Digital Anatomist Project: Interactive Atlases</i>	University of Washington	www9.biostr.washington.edu/da.html	Review	Free
B⁻	<i>Picmonic</i>		http://www.picmonic.com	Review	\$24.99/month

Mobile Apps

		AUTHOR	PUBLISHER	TYPE	PRICE
A	<i>Anki</i>		http://ankisrs.net	Flash cards	Free/\$24.99
B⁺	<i>Cram Fighter</i>		www.cramfighter.com	Study plan	\$14.99/month
B	<i>Osmosis</i>		www.osmosis.org	Test	Variable

Comprehensive

		AUTHOR	PUBLISHER	TYPE	PRICE
A	<i>First Aid for the Basic Sciences: General Principles</i>	Le	McGraw-Hill, 2011, 576 pages	Review	\$72.00
A	<i>First Aid for the Basic Sciences: Organ Systems</i>	Le	McGraw-Hill, 2011, 880 pages	Review	\$93.00
A	<i>medEssentials for the USMLE Step 1</i>	Manley	Kaplan, 2012, 588 pages	Review	\$54.99
A⁻	<i>USMLE Step 1 Secrets</i>	Brown	Elsevier, 2012, 880 pages	Review	\$42.95
A⁻	<i>First Aid Cases for the USMLE Step 1</i>	Le	McGraw-Hill, 2012, 448 pages	Cases	\$50.00
B⁺	<i>Step-Up to USMLE Step 1 2015</i>	Jenkins	Lippincott Williams & Wilkins, 2014, 528 pages	Review	\$52.99
B⁺	<i>Cracking the USMLE Step 1</i>	Princeton Review	Princeton Review, 2013, 832 pages	Review	\$44.99
B⁺	<i>USMLE Images for the Boards: A Comprehensive Image-Based Review</i>	Tully	Elsevier, 2012, 296 pages	Review	\$42.95
B	<i>First Aid Step 1 Flash Facts</i>		https://www.usmle-rx.com	Flash cards	\$49.00–\$99.00
B	<i>Déjà Review: USMLE Step 1</i>	Naheedy	McGraw-Hill, 2010, 412 pages	Review	\$24.00
B⁻	<i>USMLE Step 1 Made Ridiculously Simple</i>	Carl	MedMaster, 2014, 400 pages	Review/Test 100 q	\$29.95

Anatomy, Embryology, and Neuroscience

		AUTHOR	PUBLISHER	TYPE	PRICE
A⁻	<i>High-Yield Embryology</i>	Dudek	Lippincott Williams & Wilkins, 2013, 176 pages	Review	\$37.99
A⁻	<i>High-Yield Neuroanatomy</i>	Fix	Lippincott Williams & Wilkins, 2008, 160 pages	Review/ Test/50 q	\$35.99
A⁻	<i>Anatomy—An Essential Textbook</i>	Gilroy	Thieme, 2013, 504 pages	Text/ Test/400 q	\$44.99
A⁻	<i>Atlas of Anatomy</i>	Gilroy	Thieme, 2012, 704 pages	Text	\$79.99
B⁺	<i>High-Yield Gross Anatomy</i>	Dudek	Lippincott Williams & Wilkins, 2014, 320 pages	Review	\$37.99
B⁺	<i>Clinical Anatomy Made Ridiculously Simple</i>	Goldberg	MedMaster, 2012, 175 pages	Review	\$29.95
B⁺	<i>PreTest Neuroscience</i>	Siegel	McGraw-Hill, 2013, 412 pages	Test/500 q	\$37.00
B⁺	<i>Crash Course: Anatomy</i>	Stenhouse	Elsevier, 2015, 288 pages	Review	\$44.99
B⁺	<i>Déjà Review: Neuroscience</i>	Tremblay	McGraw-Hill, 2010, 266 pages	Review	\$24.00
B⁺	<i>USMLE Road Map: Neuroscience</i>	White	McGraw-Hill, 2008, 224 pages	Review/ Test/300 q	\$40.00
B	<i>BRS Embryology</i>	Dudek	Lippincott Williams & Wilkins, 2014, 336 pages	Review/ Test/220 q	\$50.99
B	<i>Anatomy Flash Cards: Anatomy on the Go</i>	Gilroy	Thieme, 2013, 565 flash cards	Flash cards	\$59.99

Anatomy, Embryology, and Neuroscience (continued)

		AUTHOR	PUBLISHER	TYPE	PRICE
B	<i>Clinical Neuroanatomy Made Ridiculously Simple</i>	Goldberg	MedMaster, 2014, 90 pages + CD-ROM	Review/Test/ Few q	\$25.95
B	<i>Rapid Review: Gross and Developmental Anatomy</i>	Moore	Elsevier, 2010, 304 pages	Review/ Test/450 q	\$42.95
B	<i>Case Files: Anatomy</i>	Toy	McGraw-Hill, 2014, 402 pages	Cases	\$35.00
B	<i>Case Files: Neuroscience</i>	Toy	McGraw-Hill, 2014, 418 pages	Cases	\$35.00
B⁻	<i>Gray's Anatomy for Students Flash Cards</i>	Drake	Elsevier, 2015, 350 flash cards	Flash cards	\$39.99
B⁻	<i>Netter's Anatomy Flash Cards</i>	Hansen	Saunders, 2014, 674 flash cards	Flash cards	\$39.95

Behavioral Science

		AUTHOR	PUBLISHER	TYPE	PRICE
A	<i>High-Yield Behavioral Science</i>	Fadem	Lippincott Williams & Wilkins, 2012, 144 pages	Review	\$36.99
A⁻	<i>BRS Behavioral Science</i>	Fadem	Lippincott Williams & Wilkins, 2013, 336 pages	Review/ Test/700 q	\$49.99
A⁻	<i>High-Yield Biostatistics, Epidemiology, and Public Health</i>	Glaser	Lippincott Williams & Wilkins, 2013, 168 pages	Review	\$41.99
A⁻	<i>Clinical Biostatistics and Epidemiology Made Ridiculously Simple</i>	Weaver	MedMaster, 2011, 104 pages	Review	\$22.95
B⁺	<i>USMLE Medical Ethics</i>	Fischer	Kaplan, 2012, 216 pages	Cases	\$42.99
B⁺	<i>Jekel's Epidemiology, Biostatistics, Preventive Medicine, and Public Health</i>	Katz	Saunders, 2013, 420 pages	Review/ Test/477 q	\$59.95
B	<i>Déjà Review: Behavioral Science</i>	Quinn	McGraw-Hill, 2010, 240 pages	Review	\$24.00

Biochemistry

		AUTHOR	PUBLISHER	TYPE	PRICE
A⁻	<i>Lange Flash Cards Biochemistry and Genetics</i>	Baron	McGraw-Hill, 2013, 184 flash cards	Flash cards	\$38.00
A⁻	<i>Rapid Review: Biochemistry</i>	Pelley	Elsevier, 2010, 208 pages	Review/ Test/350 q	\$42.95
B⁺	<i>Lippincott's Illustrated Reviews: Biochemistry</i>	Ferrier	Lippincott Williams & Wilkins, 2013, 560 pages	Review/ Test/500 q	\$75.99
B⁺	<i>Déjà Review: Biochemistry</i>	Manzoul	McGraw-Hill, 2010, 206 pages	Review	\$24.00
B⁺	<i>Medical Biochemistry—An Illustrated Review</i>	Panini	Thieme, 2013, 441 pages	Review/ Test/400 q	\$39.99
B⁺	<i>PreTest Biochemistry and Genetics</i>	Wilson	McGraw-Hill, 2013, 592 pages	Test/500 q	\$36.00
B	<i>Clinical Biochemistry Made Ridiculously Simple</i>	Goldberg	MedMaster, 2010, 95 pages + foldout	Review	\$24.95
B	<i>BRS Biochemistry, Molecular Biology, and Genetics</i>	Lieberman	Lippincott Williams & Wilkins, 2013, 432 pages	Review/Test	\$49.99

Biochemistry (continued)

		AUTHOR	PUBLISHER	TYPE	PRICE
B⁻	<i>Case Files: Biochemistry</i>	Toy	McGraw-Hill, 2014, 480 pages	Cases	\$35.00
B⁻	<i>High-Yield Biochemistry</i>	Wilcox	Lippincott Williams & Wilkins, 2009, 128 pages	Review	\$40.99

Cell Biology and Histology

		AUTHOR	PUBLISHER	TYPE	PRICE
A⁻	<i>High-Yield Cell and Molecular Biology</i>	Dudek	Lippincott Williams & Wilkins, 2010, 151 pages	Review	\$36.99
B	<i>Elsevier's Integrated Review: Genetics</i>	Adkison	Elsevier, 2011, 272 pages	Review	\$42.95
B	<i>High-Yield Genetics</i>	Dudek	Lippincott Williams & Wilkins, 2008, 134 pages	Review	\$36.99
B	<i>BRS Cell Biology and Histology</i>	Gartner	Lippincott Williams & Wilkins, 2014, 432 pages	Review/ Test/320 q	\$45.99
B	<i>PreTest Anatomy, Histology, and Cell Biology</i>	Klein	McGraw-Hill, 2010, 654 pages	Test/500 q	\$37.00
B	<i>USMLE Road Map: Genetics</i>	Sack	McGraw-Hill, 2008, 224 pages	Review	\$40.00
B	<i>Déjà Review: Histology and Cell Biology</i>	Song	McGraw-Hill, 2010, 300 pages	Review	\$24.00
B	<i>Crash Course: Cell Biology and Genetics</i>	Stubbs	Elsevier, 2015, 216 pages	Review	\$46.99
B⁻	<i>Wheater's Functional Histology</i>	Young	Elsevier, 2013, 464 pages	Text	\$82.95

Microbiology and Immunology

		AUTHOR	PUBLISHER	TYPE	PRICE
A	<i>Déjà Review: Microbiology & Immunology</i>	Chen	McGraw-Hill, 2010, 424 pages	Review	\$24.00
A	<i>Clinical Microbiology Made Ridiculously Simple</i>	Gladwin	MedMaster, 2014, 400 pages	Review	\$36.95
A	<i>Lange Microbiology & Infectious Diseases Flash Cards</i>	Somers	McGraw-Hill, 2010, 189 flash cards	Flash cards	\$43.00
A⁻	<i>Basic Immunology</i>	Abbas	Elsevier, 2012, 336 pages	Review	\$71.95
A⁻	<i>Microcards: Microbiology Flash Cards</i>	Harpavat	Lippincott Williams & Wilkins, 2011, 310 flash cards	Flash cards	\$46.99
A⁻	<i>Medical Microbiology and Immunology Flash Cards</i>	Rosenthal	Elsevier, 2008, 324 flash cards	Flash cards	\$39.95
B⁺	<i>Elsevier's Integrated Immunology and Microbiology</i>	Actor	Elsevier, 2011, 192 pages	Review	\$42.95
B⁺	<i>Lippincott's Illustrated Reviews: Immunology</i>	Doan	Lippincott Williams & Wilkins, 2012, 384 pages	Review/Test/ Few q	\$65.99
B⁺	<i>Lippincott's Illustrated Reviews: Microbiology</i>	Harvey	Lippincott Williams & Wilkins, 2012, 448 pages	Review/Test/ Few q	\$67.99
B⁺	<i>Review of Medical Microbiology and Immunology</i>	Levinson	McGraw-Hill, 2014, 800 pages	Review/ Test/654 q	\$55.00

Microbiology and Immunology (continued)

		AUTHOR	PUBLISHER	TYPE	PRICE
B	<i>The Big Picture: Medical Microbiology</i>	Chamberlain	McGraw-Hill, 2008, 456 pages	Review/100 q	\$65.00
B	<i>Case Studies in Immunology: Clinical Companion</i>	Geha	Garland Science, 2011, 376 pages	Cases	\$59.00
B	<i>Pretest: Microbiology</i>	Kettering	McGraw-Hill, 2013, 480 pages	Test/500 q	\$36.00
B	<i>Rapid Review: Microbiology and Immunology</i>	Rosenthal	Elsevier, 2010, 240 pages	Review/ Test/400 q	\$42.95
B	<i>Case Files: Microbiology</i>	Toy	McGraw-Hill, 2014, 401 pages	Cases	\$35.00

Pathology

		AUTHOR	PUBLISHER	TYPE	PRICE
A⁺	<i>Rapid Review: Pathology</i>	Goljan	Elsevier, 2013, 784 pages	Review/ Test/400 q	\$55.95
A⁺	<i>Pathoma: Fundamentals of Pathology</i>	Sattar	Pathoma, 2011, 218 pages	Review/ Lecture	\$82.95
A⁻	<i>Lange Pathology Flash Cards</i>	Baron	McGraw-Hill, 2013, 300 flash cards	Flash cards	\$39.00
A⁻	<i>Déjà Review: Pathology</i>	Davis	McGraw-Hill, 2010, 474 pages	Review	\$24.00
A⁻	<i>Lippincott's Illustrated Q&A Review of Rubin's Pathology</i>	Fenderson	Lippincott Williams & Wilkins, 2010, 336 pages	Test/1000 q	\$57.99
A⁻	<i>The Big Picture: Pathology</i>	Kemp	McGraw-Hill, 2007, 512 pages	Review/ Test/130 q	\$61.00
A⁻	<i>Robbins and Cotran Review of Pathology</i>	Klatt	Elsevier, 2014, 504 pages	Test/1100 q	\$49.95
A⁻	<i>BRS Pathology</i>	Schneider	Lippincott Williams & Wilkins, 2013, 480 pages	Review/ Test/450 q	\$49.99
A⁻	<i>Color Atlas of Physiology</i>	Silbernagl	Thieme, 2015, 472 pages	Review	\$49.99
A⁻	<i>Crash Course: Pathology</i>	Xiu	Elsevier, 2012, 356 pages	Review	\$44.95
B⁺	<i>Cases & Concepts Step 1: Pathophysiology Review</i>	Caughey	Lippincott Williams & Wilkins, 2009, 376 pages	Cases	\$48.99
B⁺	<i>Case Files: Pathology</i>	Toy	McGraw-Hill, 2008, 456 pages	Cases	\$38.00
B	<i>PreTest Pathology</i>	Brown	McGraw-Hill, 2010, 612 pages	Test/500 q	\$37.00
B	<i>High-Yield Histopathology</i>	Dudek	Lippincott Williams & Wilkins, 2011, 328 pages	Review	\$36.00
B	<i>Pathophysiology of Disease: Introduction to Clinical Medicine</i>	McPhee	McGraw-Hill, 2014, 784 pages	Text	\$78.00
B	<i>Haematology at a Glance</i>	Mehta	Blackwell Science, 2014, 136 pages	Review	\$46.95
B	<i>Pocket Companion to Robbins and Cotran Pathologic Basis of Disease</i>	Mitchell	Elsevier, 2011, 800 pages	Review	\$40.95

Pharmacology

		AUTHOR	PUBLISHER	TYPE	PRICE
A⁻	<i>Lange Pharmacology Flash Cards</i>	Baron	McGraw-Hill, 2013, 230 flash cards	Flash cards	\$39.00
A⁻	<i>Master the Boards USMLE Step 1 Pharmacology Flashcards</i>	Fischer	Kaplan, 2015, 408 flash cards	Flash cards	\$54.99
A⁻	<i>Déjà Review: Pharmacology</i>	Gleason	McGraw-Hill, 2010, 236 pages	Review	\$24.00
A⁻	<i>Lippincott's Illustrated Reviews: Pharmacology</i>	Harvey	Lippincott Williams & Wilkins, 2014, 680 pages	Review/ Test/380 q	\$69.99
A⁻	<i>PharmCards: Review Cards for Medical Students</i>	Johannsen	Lippincott Williams & Wilkins, 2010, 240 flash cards	Flash cards	\$44.99
B⁺	<i>Crash Course: Pharmacology</i>	Battista	Elsevier, 2015, 236 pages	Review	\$44.99
B⁺	<i>Pharmacology Flash Cards</i>	Brenner	Elsevier, 2012, 200 flash cards	Flash cards	\$39.95
B⁺	<i>Elsevier's Integrated Pharmacology</i>	Kester	Elsevier, 2011, 264 pages	Review	\$42.95
B⁺	<i>Rapid Review: Pharmacology</i>	Pazdernik	Elsevier, 2010, 360 pages	Review/ Test/450 q	\$42.95
B⁺	<i>BRS Pharmacology</i>	Rosenfeld	Lippincott Williams & Wilkins, 2013, 384 pages	Review/ Test/200 q	\$49.99
B	<i>PreTest Pharmacology</i>	Shlafer	McGraw-Hill, 2013, 567 pages	Test/500 q	\$36.00
B	<i>Case Files: Pharmacology</i>	Toy	McGraw-Hill, 2013, 453 pages	Cases	\$35.00
B	<i>Katzung & Trevor's Pharmacology: Examination and Board Review</i>	Trevor	McGraw-Hill, 2015, 592 pages	Review/ Test/1000 q	\$54.00
B	<i>High-Yield Pharmacology</i>	Weiss	Lippincott Williams & Wilkins, 2009, 160 pages	Review	\$35.99

Physiology

		AUTHOR	PUBLISHER	TYPE	PRICE
A⁺	<i>BRS Physiology</i>	Costanzo	Lippincott Williams & Wilkins, 2014, 328 pages	Review/ Test/350 q	\$51.99
A	<i>Acid-Base, Fluids, and Electrolytes Made Ridiculously Simple</i>	Preston	MedMaster, 2010, 156 pages	Review	\$22.95
A⁻	<i>Physiology</i>	Costanzo	Saunders, 2013, 520 pages	Text	\$62.95
B⁺	<i>BRS Physiology Cases and Problems</i>	Costanzo	Lippincott Williams & Wilkins, 2012, 368 pages	Cases	\$49.99
B⁺	<i>Déjà Review: Physiology</i>	Gould	McGraw-Hill, 2010, 298 pages	Review	\$24.00
B⁺	<i>The Big Picture: Medical Physiology</i>	Kibble	McGraw-Hill, 2009, 448 pages	Review/ Test/108 q	\$58.00
B⁺	<i>PreTest Physiology</i>	Metting	McGraw-Hill, 2013, 505 pages	Test/500 q	\$36.00
B	<i>Rapid Review: Physiology</i>	Brown	Elsevier, 2011, 288 pages	Test/350 q	\$42.95
B	<i>Vander's Renal Physiology</i>	Eaton	McGraw-Hill, 2013, 240 pages	Text	\$45.00
B	<i>Endocrine Physiology</i>	Molina	McGraw-Hill, 2013, 320 pages	Review	\$48.00
B	<i>Netter's Physiology Flash Cards</i>	Mulroney	Saunders, 2009, 200+ flash cards	Flash cards	\$39.95

Physiology (continued)

		AUTHOR	PUBLISHER	TYPE	PRICE
B	<i>Case Files: Physiology</i>	Toy	McGraw-Hill, 2008, 456 pages	Cases	\$37.00
B	<i>Pulmonary Pathophysiology: The Essentials</i>	West	Lippincott Williams & Wilkins, 2012, 208 pages	Review/ Test/50 q	\$51.99
B⁻	<i>Clinical Physiology Made Ridiculously Simple</i>	Goldberg	MedMaster, 2010, 160 pages	Review	\$24.95

SECTION IV

Abbreviations and Symbols

ABBREVIATION	MEANING
⊕	positive
⊖	negative
1°	primary
2°	secondary
3°	tertiary
A-a	alveolar-arterial [gradient]
AA	Alcoholics Anonymous, amyloid A
AAMC	Association of American Medical Colleges
Ab	antibody
ABP	androgen-binding protein
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	adrenocorticotrophic hormone
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
AL	amyloid light [chain]
ALA	aminolevulinic acid
ALL	acute lymphoblastic (lymphocytic) leukemia
ALP	alkaline phosphatase
α ₁ , α ₂	sympathetic receptors
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
ANP	atrial natriuretic peptide

ABBREVIATION	MEANING
ANS	autonomic nervous system
anti-CCP	anti-cyclic citrullinated peptide
AOA	American Osteopathic Association
AP	action potential, A & P [ribosomal binding sites]
AAPAF-1	apoptotic protease activating factor 1
APC	antigen-presenting cell, activated protein C
Apo	apolipoprotein
APP	amyloid precursor protein
APRT	adenine phosphoribosyltransferase
APSAC	anistreplase
aPTT	activated partial thromboplastin time
APUD	amine precursor uptake decarboxylase
AR	attributable risk, autosomal recessive, aortic regurgitation
ara-C	arabinofuranosyl cytidine (cytarabine)
ARB	angiotensin receptor blocker
ARDS	acute respiratory distress syndrome
Arg	arginine
ARMG	age-related macular degeneration
ARPKD	autosomal-recessive polycystic kidney disease
AS	aortic stenosis
ASA	anterior spinal artery
ASD	atrial septal defect
ASO	anti-streptolysin O
AST	aspartate transaminase
AT	angiotensin, antithrombin
ATCase	aspartate transcarbamoylase
ATN	acute tubular necrosis
ATP	adenosine triphosphate
ATPase	adenosine triphosphatase
ATTR	transthyretin-mediated amyloidosis
AV	atrioventricular
AZT	azidothymidine
β ₁ , β ₂	sympathetic receptors
BAL	British anti-Lewisite [dimercaprol]
BCG	bacille Calmette-Guérin
BH ₄	tetrahydrobiopterin
BIMS	Biometric Identity Management System
BM	basement membrane
BMI	body-mass index
BMR	basal metabolic rate
BP	bisphosphate, blood pressure
BPG	bisphosphoglycerate
BPH	benign prostatic hyperplasia
BT	bleeding time
BUN	blood urea nitrogen

ABBREVIATION	MEANING
Ca ²⁺	calcium ion
CAD	coronary artery disease
CAF	common application form
CALLA	common acute lymphoblastic leukemia antigen
cAMP	cyclic adenosine monophosphate
CBG	corticosteroid-binding globulin
Cbl	cobalamin
CBSE	Comprehensive Basic Science Examination
CBSSA	Comprehensive Basic Science Self-Assessment
CBT	computer-based test, cognitive behavioral therapy
CCK	cholecystokinin
CCS	computer-based case simulation
CD	cluster of differentiation
CDK	cyclin-dependent kinase
cDNA	complementary deoxyribonucleic acid
CEA	carcinoembryonic antigen
CETP	cholesterol-ester transfer protein
CF	cystic fibrosis
CFTR	cystic fibrosis transmembrane conductance regulator
CFX	circumflex [artery]
CGD	chronic granulomatous disease
cGMP	cyclic guanosine monophosphate
CGN	<i>cis</i> -Golgi network
C _H 1–C _H 3	constant regions, heavy chain [antibody]
ChAT	choline acetyltransferase
χ 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
CK-MB	creatine kinase, MB fraction
C _L	constant region, light chain [antibody]
CL	clearance
Cl ⁻	chloride ion
CLL	chronic lymphocytic leukemia
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 ₂	carbon dioxide
CoA	coenzyme A
COL1A1	collagen, type I, alpha 1
COL1A2	collagen, type I, alpha 2
COMT	catechol-O-methyltransferase
COOH	carboxyl group
COP	coat protein
COPD	chronic obstructive pulmonary disease
CoQ	coenzyme Q
COX	cyclooxygenase
C _p	plasma concentration
CPAP	continuous positive airway pressure

ABBREVIATION	MEANING
CPK	creatine phosphokinase
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
CVA	cerebrovascular accident
CVID	common variable immunodeficiency
CXR	chest x-ray
Cys	cysteine
DAF	decay-accelerating factor
DAG	diacylglycerol
dATP	deoxyadenosine triphosphate
DCIS	ductal carcinoma in situ
DCT	distal convoluted tubule
ddC	dideoxycytidine [zalcitabine]
ddI	didanosine
DES	diethylstilbestrol
DHAP	dihydroxyacetone phosphate
DHB	dihydrobiopterin
DHEA	dehydroepiandrosterone
DHF	dihydrofolic acid
DHS	Department of Homeland Security
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
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
d4T	didehydrodeoxythymidine [stavudine]
dTMP	deoxythymidine monophosphate
DTR	deep tendon reflex
DTs	delirium tremens
dUDP	deoxyuridine diphosphate
dUMP	deoxyuridine monophosphate
DVT	deep venous thrombosis
EBV	Epstein-Barr virus

ABBREVIATION	MEANING
EC	ejection click
ECF	extracellular fluid
ECFMG	Educational Commission for Foreign Medical Graduates
ECCG	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 <i>E coli</i>
ELISA	enzyme-linked immunosorbent assay
EM	electron micrograph/microscopy
EMB	eosin–methylene blue
Epi	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
FAD ⁺	oxidized flavin adenine dinucleotide
FADH ₂	reduced flavin adenine dinucleotide
FAP	familial adenomatous polyposis
F1,6BP	fructose-1,6-bisphosphate
F2,6BP	fructose-2,6-bisphosphate
FBPase	fructose biphosphatase
Fc	fragment, crystallizable
FcR	Fc receptor
5F-dUMP	5-fluorodeoxyuridine monophosphate
Fe ²⁺	ferrous ion
Fe ³⁺	ferric ion
FENa	excreted fraction of filtered sodium
FEV ₁	forced expiratory volume in 1 second
FF	filtration fraction
FFA	free fatty acid
FGF	fibroblast growth factor
FGFR	fibroblast growth factor receptor

ABBREVIATION	MEANING
FISH	fluorescence in situ hybridization
FKBP	FK506 binding protein
FLAIR	fluid-attenuated inversion recovery
f-met	formylmethionine
FMG	foreign medical graduate
FMN	flavin mononucleotide
FN	false negative
FNHTR	febrile nonhemolytic transfusion reaction
FP	false positive
F1P	fructose-1-phosphate
F6P	fructose-6-phosphate
FRC	functional residual capacity
FSH	follicle-stimulating hormone
FSMB	Federation of State Medical Boards
FTA-ABS	fluorescent treponemal antibody—absorbed
5-FU	5-fluorouracil
FVC	forced vital capacity
GABA	γ-aminobutyric acid
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 ₁	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
G3P	glucose-3-phosphate
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 _S	G protein, S polypeptide
GS	glycogen synthase
GSH	reduced glutathione
GSSG	oxidized glutathione
GTP	guanosine triphosphate
GTPase	guanosine triphosphatase
GU	genitourinary
H ⁺	hydrogen ion
H ₁ , H ₂	histamine receptors

ABBREVIATION	MEANING
H ₂ S	hydrogen sulfide
HAART	highly active antiretroviral therapy
HAV	hepatitis A virus
HAVAb	hepatitis A antibody
Hb	hemoglobin
Hb ⁺	oxidized hemoglobin
Hb ⁻	ionized hemoglobin
HBcAb	hepatitis B core antibody
HBcAg	hepatitis B core antigen
HBeAb	hepatitis B early antibody
HBeAg	hepatitis B early antigen
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HbCO ₂	carbamino hemoglobin
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
hCG	human chorionic gonadotropin
HCO ₃ ⁻	bicarbonate
Hct	hematocrit
HCTZ	hydrochlorothiazide
HCV	hepatitis C virus
HDL	high-density lipoprotein
HDV	hepatitis D virus
H&E	hematoxylin and eosin
HEV	hepatitis E virus
HF	heart failure
Hfr	high-frequency recombination [cell]
HGPRT	hypoxanthine-guanine phosphoribosyltransferase
HHb	human hemoglobin
HHV	human herpesvirus
5-HIAA	5-hydroxyindoleacetic acid
HIE	hypoxic ischemic encephalopathy
His	histidine
HIT	heparin-induced thrombocytopenia
HIV	human immunodeficiency virus
HL	hepatic lipase
HLA	human leukocyte antigen
HMG-CoA	hydroxymethylglutaryl-coenzyme A
HMP	hexose monophosphate
HMSN	hereditary motor and sensory neuropathy
HMWK	high-molecular-weight kininogen
HNPCC	hereditary nonpolyposis colorectal cancer
hnRNA	heterogeneous nuclear ribonucleic acid
H ₂ O	water
H ₂ O ₂	hydrogen peroxide
HPA	hypothalamic-pituitary-adrenal [axis]
HPL	human placental lactogen
HPO	hypothalamic-pituitary-ovarian [axis]
HPV	human papillomavirus
HR	heart rate
HRE	hormone receptor element
HSV	herpes simplex virus
5-HT	5-hydroxytryptamine (serotonin)
HTLV	human T-cell leukemia virus
HTN	hypertension

ABBREVIATION	MEANING
HTR	hemolytic transfusion reaction
HUS	hemolytic-uremic syndrome
HVA	homovanillic acid
HZV	herpes zoster virus
IBD	inflammatory bowel disease
IBS	irritable bowel syndrome
IC	inspiratory capacity, immune complex
I _{Ca}	calcium current [heart]
I _f	funny current [heart]
ICA	internal carotid artery
ICAM	intracellular adhesion molecule
ICD	implantable cardioverter defibrillator
ICE	Integrated Clinical Encounter
ICF	intracellular fluid
ICP	intracranial pressure
ID	identification
ID ₅₀	median infective dose
IDDM	insulin-dependent diabetes mellitus
IDL	intermediate-density lipoprotein
I/E	inspiratory/expiratory [ratio]
IF	immunofluorescence, initiation factor
IFN	interferon
Ig	immunoglobulin
IGF	insulin-like growth factor
I _K	potassium current [heart]
IL	interleukin
IM	intramuscular
IMA	inferior mesenteric artery
IMED	International Medical Education Directory
IMG	international medical graduate
IMP	inosine monophosphate
IMV	inferior mesenteric vein
I _{Na}	sodium current [heart]
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 ⁺	potassium ion
KatG	catalase-peroxidase produced by <i>M tuberculosis</i>

ABBREVIATION	MEANING
K_e	elimination constant
K_f	filtration constant
KG	ketoglutarate
K_m	Michaelis-Menten constant
KOH	potassium hydroxide
L	left
LA	left atrial, left atrium
LAD	left anterior descending [artery]
LAF	left anterior fascicle
LCA	left coronary artery
LCAT	lecithin-cholesterol acyltransferase
LCFA	long-chain fatty acid
LCL	lateral collateral ligament
LCME	Liaison Committee on Medical Education
LCMV	lymphocytic choriomeningitis virus
LCX	left circumflex artery
LD	loading dose
LD_{50}	median lethal dose
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LES	lower esophageal sphincter
LFA	leukocyte function-associated antigen
LFT	liver function test
LGN	lateral geniculate nucleus
LGV	left gastric vein
LH	luteinizing hormone
LLQ	left lower quadrant
LM	light microscopy
LMN	lower motor neuron
LOS	lipooligosaccharide
LP	lumbar puncture
LPL	lipoprotein lipase
LPS	lipopolysaccharide
LR	lateral rectus [muscle]
LT	labile toxin leukotriene
LV	left ventricle, left ventricular
Lys	lysine
M_1 - M_5	muscarinic (parasympathetic) ACh receptors
MAC	membrane attack complex, minimal alveolar concentration
MALT	mucosa-associated lymphoid tissue
MAO	monoamine oxidase
MAOI	monoamine oxidase inhibitor
MAP	mean arterial pressure, mitogen-activated protein
MASP	mannose-binding lectin-associated serine protease
MBL	mannose-binding lectin
MC	midystolic 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
MELAS syndrome	mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes

ABBREVIATION	MEANING
MEN	multiple endocrine neoplasia
Mg^{2+}	magnesium ion
MGN	medial geniculate nucleus
$MgSO_4$	magnesium sulfate
MGUS	monoclonal gammopathy of undetermined significance
MHC	major histocompatibility complex
MI	myocardial infarction
MIF	müllerian inhibiting factor
MLCK	myosin light-chain kinase
MLF	medial longitudinal fasciculus
MMC	migrating motor complex
MMR	measles, mumps, rubella [vaccine]
MOPP	mechlorethamine-vincristine (Oncovin)-prednisone-procarbazine [chemotherapy]
6-MP	6-mercaptopurine
MPGN	membranoproliferative glomerulonephritis
MPO	myeloperoxidase
MPO-ANCA/ p-ANCA	perinuclear antineutrophil cytoplasmic antibody
MR	medial rectus [muscle], mitral regurgitation
MRI	magnetic resonance imaging
miRNA	microribonucleic acid
mRNA	messenger ribonucleic acid
MRSA	methicillin-resistant <i>S aureus</i>
MS	mitral stenosis, multiple sclerosis
MSH	melanocyte-stimulating hormone
MSM	men who have sex with men
mtDNA	mitochondrial DNA
mtRNA	mitochondrial RNA
mTOR	mammalian target of rapamycin
MTP	metatarsophalangeal [joint]
MTX	methotrexate
MUA/P	Medically Underserved Area and Population
MVO_2	myocardial oxygen consumption
MVP	mitral valve prolapse
N/A	not applicable
Na^+	sodium ion
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
NC	no change
NE	norepinephrine
NF	neurofibromatosis
NFAT	nuclear factor of activated T-cell
NH_3	ammonia
NH_4^+	ammonium
NIDDM	non-insulin-dependent diabetes mellitus
NK	natural killer [cells]
N_M	muscarinic ACh receptor in neuromuscular junction
NMDA	N-methyl-D-aspartate
NMJ	neuromuscular junction

ABBREVIATION	MEANING
NMS	neuroleptic malignant syndrome
N _N	nicotinic ACh receptor in autonomic ganglia
NRMP	National Residency Matching Program
NNRTI	non-nucleoside reverse transcriptase inhibitor
NO	nitric oxide
N ₂ O	nitrous oxide
NPH	neutral protamine Hagedorn, normal pressure hydrocephalus
NPV	negative predictive value
NRI	norepinephrine receptor inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
NSAID	nonsteroidal anti-inflammatory drug
NSE	neuron-specific enolase
NSTEMI	non-ST-segment elevation myocardial infarction
OAA	oxaloacetic acid
OCD	obsessive-compulsive disorder
OCP	oral contraceptive pill
OH	hydroxy
OH ₂	dihydroxy
1,25-OH D ₃	calcitriol (active form of vitamin D)
25-OH D ₃	storage form of vitamin D
3' OH	hydroxyl
OMT	osteopathic manipulative technique
OPV	oral polio vaccine
OR	odds ratio
OS	opening snap
OTC	ornithine transcarbamoylase
OVLIT	organum vasculosum of the lamina terminalis
P-body	processing body (cytoplasmic)
P-450	cytochrome P-450 family of enzymes
PA	posteroanterior
PABA	<i>para</i> -aminobenzoic acid
Paco ₂	arterial PCO ₂
Paco ₂	alveolar PCO ₂
PAH	<i>para</i> -aminohippuric acid
PAN	polyarteritis nodosa
Pao ₂	partial pressure of oxygen in arterial blood
PAo ₂	partial pressure of oxygen in alveolar blood
PAP	Papanicolaou [smear], prostatic acid phosphatase
PAS	periodic acid–Schiff
PBP	penicillin-binding protein
PC	plasma colloid osmotic pressure, platelet count, pyruvate carboxylase
PCA	posterior cerebral artery
PCL	posterior cruciate ligament
Pco ₂	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
PCWP	pulmonary capillary wedge pressure
PD	posterior descending [artery]
PDA	patent ductus arteriosus, posterior descending artery
PDC	pyruvate dehydrogenase complex

ABBREVIATION	MEANING
PDE	phosphodiesterase
PDGF	platelet-derived growth factor
PDH	pyruvate dehydrogenase
PE	pulmonary embolism
PECAM	platelet–endothelial cell adhesion molecule
PECO ₂	expired air PCO ₂
PEP	phosphoenolpyruvate
PF	platelet factor
PFK	phosphofructokinase
PFT	pulmonary function test
PG	phosphoglycerate
P _i	plasma interstitial osmotic pressure, inorganic phosphate
PICA	posterior inferior cerebellar artery
PID	pelvic inflammatory disease
PiO ₂	PO ₂ in inspired air
PIP	proximal interphalangeal [joint]
PIP ₂	phosphatidylinositol 4,5-bisphosphate
PKD	polycystic kidney disease
PKR	interferon- α -induced protein kinase
PKU	phenylketonuria
PLP	pyridoxal phosphate
PLS	Personalized Learning System
PML	progressive multifocal leukoencephalopathy
PMN	polymorphonuclear [leukocyte]
P _{net}	net filtration pressure
PNET	primitive neuroectodermal tumor
PNS	peripheral nervous system
PO ₂	partial pressure of oxygen
PO ₄	salt of phosphoric acid
PO ₄ ³⁻	phosphate
PPAR	peroxisome proliferator-activated receptor
PPD	purified protein derivative
PPI	proton pump inhibitor
PPV	positive predictive value
PR3-ANCA/ c-ANCA	cytoplasmic antineutrophil cytoplasmic antibody
PrP	prion protein
PRPP	phosphoribosylpyrophosphate
PSA	prostate-specific antigen
PSS	progressive systemic sclerosis
PT	prothrombin time
PTH	parathyroid hormone
PTHrP	parathyroid hormone–related protein
PTSD	post-traumatic stress disorder
PTT	partial thromboplastin time
PV	plasma volume, venous pressure
PVC	polyvinyl chloride
PVR	pulmonary vascular resistance
R	correlation coefficient, right, R variable [group]
R ₃	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
RBC	red blood cell

ABBREVIATION	MEANING
RBF	renal blood flow
RCA	right coronary artery
REM	rapid eye movement
RER	rough endoplasmic reticulum
Rh	<i>rhesus</i> antigen
RLQ	right lower quadrant
RNA	ribonucleic acid
RNP	ribonucleoprotein
ROS	reactive oxygen species
RPF	renal plasma flow
RPCN	rapidly progressive glomerulonephritis
RPR	rapid plasma reagin
RR	relative risk, respiratory rate
rRNA	ribosomal ribonucleic acid
RS	Reed-Sternberg [cells]
RSV	respiratory syncytial virus
RTA	renal tubular acidosis
RUQ	right upper quadrant
RV	residual volume, right ventricle, right ventricular
RVH	right ventricular hypertrophy
Rx	medical prescription
[S]	substrate concentration
SA	sinoatrial
SAA	serum amyloid-associated [protein]
SAM	S-adenosylmethionine
SARS	severe acute respiratory syndrome
SAT	Scholastic Aptitude Test
SC	subcutaneous
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
SEM	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
SLE	systemic lupus erythematosus
SLL	small lymphocytic lymphoma
SLT	Shiga-like toxin
SMA	superior mesenteric artery
SMX	sulfamethoxazole
SNARE	soluble NSF attachment protein receptor
SNe	substantia nigra pars compacta
SNP	single nucleotide polymorphism
SNr	substantia nigra pars reticulata
SNRI	serotonin and norepinephrine receptor inhibitor
snRNP	small nuclear ribonucleoprotein

ABBREVIATION	MEANING
SO	superior oblique [muscle]
SOAP	Supplemental Offer and Acceptance Program
spp.	species
SR	superior rectus [muscle]
SS	single stranded
ssDNA	single-stranded deoxyribonucleic acid
SSPE	subacute sclerosing panencephalitis
SSRI	selective serotonin reuptake inhibitor
ssRNA	single-stranded ribonucleic acid
SSSS	staphylococcal scalded-skin syndrome
ST	Shiga toxin
STEMI	ST-segment elevation myocardial infarction
STI	sexually transmitted infection
STN	subthalamic nucleus
SV	splenic vein, stroke volume
SVC	superior vena cava
SVT	supraventricular tachycardia
$t_{1/2}$	half-life
T_3	triiodothyronine
T_4	thyroxine
TAPVR	total anomalous pulmonary venous return
TB	tuberculosis
TBG	thyroxine-binding globulin
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
TFT	thyroid function test
TG	triglyceride
TGA	<i>trans</i> -Golgi apparatus
TGF	transforming growth factor
TGN	<i>trans</i> -Golgi network
Th cell	helper T cell
THF	tetrahydrofolic acid
TI	therapeutic index
TIA	transient ischemic attack
TIBC	total iron-binding capacity
TIPS	transjugular intrahepatic portosystemic shunt
TLC	total lung capacity
T_m	maximum rate of transport
TMP	trimethoprim
TN	true negative
TNF	tumor necrosis factor
TNM	tumor, node, metastases [staging]
TOEFL	Test of English as a Foreign Language
ToRCHeS	<i>Toxoplasma gondii</i> , rubella, CMV, HIV, HSV-2, syphilis
TP	true positive
tPA	tissue plasminogen activator
TPP	thiamine pyrophosphate
TPR	total peripheral resistance
TR	tricuspid regurgitation
TRAP	tartrate-resistant acid phosphatase
TRH	thyrotropin-releasing hormone

ABBREVIATION	MEANING
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
Tx	translation [factor]
TXA ₂	thromboxane A ₂
UCV	Underground Clinical Vignettes
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
UV	ultraviolet
V ₁ , V ₂	Vasopressin receptors
VA	Veterans Affairs
VC	vital capacity
V _d	volume of distribution
VD	physiologic dead space
V(D)J	heavy-chain hypervariable region [antibody]
VDRL	Venereal Disease Research Laboratory

ABBREVIATION	MEANING
VEGF	vascular endothelial growth factor
V _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]
VL	ventral lateral [nucleus]; variable region, light chain [antibody]
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]
V/Q	ventilation/perfusion [ratio]
VRE	vancomycin-resistant enterococcus
VSD	ventricular septal defect
V _T	tidal volume
vWF	von Willebrand factor
VZV	varicella-zoster virus
WBC	white blood cell
VMAT	vesicular monoamine transporter
XR	X-linked recessive
XX	normal complement of sex chromosomes for female
XY	normal complement of sex chromosomes for male
ZDV	zidovudine [formerly AZT]

SECTION IV


Image Acknowledgments

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

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


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






















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

























Biochemistry

- 60 **Cilia structure.**  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.
- 63 **Osteogenesis imperfecta: Image A.** Skeletal deformities in lower body 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.
- 63 **Osteogenesis imperfecta: Image B.** 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.
- 63 **Osteogenesis imperfecta: Image C.** Blue sclera. This image is a derivative work, adapted from the following source, available under . Courtesy of Fred H, van Dijk H. Images of memorable cases: cases 40, 41 & 42. Connexions website. December 3, 2008. Available at: <http://cnx.org/content/m15020/1.3/>. The image may have been modified by cropping, labeling, and/or captions. MediQ Learning, LLC makes this image available under .
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- 68 **Obstructive lung disease: Image E.** Curschmann spirals.  Courtesy of Dr. James Heilman.
- 73 **Muscular dystrophies.** Fibrofatty replacement of muscle.  Courtesy of the US 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.
- 78 **Vitamin B₃ (niacin).** Pellagra. This image is a derivative work, adapted from the following source, available under : van Dijk HA, Fred H. Images of memorable cases: case 2. Connexions website. Dec 4, 2008. Available at: <http://cnx.org/contents/3d3dcb2e-8e98-496f-91c2-fe94e93428a1@3@3/>.
- 81 **Vitamin D.** X-ray of lower extremity in child with rickets. This image is a derivative work, adapted from the following source, available under . Courtesy of Dr. Michael L. Richardson. The image may have been modified by cropping, labeling, and/or captions. MediQ Learning, LLC makes this image available under .
- 82 **Malnutrition.** Child with kwashiorkor.  Courtesy of the US Department of Health and Human Services and Dr. Lyle Conrad.
- 96 **Alkaptonuria.** Pigment granules on dorsum of hand. This image is a derivative work, adapted from the following source, available under : Vasudevan B, Sawhney MPS, Radhakrishnan S. Alkaptonuria associated with degenerative collagenous palmar plaques. *Indian J Dermatol* 2009;54:299-301. doi 10.4103/0019-5154.55650.
- 96 **Cystinuria.** Hexagonal stones in urine. This image is a derivative work, adapted from the following source, available under : Courtesy of Cayla Devine.

- 100 Lysosomal storage diseases: Image A.** 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.
- 100 Lysosomal storage diseases: Image B.** Gaucher cells in Gaucher disease. This image is a derivative work, adapted from the following source, available under : Sokolowska B, Skomra D, Czartoryska B. et al. Gaucher disease diagnosed after bone marrow trephine biopsy—a report of two cases. *Folia Histochemica et Cytobiologica* 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.
- 100 Lysosomal storage diseases: Image C.** Foam cells in Niemann-Pick disease. This image is a derivative work, adapted from the following source, available under : Hypercholesterolemia boosts joint destruction in chronic arthritis. An experimental model aggravated by foam macrophage infiltration. Prieto-Potin I, Roman-Blas JA, Martinez-Calatrava MJ, et al. *Arthritis Res Ther* 2013;15:R81. doi 10.1186/ar4261.
- 100 Lysosomal storage diseases: Image D.** “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.





























Microbiology
































- 110 Stains: Image A.** *Trypanosoma lewisi* on Giemsa stain.  Courtesy of the US Department of Health and Human Services and Dr. Mae Melvin.
- 110 Stains: Image B.** *Tropheryma whipplei* on periodic acid–schiff stain. This image is a derivative work, adapted from the following source, available under : Dr. Ed Uthman.
- 110 Stains: Image C.** *Mycobacterium tuberculosis* on Ziehl-Neelsen stain.  Courtesy of the US Department of Health and Human Services and Dr. George P. Kubica.
- 110 Stains: Image D.** *Cryptococcus neoformans* on India ink stain.  Courtesy of the US Department of Health and Human Services.
- 110 Stains: Image E.** *Coccidioides immitis* on silver stain.  Courtesy of the US Department of Health and Human Services and Dr. Edwin P. Ewing, Jr.
- 112 Encapsulated bacteria.** Capsular swelling of *Streptococcus pneumoniae* using the Neufeld-Quellung test.  Courtesy of the US Department of Health and Human Services.
- 112 Catalase-positive organisms.** Oxygen bubbles released during catalase reaction. This image is a derivative work, adapted from the following source, available under : Courtesy of Stefano Nase. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this image available under .
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- 119 α -hemolytic bacteria.** α -hemolysis. This image is a derivative work, adapted from the following source, available under : Courtesy of Y. Tambe. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this image available under .
- 119 β -hemolytic bacteria.** β -hemolysis. This image is a derivative work, adapted from the following source, available under : Courtesy of Y. Tambe. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this image available under .
- 119 *Staphylococcus aureus*.** Gram stain.  Courtesy of the US Department of Health and Human Services and Dr. Richard Facklam.
- 120 *Streptococcus pneumoniae*.**  Courtesy of the US Department of Health and Human Services and Dr. Mike Miller.
- 120 *Streptococcus pyogenes* (group A streptococci).** Gram stain. This image is a derivative work, adapted from the following source, available under : Courtesy of Y. Tambe. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this image available under .
- 121 *Bacillus anthracis*.** Ulcer with black eschar.  Courtesy of the US Department of Health and Human Services and James H. Steele.
- 122 Clostridia (with exotoxins): Image A.** Gas gangrene due to *Clostridium perfringens* infection. This image is a derivative work, adapted from the following source, available under : Courtesy of Engelbert Schröpfer, Stephan Rauthe, and Thomas Meyer.
- 122 Clostridia (with exotoxins): Image B.** Pseudomembranous enterocolitis on colonoscopy. This image is a derivative work, adapted from the following source, available under : Courtesy of Klinikum Dritter Orden für die Überlassung des Bildes zur Veröffentlichung. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this image available under .
- 123 *Corynebacterium diphtheriae*.** Pseudomembranous pharyngitis. This image is a derivative work, adapted from the following source, available under : Courtesy of Wikimedia Commons. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this image available under .
- 123 *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.
- 123 *Nocardia* vs *Actinomyces*: Image A.** *Nocardia* on acid-fast stain. This image is a derivative work, adapted from the following source, available under : Adhikari L, Dey S, Pal R. Mycetoma due to *Nocardia farcinica*. *J Glob Infect Dis* 2010;2:194-195. doi 0.4103/0974-777X.62868.



















- 123 **Nocardia vs Actinomyces: Image B.** *Actinomyces israelii* on Gram stain.  Courtesy of the US Department of Health and Human Services.
- 124 **Mycobacteria.** Acid-fast stain.  Courtesy of the US Department of Health and Human Services and Dr. Edwin P. Ewing, Jr.
- 125 **Leprosy (Hansen disease): Image A.** “Glove and stocking” distribution. This image is a derivative work, adapted from the following source, available under : Bruno Jehle.
- 126 **Neisseria: Image A.** Photomicrograph.  Courtesy of the US Department of Health and Human Services and Dr. Mike Miller.
- 126 **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.
- 127 **Legionella pneumophila.**  Courtesy of the US Department of Health and Human Services and Grottola A, Forghieri F, Meacci M, et al. Severe pneumonia caused by *Legionella pneumophila* serogroup 11, Italy. *Emerg Infect Dis* 2012. doi 10.3201/eid1811.120216.
- 127 **Pseudomonas aeruginosa: Image A.** Blue-green pigment. This image is a derivative work, adapted from the following source, available under . Courtesy of Hansen. The image may have been modified by cropping, labeling, and/or captions. MediQ Learning, LLC makes this image available under .
- 127 **Pseudomonas aeruginosa: Image B.** Ecthyma gangrenosum. This image is a derivative work, adapted from the following source, available under : Gencer S, Ozer S, Gul AE, et al. Ecthyma gangrenosum without bacteremia in a previously healthy man: a case report. *J Med Case Rep* 2008;2:14. doi 10.1186/1752-1947-2-14. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MediQ Learning, LLC are reserved.
- 128 **Klebsiella.**  Courtesy of the US Department of Health and Human Services.
- 128 **Campylobacter jejuni.**  Courtesy of the US Department of Health and Human Services.
- 129 **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.
- 130 **Helicobacter pylori.**  Courtesy of the US Department of Health and Human Services, Dr. Patricia Fields, and Dr. Collette Fitzgerald.
- 130 **Spirochetes.** Dark-field microscopic appearance.  Courtesy of the US Department of Health and Human Services.
- 130 **Lyme disease: Image A.** *Ixodes* tick.  Courtesy of the US Department of Health and Human Services and Dr. Michael L. Levin.
- 130 **Lyme disease: Image B.** Erythema migrans.  Courtesy of the US Department of Health and Human Services and James Gathany.
- 131 **Syphilis: Image A.** Painless chancre in 1° syphilis.  Courtesy of the US Department of Health and Human Services and M. Rein.
- 131 **Syphilis: Image B.** Treponeme on dark-field microscopy.  Courtesy of the US Department of Health and Human Services and Renelle Woodall.
- 131 **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.
- 131 **Syphilis: Image E.** Condyloma lata.  Courtesy of the US Department of Health and Human Services and Susan Lindsley.
- 131 **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.
- 131 **Syphilis: Image G.** Congenital syphilis.  Courtesy of the US Department of Health and Human Services and Dr. Norman Cole.
- 131 **Syphilis: Image H.** Hutchinson teeth.  Courtesy of the US Department of Health and Human Services and Susan Lindsley.
- 132 **Gardnerella vaginalis.**  Courtesy of the US Department of Health and Human Services and M. Rein.
- 133 **Rickettsial diseases and vector-borne illnesses: Image A.** Rash of Rocky Mountain spotted fever.  Courtesy of the US Department of Health and Human Services.
- 133 **Rickettsial diseases and vector-borne illnesses: Image B.** *Ehrlichia morulae*. This image is a derivative work, adapted from the following source, available under : 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.
- 133 **Rickettsial diseases and vector-borne illnesses: Image C.** *Anaplasma phagocytophilum* in neutrophil.  Courtesy of the US 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.
- 134 **Mycoplasma pneumoniae.** This image is a derivative work, adapted from the following source, available under : Rottem S, Kosower NS, Kornspan JD. Contamination of tissue cultures by Mycoplasma. In: Ceccherini-Nelli L, ed: Biomedical tissue culture. doi 10.5772/51518.
- 135 **Systemic mycoses: Image A.** *Histoplasma*.  Courtesy of the US Department of Health and Human Services and Dr. D.T. McClenan.
- 135 **Systemic mycoses: Image B.** *Blastomyces dermatitidis* undergoing broad-base budding.  Courtesy of the US Department of Health and Human Services and Dr. Libero Ajello.
- 135 **Systemic mycoses: Image D.** “Captain’s wheel” shape of *Paracoccidioides*.  Courtesy of the US Department of Health and Human Services and Dr. Lucille K. Georg.

- 136 Cutaneous mycoses: Image G.** *Tinea versicolor*. This image is a derivative work, adapted from the following source, available under . Courtesy of Sarah (Rosenau) Korf. The image may have been modified by cropping, labeling, and/or captions. MediQ Learning, LLC makes this image available under .
- 137 Opportunistic fungal infections: Image A.** Budding yeast of *Candida albicans*. This image is a derivative work, adapted from the following source, available under . Courtesy of Y. Tambe. The image may have been modified by cropping, labeling, and/or captions. MediQ Learning, LLC makes this image available under .
- 137 Opportunistic fungal infections: Image B.** Germ tubes of *Candida albicans*. This image is a derivative work, adapted from the following source, available under . Courtesy of Y. Tambe. The image may have been modified by cropping, labeling, and/or captions. MediQ Learning, LLC makes this image available under .
- 137 Opportunistic fungal infections: Image C.** Oral thrush. Courtesy of the US Department of Health and Human Services and Dr. Sol Silverman, Jr.
- 137 Opportunistic fungal infections: Image E.** Conidiophores of *Aspergillus fumigatus*. Courtesy of the US Department of Health and Human Services.
- 137 Opportunistic fungal infections: Image F.** *Cryptococcus neoformans*. Courtesy of the US Department of Health and Human Services and Dr. Leonor Haley.
- 137 Opportunistic fungal infections: Image G.** *Cryptococcus neoformans* on mucicarmine stain. Courtesy of the US Department of Health and Human Services and Dr. Leonor Haley.
- 137 Opportunistic fungal infections: Image H.** *Mucor*. Courtesy of the US Department of Health and Human Services and Dr. Libero Ajello.
- 138 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 Reports* 2007;1:15. doi 10.1186/1752-1947-1-115.
- 138 Pneumocystis jirovecii: Image B.** Ground-glass opacities on CT. This image is a derivative work, adapted from the following source, available under . Oikonomou A and Prassopoulos P. Mimics in chest disease: interstitial opacities. *Insights Imaging* 2013; 4: 9-27. doi 0.1007/s13244-012-0207-7. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MediQ Learning, LLC are reserved.
- 139 Protozoa—GI 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.
- 139 Protozoa—GI infections: Image B.** *Giardia lamblia* cyst. Courtesy of the US Department of Health and Human Services.
- 139 Protozoa—GI infections: Image C.** *Entamoeba histolytica* trophozoites. Courtesy of the US Department of Health and Human Services.
- 139 Protozoa—GI infections: Image D.** *Entamoeba histolytica* cyst. Courtesy of the US Department of Health and Human Services.
- 139 Protozoa—GI infections: Image E.** *Cryptosporidium* oocysts. Courtesy of the US Department of Health and Human Services.
- 140 Protozoa—CNS infections: Image A.** Cerebral toxoplasmosis. This image is a derivative work, adapted from the following source, available under . Adurthi S, Mahadevan A, Bantwal R, et al. Utility of molecular and serodiagnostic tools in cerebral toxoplasmosis with and without tuberculous meningitis in AIDS patients: a study from South India. *Ann Indian Acad Neurol* 2010;13:263-270. doi 10.4103/0972-2327.74197. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MediQ Learning, LLC are reserved.
- 140 Protozoa—CNS infections: Image B.** *Toxoplasma gondii* tachyzoite. Courtesy of the US Department of Health and Human Services and Dr. L.L. Moore, Jr.
- 140 Protozoa—CNS infections: Image C.** *Naegleria fowleri* amoebas. Courtesy of the US Department of Health and Human Services.
- 140 Protozoa—CNS infections: Image D.** *Trypanosoma brucei gambiense*. Courtesy of the US Department of Health and Human Services and Dr. Mae Melvin.
- 141 Protozoa—hematologic infections: Image A.** *Plasmodium* trophozoite ring form. Courtesy of the US Department of Health and Human Services.
- 141 Protozoa—hematologic infections: Image B.** *Plasmodium* schizont containing merozoites. Courtesy of the US Department of Health and Human Services and Steven Glenn.
- 141 Protozoa—hematologic infections: Image C.** *Babesia*. Courtesy of the US Department of Health and Human Services.
- 142 Protozoa—others: Image A.** *Trypanosoma cruzi*. Courtesy of the US Department of Health and Human Services and Dr. Mae Melvin.
- 142 Protozoa—others: Image B.** *Leishmania donovani*. Courtesy of the US 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.
- 142 Protozoa—Others: Image C.** *Trichomonas vaginalis*. Courtesy of the US Department of Health and Human Services.
- 143 Nematodes (roundworms): Image A.** *Enterobius vermicularis* eggs. Courtesy of the US Department of Health and Human Services, B.G. Partin, and Dr. Moore.
- 143 Nematodes (roundworms): Image B.** *Ascaris lumbricoides* egg. Courtesy of the US Department of Health and Human Services.
- 143 Nematodes (roundworms): Image C.** Elephantiasis. Courtesy of the US Department of Health and Human Services.
- 144 Cestodes (tapeworms): Image A.** *Taenia solium* scolex. This image is a derivative work, adapted from the following source, available under . Courtesy of Robert J. Galindo. The image may have been modified by cropping, labeling, and/or captions. MediQ Learning, LLC makes this image available under .


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- 144 **Cestodes (tapeworms): Image C.** *Echinococcus granulosus* scolex. [CC-BY](#) Courtesy of the US Department of Health and Human Services and Dr. L.A.A. Moore, Jr.
- 144 **Cestodes (tapeworms): Image D.** Gross hyatid cyst of *Echinococcus granulosus*. [CC-BY](#) Courtesy of the US Department of Health and Human Services and Dr. I. Kagan.
- 144 **Cestodes (tapeworms): Image E.** *Echinococcus granulosus* cyst in liver. This image is a derivative work, adapted from the following source, available under [CC-BY](#): 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.
- 144 **Trematodes (flukes): Image A.** *Schistosoma mansoni* egg with lateral spine. [CC-BY](#) Courtesy of the US Department of Health and Human Services.
- 144 **Trematodes (flukes): Image B.** *Schistosoma mansoni* egg with terminal spine. [CC-BY](#) Courtesy of the US Department of Health and Human Services.
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- 145 **Ectoparasites: Image B.** Lice. [CC-BY](#) Courtesy of the US Department of Health and Human Services and Joe Miller.
- 149 **Herpesviruses: Image A.** Keratoconjunctivitis in HSV-1 infection. This image is a derivative work, adapted from the following source, available under [CC-BY](#): Yang 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.
- 149 **Herpesviruses: Image B.** Herpes labialis. [CC-BY](#) Courtesy of the US Department of Health and Human Services and Dr. Herrmann.
- 149 **Herpesviruses: Image E.** Shingles (varicella-zoster virus infection). This image is a derivative work, adapted from the following source, available under [CC-BY](#). Courtesy of Fisle. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this image available under [CC-BY](#).
- 149 **Herpesviruses: Image F.** Lymphadenopathy in VZV infection. This image is a derivative work, adapted from the following source, available under [CC-BY](#). Courtesy of Dr. James Heilman. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this image available under [CC-BY](#).
- 149 **Herpesviruses: Image G.** Atypical lymphocytes in Epstein-Barr virus infection. This image is a derivative work, adapted from the following source, available under [CC-BY](#): 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.
- 149 **Herpesviruses: Image I.** Roseola. [CC-BY](#) Courtesy of Emiliano Burzagli.
- 149 **Herpesvirus: Image J.** Kaposi sarcoma. [CC-BY](#) Courtesy of the US Department of Health and Human Services.
- 150 **HSV identification.** Positive Tzanck smear in HSV-2 infection. This image is a derivative work, adapted from the following source, available under [CC-BY](#). Courtesy of Yale Rosen. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this image available under [CC-BY](#).
- 152 **Yellow fever virus.** *Aedes aegypti* mosquito. [CC-BY](#) Courtesy of the US Department of Health and Human Services and James Gathany.
- 152 **Rotavirus.** [CC-BY](#) Courtesy of the US Department of Health and Human Services and Erskine Palmer.
- 153 **Rubella virus.** Rubella rash. [CC-BY](#) Courtesy of the US Department of Health and Human Services.
- 154 **Croup (acute laryngotracheobronchitis).** Steeple sign. Reproduced, with permission, from Dr. Frank Gaillard and www.radiopaedia.org.
- 154 **Measles (rubeola) virus: Image A.** Koplik spots. [CC-BY](#) Courtesy of the US 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.
- 154 **Measles (rubeola) virus: Image B.** Rash of measles. [CC-BY](#) Courtesy of the US Department of Health and Human Services.
- 155 **Mumps virus.** Swollen neck and parotid glands. [CC-BY](#) Courtesy of the US Department of Health and Human Services.
- 155 **Rabies virus: Image A.** Transmission electron micrograph. [CC-BY](#) Courtesy of the US Department of Health and Human Services Dr. Fred Murphy, and Sylvia Whitfield.
- 155 **Rabies virus: Image B.** Negri bodies. [CC-BY](#) Courtesy of the US Department of Health and Human Services and Dr. Daniel P. Perl.
- 156 **Ebola virus.** [CC-BY](#) Courtesy of the US Department of Health and Human Services and Cynthia Goldsmith.
- 161 **Prions.** Spongiform changes in Creutzfeld-Jacob disease. This image is a derivative work, adapted from the following source, available under [CC-BY](#). Courtesy of DRdoubleB. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this image available under [CC-BY](#).
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- 164 **Common vaginal infections: Image C.** *Candida* vulvovaginitis. [CC-BY](#) Courtesy of Mikael Haggström.
- 165 **ToRCHeS infections: Image A.** “Blueberry muffin” rash. This image is a derivative work, adapted from the following source, available under [CC-BY](#): Benmiloud S, Elhaddou G, Belghiti ZA, et al. Blueberry muffin syndrome. *Pan Afr Med J* 2012;13:23. PMID: PMC3527055.

























- 165 ToRCHeS infections: Image B.** 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.
- 166 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.
- 167 Pelvic inflammatory disease: Image A.** Purulent cervical discharge. This image is a derivative work, adapted from the following source, available under : Courtesy of SOS-AIDS Amsterdam. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this image available under .
- 167 Pelvic inflammatory disease: Image B.** Adhesions in Fitz-Hugh–Curtis syndrome.  Courtesy of Hic et nunc.
- 173 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.
- ### Immunology
- 191 Sinusoids of 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.
- 209 Immunodeficiencies.** 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.
- ### Pathology
- 217 Necrosis: Image A.** Coagulative necrosis.  Courtesy of the US Department of Health and Human Services and Dr. Steven Rosenberg.
- 217 Necrosis: Image B.** Liquefactive necrosis.  Courtesy of Daftblogger.
- 217 Necrosis: Image C.** Caseous necrosis. This image is a derivative work, adapted from the following source, available under . Courtesy of Dr. Yale Rosen. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this image available under .
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- 217 Necrosis: Image E.** Fibrinoid necrosis. This image is a derivative work, adapted from the following source, available under . Courtesy of Dr. Yale Rosen. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this image available under .
- 217 Necrosis: Image F.** Acral gangrene.  Courtesy of the US Department of Health and Human Services and William Archibald.
- 219 Infarcts: red vs. pale: Image B.** Pale infarct.  Courtesy of the US Department of Health and Human Services and Armed Forces Institute of Pathology.
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- 220 Types of calcification: Image B.** Metastatic calcification. This image is a derivative work, adapted from the following source, available under . Courtesy of Dr. Yale Rosen. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this image available under .
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- 222 Scar formation: Image A.** Hypertrophic scar. This image is a derivative work, adapted from the following source, available under : 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.
- 222 Scar formation: Image B.** Keloid scar. This image is a derivative work, adapted from the following source, available under . Courtesy of Dr. Andreas Settje. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this image available under .
- 223 Granulomatous diseases.** Granuloma.  Courtesy of Sanjay Mukhopadhyay.

- 225 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.
- 225 Amyloidosis: Image B.** Amyloid deposits on Congo red stain under polarized light. 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. MediQ Learning, LLC makes this image available under .
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- 232 Psammoma bodies.** Psammoma body in papillary carcinoma.  Courtesy of the US Department of Health and Human Services and Armed Forces Institute of Pathology.
- 233 Common metastases: Image A.** Breast cancer metastases to brain. This image is a derivative work, adapted from the following source, available under . Courtesy of Jordi March i Nogué. The image may have been modified by cropping, labeling, and/or captions. MediQ Learning, LLC makes this image available under .
- 233 Common metastases: Image B.** Thyroid cancer metastasis to brain.  Courtesy of the US Department of Health and Human Services and Armed Forces Institute of Pathology.
- 233 Common metastases: Image C.** Multiple metastases to liver. This image is a derivative work, adapted from the following source, available under . Courtesy of Dr. James Heilman. The image may have been modified by cropping, labeling, and/or captions. MediQ Learning, LLC makes this image available under .
- 233 Common metastases: Image D.** Pancreatic metastases to liver.  Courtesy of J. Hayman.
- 233 Common metastases: Image E.** Renal cell carcinoma metastases to bone. This image is a derivative work, adapted from the following source, available under . Courtesy of Hellerhoff. The image may have been modified by cropping, labeling, and/or captions. MediQ Learning, LLC makes this image available under .
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- 290 Myocardial infarction complications: Image B.** Drawing of pseudoaneurysm. This image is a derivative work, adapted from the following source, available under : Patrick J. Lynch and Dr. C. Carl Jaffe.
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- 291 Cardiomyopathies: Image A.** Dilated cardiomyopathy. This image is a derivative work, adapted from the following source, available under : Gho 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.
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- 297 Vasculitides: Image G.** Granulomatosis with polyangiitis (formerly Wegener) and PR3-ANCA/c-ANCA. Courtesy of M.A. Little.
- 297 Vasculitides: Image H.** Microscopic polyangiitis and MPO-ANCA/p-ANCA. Courtesy of the US Department of Health and Human Services and M.A. Little.
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Endocrine





























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















Gastrointestinal

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- 365 Cirrhosis and portal hypertension.** Splenomegaly and liver nodularity in cirrhosis. This image is a derivative work, adapted from the following source, available under [CC-BY](#). Courtesy of Inversitus. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this image available under [CC-BY](#).
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- 368 Hepatocellular carcinoma/hepatoma: Image A.** Gross specimen. Reproduced, with permission, from Jean-Christophe Fournet and Humpath.
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- 369 Jaundice.** Yellow sclera. [CC-BY](#) Courtesy of the US Department of Health and Human Services and Dr. Thomas F. Sellers.





























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- 386 Pathologic RBC forms: Image C.** Dacrocyte (“teardrop cell”). Image courtesy of Dr. Kristine Krafts.
- 386 Pathologic RBC forms: Image D.** Degmacyte (“bite cell”). Image courtesy of Dr. Kristine Krafts.
- 386 Pathologic RBC forms: Image E.** Echinocyte (“burr cell”). Image courtesy of Dr. Kristine Krafts.
- 386 Pathologic RBC forms: Image F.** Elliptocyte. Image courtesy of Dr. Kristine Krafts.
- 386 Pathologic RBC forms: Image G.** Macro-ovalocyte. Image courtesy of Dr. Kristine Krafts.
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

Hematology and Oncology

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- 387 Pathologic RBC forms: Image J.** Sickle cell.  Courtesy of the US Department of Health and Human Services and the Sickle Cell Foundation of Georgia, Jackie George, and Beverly Sinclair.
- 387 Pathologic RBC forms: Image K.** Spherocyte. Image courtesy of Dr. Kristine Krafts.
- 387 Pathologic RBC forms: Image L.** Target cell. Image courtesy of Dr. Kristine Krafts.
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- 392 Intrinsic hemolytic anemia: Image B.** Dactylitis. This image is a derivative work, adapted from the following source, available under . Pedram M, Jaseb K, Haghi S, et al. First presentation of sickle cell anemia in a 3.5-year-old girl: a case report. *Iran Red Crescent Med J* 2012;14:184-185.
- 393 Extrinsic hemolytic anemia: Image A.** Autoimmune hemolytic anemia. Image courtesy of Dr. Kristine Krafts.
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- 396 Coagulation disorders.** Hemarthrosis. This image is a derivative work, adapted from the following source, available under : Rodriguez-Merchan EC. Prevention of the musculoskeletal complications of hemophilia. *Adv Prev Med* 2012;2012:201271. doi 10.1155/2012/201271.
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- 401 Multiple myeloma: Image B.** RBC rouleaux formation. Image courtesy of Dr. Kristine Krafts.
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- 402 Leukemias: Image C.** Hairy cell leukemia. Image courtesy of Dr. Kristine Krafts.
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- 404 Chronic myeloproliferative disorders: Image B.** Essential thrombocytosis with enlarged megakaryocytes. Image courtesy of Dr. Kristine Krafts.
- 404 Chronic myeloproliferative disorders: Image C.** Myelofibrosis. This image is a derivative work, adapted from the following source, available under : Dr. Ed Uthman.
- 404 Chronic myeloproliferative disorders: Image D.** Dacrococyte (“teardrop cell”). Image courtesy of Dr. Kristine Krafts.
- 406 Warfarin.** Toxic effect. This image is a derivative work, adapted from the following source, available under : Fred H, van Dijk H. Images of memorable cases: cases 84 and 85. Connexions website. December 2, 2008. Available at <http://cnx.org/content/m14932/1.3/>.





















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





















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


























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- 431 **Calcium pyrophosphate deposition disease.** Calcium phosphate crystals. Image courtesy of Medical Research Council and Drs. P. Diepke and K. Swan.
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- 433 **Seronegative spondyloarthropathies: Image C, right.** Bamboo spine.  Courtesy of Heather Hawker.
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- 441 **Vascular tumors: Image C.** Cystic hygroma. This image is a derivative work, adapted from the following source, available under : Sannoh S, Quezada E, Merer DM, et al. Cystic hygroma and potential airway obstruction in a newborn: a case report and review of the literature. *Cases J* 2009;2:48. doi 10.1186/1757-1626-2-48. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.
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Neurology


















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- 452 **Syringomyelia.** Reproduced, with permission, from Dr. Frank Gaillard and www.radiopaedia.org.
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- 484 **Glaucoma: Images A (normal optic cup) and B (optic cup in glaucoma).** Image courtesy of EyeRounds.

- 484 **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. PMID: PMC3171497. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.
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- 489 **Cranial nerve 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.
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- 495 **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.
- 495 **Neurocutaneous disorders: Image B.** Leptomeningeal angioma in Sturge-Weber syndrome. Reproduced, with permission, from Dr. Frank Gaillard and www.radiopaedia.org.
- 495 **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 website. December 4, 2008. Available at: <http://cnx.org/content/m14923/1.3/>.
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- 495 **Neurocutaneous disorders: Image E.** Angiomyolipoma in tuberous sclerosis. This image is a derivative work, adapted from the following source, available under . Courtesy of KGH. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this image available under .
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- 495 **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.
- 495 **Neurocutaneous disorders: Image I.** Cerebellar hemangioblastoma histology. This image is a derivative work, adapted from the following source, available under . Courtesy of Nephron. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this image available under .
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- 496 **Adult primary brain tumors: Image A.** Glioblastoma multiforme at autopsy.  Courtesy of the US Department of Health and Human Services and Armed Forces Institute of Pathology.
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- 496 **Adult primary brain tumors: Image L.** Field of vision in bitemporal hemianopia. This image is a derivative work, adapted from the following source, available under . Courtesy of Wikimedia Commons. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this image available under .
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- 497 **Childhood primary brain tumors: Image C.** CT of medulloblastoma.  Courtesy of the US Department of Health and Human Services and Armed Forces Institute of Pathology.
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






















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- 547 **Nephritic syndrome: Image C.** Histology of rapidly progressive glomerulonephritis. Courtesy of the US Department of Health and Human Services and Uniformed Services University of the Health Sciences.
- 548 **Nephrotic syndrome: Image B.** Histology of focal segmental glomerulosclerosis. This image is a derivative work, adapted from the following source, available under . Courtesy of Nephron. The image may have been modified by cropping, labeling, and/or captions. MediQ Learning, LLC makes this image available under .
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- 552 **Pyelonephritis: Image B.** CT scan. Courtesy of the US Department of Health and Human Services and Armed Forces Institute of Pathology.
- 554 **Acute tubular necrosis: Image A.** Muddy brown casts. This image is a derivative work, adapted from the following source, available under . Courtesy of Dr. Serban Nicolescu.
- 554 **Renal papillary necrosis.** Courtesy of the US Department of Health and Human Services and William D. Craig, Dr. Brent J. Wagner, and Mark D. Travis.
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Reproductive

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- 574 Female reproductive epithelial histology.** Transformation zone. 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.
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- 592 Ovarian neoplasms: Image C.** Mature cystic teratoma. This image is a derivative work, adapted from the following source, available under . Courtesy of Nephron. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this image available under .
- 593 Ovarian neoplasms: Image D.** Call-Exner bodies. This image is a derivative work, adapted from the following source, available under . 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.
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- 594 Endometrial conditions: Image B.** 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.
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- 594 Endometrial conditions: Image E.** Endometritis. This image is a derivative work, adapted from the following source, available under . Courtesy of Nephron. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this image available under .
- 597 Malignant breast tumors: Image B.** 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.
- 597 Malignant breast tumors: Image C.** Paget disease of breast. This image is a derivative work, adapted from the following source, available under . Muttarak M, Siriya B, Kongmebol 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/bij.7.2.e16.
- 597 Malignant breast tumors: Image D.** Invasive ductal carcinoma. This image is a derivative work, adapted from the following source, available under . Zhou X-C, Zhou, Ye Y-H, et al. Invasive ductal breast cancer metastatic to the sigmoid colon. *World J Surg Oncol* 2012;10:256. doi 10.1186/1477-7819-10-256.
- 597 Malignant breast tumors: 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.
- 597 Malignant breast tumors: Image F.** Peau d'orange of inflammatory breast cancer. Courtesy of the US Department of Health and Human Services.
- 597 Varicocele.** Dilated pampiniform veins. Image courtesy of Dr. Bruce R. Gilbert.

Respiratory

- 607 Pneumocytes.** Type II pneumocyte. This image is a derivative work, adapted from the following source, available under . Courtesy of Dr. Thomas Cacceti.
- 607 Neonatal respiratory distress syndrome.** 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.

- 616 Rhinosinusitis.** This image is a derivative work, adapted from the following source, available under : Strek P, Zagolski O, Sktadzien J. Fatty tissue within the maxillary sinus: a rare finding. *Head Face Med* 2006;2:28. doi 10.1186/1746-160X-2-28.
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- 618 Obstructive lung diseases: Image B.** Centriacinar emphysema, gross specimen.  Courtesy of the US Department of Health and Human Services and Dr. Edwin P. Ewing, Jr.
- 618 Obstructive lung diseases: Image C.** CT of centriacinar emphysema. This image is a derivative work, adapted from the following source, available under : Oikonomou A, Prassopoulou P. Mimics in chest disease: interstitial opacities. *Insights Imaging* 2013;4:9-27. doi 10.1007/s13244-012-0207-7.
- 618 Obstructive lung diseases: Image D.** Barrel-shaped chest in emphysema. This image is a derivative work, adapted from the following source, available under . Courtesy of Dr. James Heilman. The image may have been modified by cropping, labeling, and/or captions. MediQ Learning, LLC makes this image available under .
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- 618 Obstructive lung disease: Image G.** Bronchiectasis in cystic fibrosis. This image is a derivative work, adapted from the following source, available under . Courtesy of Dr. Yale Rosen. The image may have been modified by cropping, labeling, and/or captions. MediQ Learning, LLC makes this image available under .
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- 620 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.
- 620 Pneumoconioses: Image C.** Ferruginous bodies in asbestosis. This image is a derivative work, adapted from the following source, available under . Courtesy of Nephron. The image may have been modified by cropping, labeling, and/or captions. MediQ Learning, LLC makes this image available under .
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- 624 Pneumonia: Image B.** Lobar pneumonia, gross specimen. This image is a derivative work, adapted from the following source, available under . Courtesy of Dr. Yale Rosen. The image may have been modified by cropping, labeling, and/or captions. MediQ Learning, LLC makes this image available under .
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- 625 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.
- 625 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. Thrombotic catheter-associated superior vena cava syndrome. *Case Rep Emerg Med* 2013; 2013: 793054. doi 10.1155/2013/793054.

- 626 **Lung cancer: Image B. Adenocarcinoma histology.**  Courtesy of the US Department of Health and Human Services and Armed Forces Institute of Pathology.
- 626 **Lung cancer: Image C. Squamous cell carcinoma.** This image is a derivative work, adapted from the following source, available under . Courtesy of Dr. James Heilman. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this image available under .
- 626 **Lung cancer: Image E. Large cell lung cancer.** This image is a derivative work, adapted from the following source, available under : Jala VR, Radde BN, Haribabu B, et al. Enhanced expression of G-protein coupled estrogen receptor (GPER/GPR30) in lung cancer. *BMC Cancer* 2012;12:624. doi 10.1186/1471-2407-12-624.

Index

A

- Abacavir, 184
for HIV, 186
- Abciximab, 214, 407
thrombogenesis and, 385
- Abdominal aorta, **342**
atherosclerosis in, 286, 645
bifurcation of, 609
- Abdominal aortic aneurysm, 286
- Abdominal colic
lead poisoning as cause, 389
- Abdominal distension
duodenal atresia as cause, 338
- Abdominal pain
Budd-Chiari syndrome as
cause, 368, 630
cilostazol/dipyridamole as
cause, 407
Clostridium difficile as cause, 630
diabetic ketoacidosis as cause, 331
ectopic pregnancy as cause, 589
Henoch-Schönlein purpura as
cause, 297, 633
hypercalcemia as cause, 542
hyperparathyroidism as cause, 326
intussusception as cause, 362
irritable bowel syndrome as
cause, 360
McBurney sign as, 633
Meckel diverticulum as cause, 567
pancreas divisum as cause, 339
pancreatic cancer as cause, 373
panic disorder as cause, 517
polyarteritis nodosa as cause, 296
porphyria as cause, 395
Rovsing sign as, 633
- Abdominal wall, developmental
defects in, 338
- Abducens nerve (6th cranial
nerve), **479**
location in brain stem, 477
ocular motility and, 488
palsy of, 489
pathway for, 478
- Abductor digiti minimi muscle, 421
- Abductor pollicis brevis muscle, 241
- Abetalipoproteinemia, 386
- Abnormal passive abduction, 416
- Abnormal passive adduction, 416
- ABO blood classification, 382
- ABO hemolytic disease of the
newborn, **382**
- Abscess, 442
- Absence seizures, 494
drug therapy for, 500
treatments for, 638
- Absolute risk reduction (ARR), 34,
646
- Absorption disorders, anemia caused
by, 388
- Abuse
confidentiality exceptions and, 41
dependent personality disorder
and, 519
- Acalculia, 464
- Acamprosate
for alcoholism, 523, 638
diarrhea caused by, 252
- Acanthocytes, 386
- Acanthocytosis, 81
- Acantholysis, 439
pemphigus vulgaris and, 443
- Acanthosis, 439
psoriasis as cause, 440
- Acanthosis nigricans, 229, 444
acanthosis and, 439
stomach cancer as cause, 356
- Acarbose, 335
diarrhea caused by, 252
- Accessory nerve (11th cranial
nerve), **479**
lesion in, 480
location in brain stem, 477
pathway for, 478
- Accessory pancreatic duct, 339, 347
- Accuracy vs. precision, **35**
- Acebutolol, 249
angina and, 299
- ACE inhibitors, **559**
for acute coronary syndromes, 290
C1 esterase inhibitor deficiency
and, 199
for dilated cardiomyopathy, 291
dry cough caused by, 254
for heart failure, 292
for hypertension, 298
naming convention for, 255
preload/afterload, effect on, 267
as teratogens, 564
- Acetaldehyde dehydrogenase, in
ethanol metabolism, 83
- Acetaldehyde, in ethanol
metabolism, 83
- Acetaminophen, **446**
vs. aspirin, in pediatric patients, 446
free radical injury and, 221
necrosis caused by, 252
for osteoarthritis, 430
for tension headaches, 494
toxicity effects, 446
toxicity treatment for, 251
- Acetazolamide, 254, **557**
for glaucoma, 498
metabolic acidosis caused by, 543
in nephron physiology, 537
for pseudotumor cerebri, 471
site of action, 556
- Acetoacetate, metabolism of, 102
- Acetone breath, in diabetic
ketoacidosis, 331
- Acetylation, 57
- Acetylcholine (ACh), 455
in Alzheimer disease, 491, 511
anticholinesterase effect on, 244
in Huntington disease, 71, 462, 511
in nervous system, 241
opioid effect on, 499
pacemaker action potential
and, 275
in Parkinson disease, 511
- Acetylcholine (ACh) receptor
agonists, 503
- Acetylcholine (ACh) receptors, **241**
in cholinergic drugs, 243
- Acetylcholine (AChR) receptor, 229
- Acetylcholinesterase (AChE)
cholinesterase inhibitor
poisoning, 244
malathion and, 183
neural tube defects and, 451
- Acetylcholinesterase (AChE)
inhibitors
for Alzheimer disease, 505
in cholinergic drugs, 243
for myasthenia gravis, 436
naming convention for, 255
toxicity treatment for, 251
- Acetyl-CoA carboxylase, 84
vitamin B₇ and, 79
- Achalasia, **354**
esophageal cancer and, 355
- Achilles reflex, 476
disc herniation and, 423
- Achilles tendon xanthomas, 285, 630
- Achlorhydria
stomach cancer and, 356
VIPomas as cause, 350
- Achondroplasia, **426**
autosomal dominance of, 71
chromosome associated with, 75
endochondral ossification in, 425
- AChR (acetylcholine receptor), 229
- Acid-base physiology, **543**
- Acidemia, 543
diuretic effect on, 558
- Acidic amino acids, 92
- Acidosis, **543**
contractility in, 267
hyperkalemia caused by, 542
- Acid phosphatase, in neutrophils, 378
- Acid reflux
esophageal strictures and, 354
esophagitis and, 354
H₂ blockers for, 374
proton pump inhibitors for, 374
sclerodermal esophageal
dysmotility as cause, 354
- Acid suppression therapy, **374**
- Acinetobacter* spp., 168
- Acinetobacter baumannii*, 181
- Acne, 440
danazol as cause, 602
glucocorticoids as cause, 212
PCOS as cause, 591
prednisone as cause, 412
as skin papules, 438
tetracyclines for, 175
- Acoustic neuromas, 453
- Acoustic schwannomas, 71, 630
- Acquired hydroceles, 598
- Acrodermatitis enteropathica, 82
- Acromegaly, **327**
GH as cause, 311
octreotide for, 375
somatostatin analogs for, 309
somatostatin for, 336
- Acromion, 417
- ACTH. *See* Adrenocorticotropic
hormone (ACTH)
- Actin filaments in epithelial cells, 438
- Acting out, as ego defense, 508
- Actinic keratosis, 444, 445
key associations, 641
- Actin, in cytoskeleton, 60
- Actinomyces* spp.
as anaerobic organism, 111
in Gram-positive algorithm, 118
morphology of, 109
vs. *Nocardia* spp., 123
penicillin G/V for, 170

- Actinomyces israelii*
 branching rods in, 169
 lab findings in, 635
 pigment produced by, 113
- Action/willpower stage of overcoming addiction, 521
- Activated carriers, **86**
- Active errors, 46
- Active immunity, **203**
- Acute chest syndrome, 392
- Acute cholestatic hepatitis
 as drug reaction, 252
 macrolides as cause, 176
- Acute closure, 484
- Acute coronary syndrome
 ADP receptor inhibitors for, 407
 heparin for, 405
 nitrates for, 299
 treatments for, **290**
- Acute cystitis, 544
- Acute disseminated encephalomyelitis, 493
- Acute dystonia, 245
- Acute gastritis, 356
- Acute glomerulonephritis, 553
- Acute hemolytic transfusion reactions, 206
 as type II hypersensitivity reactions, 204
- Acute hemorrhagic cystitis, 148
- Acute inflammation, 219
- Acute inflammatory demyelinating polyradiculopathy, **493**
- Acute intermittent porphyria, 395
- Acute interstitial nephritis, **554**
- Acute lymphoblastic leukemia (ALL), 402
 key associations, 644
 methotrexate for, 409
 oncogenes and, 230
- Acute mesenteric ischemia, 362
 presentation of, 633
- Acute myeloid leukemia (AML), 402
 chromosomal translocations and, 403
 cytarabine for, 409
 key associations, 644
 myelodysplastic syndromes and, 401
- Acute pancreatitis, **373**
 DIC and, 643
 hyperparathyroidism as cause, 326
 hypertriglyceridemia as cause, 105
 key associations, 644
 necrosis and, 217
- Acute pericarditis, **294**
- Acute-phase proteins, 200
- Acute-phase reactants, **198**
- Acute poststreptococcal glomerulonephritis, 546
- Acute promyelocytic leukemia
 all-*trans* retinoic acid for, 77
 treatments for, 638
- Acute pulmonary edema, 499
- Acute pyelonephritis, 552
 lab findings in, 638
 renal papillary necrosis and, 554
 WBC casts in, 544
- Acute renal failure, 553
- Acute respiratory distress syndrome (ARDS), **621**
 acute pancreatitis as cause, 373
 eclampsia as cause, 590
 as inhalational injury, 222
 as restrictive lung disease, 619
- Acute stress disorder, 517
- Acute transplant rejection, 211
- Acute tubular necrosis, **554**
 granular casts in, 544
 intrinsic renal failure caused by, 553
- Acyclovir, **184**
- Adalimumab, 214, 448
 for Crohn disease, 359
- Adaptive immunity, **192**
- Addison disease, 318
 metabolic acidosis caused by, 543
 presentation of, 633
- Additive drug interactions, 237
- Adductor longus muscle, 347
- Adenine
 methylation of, 48
 Shiga/Shiga-like toxins and, 116
- Adenocarcinomas
 carcinogens causing, 231
 of esophagus, 355
 of gallbladder, 372
 gastrointestinal, 229
 of lungs, 626
 nomenclature for, 228
 nonbacterial thrombotic endocarditis and, 229
 of pancreas, **373**
 pectinate line and, 345
 of prostate, 599
 of stomach, 356, 645
 Trousseau's syndrome and, 229
- Adenohypophysis, 307
 embryologic derivatives of, 563
 hypothalamus and, 456
- Adenomas
 of adrenal cortex, 645
 of bone, 428
 colorectal, 364
 hyperparathyroidism as cause, 645
 nomenclature for, 228
 of pituitary, 326
 in primary hyperparathyroidism, 325
 of thyroid, 324
- Adenomatous colonic polyps, 363
- Adenomyosis of endometrium, 594
- Adenopathy
 Kawasaki disease as cause, 296
 Whipple disease as cause, 634
- Adenosine
 as antiarrhythmic drug, 304
 cutaneous flushing caused by, 251
 pacemaker action potential and, 275
- Adenosine deaminase deficiency, **50**, 209
- Adenosine diphosphate (ADP), 385
- Adenosine triphosphate (ATP)
 ATP synthase production of, 89
 cell injury and, 218
 in electron transport chain, 89
 expenditure vs. time, 103
 in glycogen regulation, 97
 in nephron physiology, 537
 production of, **86**
 in TCA cycle, 88
 in urea cycle, 93
- Adenosine triphosphate (ATP)
 synthase inhibitors, 89
- Adenoviruses
 characteristics of, 148
 conjunctivitis caused by, 484
 as DNA viruses, 147
 as naked viruses, 147
 pneumonia caused by, 624
 watery diarrhea caused by, 162
- Adherens junctions, 438
- Adhesion, 362
- Adipose lipolysis, 300
- Adipose stores, in fasting/starvation states, 103
- Adipose tissue, estrogen production by, 577
- Adjustment disorder, 517
- Adoption studies, 32
- ADP receptor inhibitors, **407**
- Adrenal adenomas
 Cushing syndrome caused by, 317
 hyperaldosteronism caused by, 318
- Adrenal carcinomas
 Cushing syndrome caused by, 317
 P-glycoprotein in, 232
- Adrenal cortex, **306**
 embryologic derivatives of, 563
 progesterone production in, 577
- Adrenal hemorrhage, 630
 Waterhouse-Friderichsen syndrome and, 318
- Adrenal hyperplasia
 Cushing syndrome caused by, 317
 hyperaldosteronism and, 318
- Adrenal insufficiency, **318**
 anovulation caused by, 591
 fludrocortisone for, 336
 glucocorticoids for, 336
 vitamin B₅ deficiency as cause, 78
- Adrenal medulla, **306**
 in nervous system, 241
 neuroblastomas of, 319
 pheochromocytomas in, 320
 tumors in, 645
- Adrenal steroids, **312**
- Adrenocortical adenomas, 642
- Adrenocortical atrophy, 336
- Adrenocortical insufficiency
 as drug reaction, 252
 presentation of, 633
- Adrenocorticotrophic hormone (ACTH)
 adrenal cortex regulation of, 306
 adrenal insufficiency and, 318
 in Cushing syndrome, 229, 317
 secretion of, 307
 signaling pathways of, 316
- Adrenoleukodystrophy, **493**
- Adrenoreceptors, in noradrenergic drugs, 243
- Adult T cell leukemia, 231
- Adult T-cell lymphoma, 400
- Advance directives, **41**
- Aedes* mosquitoes, yellow fever transmitted, by, 152
- Aerobic metabolism, 103
- Aerobic organisms, **111**
- Afferent arteriole, 532
 ANP/BNP effect on, 540
 constriction of, 535
 dopamine, effect on, 541
 in filtration, 535
- Afferent nerves, 279
- Aflatoxin
 as carcinogens, 231
 hepatocellular carcinoma and, 368
- Aflatoxins, 137
- African sleeping sickness, 140
- Afterload, in cardiac output, 267
- Agammaglobulinemia
 chromosome associated with, 75
- Agarose gel electrophoresis, 64
- Agars for bacterial culture, 111
- Agenesis, 563
- Age-related macular degeneration, **485**
- Aggregatibacter actinomycetemcomitans*, 293
- Agnosia, in dementia, 513
- Agonist potency and efficacy, 240
- Agoraphobia, 517
- Agranulocytosis
 clozapine as cause, 525
 as drug reaction, 252
 epilepsy drugs causing, 500
 sulfa drug allergies as cause, 254
 thionamides as cause, 335
- Agraphia, cause of, 464
- AIDS (acquired immunodeficiency syndrome)
 bacillary angiomatosis and, 441
 diagnosis of, 158
 marijuana as appetite stimulant in, 523
 opportunistic infections in, 644
 primary central nervous system lymphoma (PCL) and, 400
 progressive multifocal leukoencephalopathy and, 493
 as STI, 167
 toxoplasmosis and, 140
- AIDS retinitis, 149
- Air emboli, 617
- Akathisia, 458
- Akinesia, in Parkinson disease, 461, 633
- ALA dehydratase, in lead poisoning, 395
- Alanine
 ammonia transport by, 93
 in pyruvate dehydrogenase complex deficiency, 88
- Alanine aminotransferase (ALT), 88, 366
- Alar plate, 450

- Albendazole
for *Echinococcus granulosus*, 144
- Albinism, 439
catecholamine synthesis/tyrosine catabolism and, 95
Chédiak-Higashi syndrome and, 209
locus heterogeneity and, 69
- Albright hereditary osteodystrophy, 325
- Albumin
as acute-phase reactant, 198
calcium and, 313
as liver marker, 366
plasma volume and, 533
- Albuminuria, 533
- Albuterol, 246
for asthma, 628
- Alcohol dehydrogenase, in ethanol metabolism, 83
- Alcoholic cirrhosis, 367, 644
alcoholism as cause, 523
cholelithiasis and, 372
zinc deficiency and, 82
- Alcoholic hallucinosis, 524
- Alcoholic hepatitis, 367
- Alcoholic liver disease, 367
- Alcoholism, 523
acute pancreatitis caused by, 373
anemia caused by, 390
in anemia taxonomy, 388
brain lesions and, 464
cardiomyopathy caused by, 291
cataracts and, 483
chronic pancreatitis caused by, 373
cirrhosis caused by, 365
common organisms affecting, 162
cytochrome P-450 and, 254
delirium tremens and, 524
esophageal cancer and, 355
ethanol metabolism and, 83
folate deficiency caused by, 390
gastritis in, 356
hepatitis caused by, 346
hypertension and, 284
ketone bodies in, 102
Klebsiella in, 128
Korsakoff syndrome and, 512
liver pathology serum markers in, 366
lung abscesses and, 624
magnesium levels in, 314
Mallory-Weiss syndrome in, 354
osteonecrosis caused by, 427
osteoporosis and, 426
pancreatitis caused by, 252
porphyria caused by, 395
sideroblastic anemia caused by, 389
subdural hematomas and, 469
treatments for, 638
vitamin B₁ deficiency in, 77
vitamin B₉ deficiency in, 79
wet beriberi as cause, 631
- Alcohol-related disorders
readmissions caused by, 45
- Alcohols, as infection control technique, 187
- Alcohol use
essential tremor, effect on, 461
gout and, 431
head and neck cancer and, 616
intoxication and withdrawal, 522
in utero, 284
loss of orientation caused by, 512
pancreatitis and, 644
sexual dysfunction caused by, 520
sleep, effect on, 457
suicide and, 516
teratogenic effects of, 564
- Alcohol withdrawal
benzodiazepines for, 512
drug therapy for, 524
tactile hallucinations in, 513
- Aldesleukin, 213
- Aldolase B, 91
- Aldose reductase, 92
- Aldosterone, 540
adrenal cortex secretion of, 306
Gitelman syndrome as cause, 538
kidney effects, 541
in nephron physiology, 537
in primary adrenal insufficiency, 318
in renal tubular acidosis, 544
in SIADH, 328
signaling pathways for, 316
in syndrome of apparent mineralocorticoid excess, 538
- Aldosterone antagonists, 298
- Aldosterone synthase, 312
- Alemtuzumab, 214
- Alendronate, 447
- Aliskiren, 559
- Alkalemia, 543
diuretic effect on, 558
- Alkaline phosphatase (ALP), 366, 427
in bone disorders, 428
in hyperparathyroidism, 326
in Paget disease of bone, 427
in thyroid storm, 323
as tumor marker, 232
- Alkalosis, 543
bulimia nervosa as cause, 520
hypokalemia caused by, 542
- Alkaptonuria, 96
catecholamine synthesis/tyrosine catabolism and, 95
- ALK gene, 230
lung cancer and, 626
- Alkylating agents, 410
as carcinogens, 231
in cell cycle, 408
targets of, 408
as teratogens, 564
- Allantois, 567
- Allelic heterogeneity, 69
- Allergic bronchopulmonary aspergillosis, 137
- Allergic contact dermatitis, 440
- Allergic reaction to blood transfusion, 206
- Allergic rhinitis, 440
- Allergies, as hypersensitivity reaction, 204
- Allotransplants, 210
- Allopurinol
for gout, 431, 448, 639
for kidney stones, 549
for Lesch-Nyhan syndrome, 50
rash caused by, 253
- All-trans retinoic acid
for acute promyelocytic leukemia, 77, 638
- Alopecia
doxorubicin as cause, 410
etoposide/teniposide as cause, 411
minoxidil for, 603
syphilis as cause, 131
tinea capitis and, 136
vitamin A toxicity as cause, 77
vitamin B₂ deficiency as cause, 78
vitamin B₇ deficiency as cause, 79
- α -1,4-glucosidase
in glycogen metabolism, 98
- α ₁-antagonists
for benign prostatic hyperplasia, 638
for BPH, 599
naming convention for, 255
- α ₁-antitrypsin
elastin and, 64
- α ₁-antitrypsin deficiency, 369
emphysema and, 618
hepatocellular carcinoma and, 368
liver cancer and, 645
- α ₂-agonists, 247
- α ₂-antagonists, 528
- α -adrenergic agonists, 627
- α -agonists, 498
- α -amanitin
RNA polymerase inhibition by, 54
- α -amylase, 352
- α -antagonists
for pheochromocytomas, 320, 640
- α -blockers, 248
for cocaine overdose, 522
- α cells, 307
glucagonomas in, 332
glucagon production by, 309
- α -dystroglycan
muscular dystrophy and, 73
- α -fetoprotein
in anencephaly, 636
anencephaly and, 451
in ataxia-telangiectasia, 209
in Down syndrome, 74, 635
in Edwards syndrome, 74
in hepatocellular carcinoma, 368
neural tube defects and, 451
in spina bifida, 636
as tumor marker, 232
in yolk sac tumors, 598
- α -galactosidase A
in Fabry disease, 100
- α -glucosidase inhibitors, 335
- α -hemolytic bacteria, 119
- α -ketoglutarate
hyperammonemia and, 93
- α -ketoglutarate dehydrogenase, 88
in metabolic pathways, 85
vitamin B₁ and, 77
- α -methyl dopa, 247
anemia and, 393
- α -methyl dopa, for gestational hypertension, 590
- α -thalassemia, 388
chromosome associated with, 75
- α toxin, 117, 122
- Alport syndrome, 547
cataracts and, 483
collagen deficiency in, 61
presentation of, 632
X-linked dominant inheritance of, 70
- Alprazolam, 501
- ALT (alanine transaminase)
in toxic shock syndrome, 119
- Alteplase, 383, 407
- Alternative hypothesis, 37
- Altitude, respiratory response to, 615
- Altitude sickness, 615
acetazolamide for, 557
- Altruism, as ego defense, 509
- Aluminum hydroxide, 375
- Alveolar gas equation, 614, 647
- Alveolar period, 606
- Alveolar PO₂, 614
- Alveolar sacs, 608
- Alveolar ventilation, 610
- Alveoli, 606
pneumocytes and, 607
- Alzheimer disease, 491
amyloidosis in, 225
dementia caused by, 513
Down syndrome and, 74
drug therapy for, 244, 505
ex vacuo ventriculomegaly caused by, 471
findings associated with, 643
lab findings in, 637
neurotransmitter changes in, 511
neurotransmitters for, 455
senile plaques in, 636
- Amanita phalloides*
necrosis caused by, 252
RNA polymerase inhibition by, 54
- Amantadine, 184, 504
- Ambiguous genitalia
46,XY DSD as cause, 586
ovotesticular disorder of sex development as cause, 585
placental aromatase deficiency as cause, 586
- Amebiasis, 139
- Amenorrhea
anorexia nervosa as cause, 520
antiandrogens as cause, 603
cirrhosis as cause, 365
Cushing syndrome as cause, 317
cystic fibrosis as cause, 72
ectopic pregnancy and, 589
key associations, 645
menopause as cause, 582
Müllerian agenesis as cause, 571
PCOS as cause, 591
pituitary prolactinomas as cause, 309
Sheehan syndrome as cause, 632
Turner syndrome as cause, 585

- Amides
as local anesthetics, 503
- Amikacin, 170, 174
- Amiloride, 558
for diabetes insipidus, 328
for Gitelman syndrome, 538
in nephron physiology, 537
- Amine precursor uptake
decarboxylase (APUD), 319
- Amines
MAO inhibitors and, 528
- Amine whiff test for bacterial
vaginosis, 132
- Amino acids, **92**
blood-brain barrier and, 455
derivatives of, **94**
in urea cycle, 93
- Aminoaciduria, 536
- Aminoacyl-tRNA, 57
- Aminoacyl-tRNA synthase, 56
- Aminocaproic acid
for thrombolytic toxicity, 407
- Aminoglycosides, 170, **174**
acute tubular necrosis caused
by, 554
magnesium levels and, 314
in pregnancy, avoiding, 187
as protein synthesis inhibitors, 174
for *Pseudomonas aeruginosa*, 127,
640
as teratogens, 564
toxicity caused by, 254
- Aminopenicillins
characteristics of, 171
for enterococci, 639
- Amiodarone, 303
cytochrome P-450 and, 254
hypothyroidism caused by, 252, 322
photosensitivity caused by, 253
pulmonary fibrosis caused by, 254
restrictive lung disease and, 619
- Amitriptyline, 527
for migraine headaches, 494, 640
for tension headaches, 494
- Amlodipine, 298
- Ammonia intoxication, **93**
- Ammonia transport, **93**
- Ammonium chloride
for amphetamine toxicity, 251
for drug overdoses, 238
- Amnesia, **512**
brain lesions causing, 464
- Amnionitis, 123
- Amniotic fluid abnormalities, **589**
- Amniotic fluid embolism, 617
acute respiratory distress syndrome
as cause, 621
- Amoxapine, 527
- Amoxicillin, 170
characteristics of, 171
for *Haemophilus influenzae*, 126
for *Helicobacter pylori*, 130
as prophylaxis, 181
- Amphetamines, 246
intoxication and withdrawal, 522
for narcolepsy, 521
as noradrenergic drug, 243
- norepinephrine and, 243
pulmonary arterial hypertension
caused by, 622
as weak bases, 238
- Amphotericin B, 181, **182**
for *Candida albicans*, 137, 639
for leishmaniasis, 142
for mucormycosis, 137
for *Naegleria fowleri*, 140
for systemic mycoses, 135
- Ampicillin, 170
characteristics of, 171
Clostridium difficile and, 122
for endometritis, 594
for *Listeria monocytogenes*, 123
for meningitis, 163
pseudomembranous colitis caused
by, 252
- Ampulla of Vater, 347
- Amygdala, 458
lesions in, 464
- Amylase, in pancreatitis, 373
- Amylin analogs, 335
- Amyloid angiopathy
intraparenchymal hemorrhage
caused by, 469
- Amyloidosis, **225**, 548
carpal tunnel syndrome and, 418
chronic inflammation as
cause, 219
lab findings in, 637
multiple myeloma and, 401
restrictive/infiltrative
cardiomyopathy caused
by, 291
serum amyloid A in, 198
- Amyotrophic lateral sclerosis
(ALS), 644
riluzole for, 505
spinal cord lesions in, 474
- Anabolic steroids
hepatic adenomas and, 368
- Anaerobic metabolism, 103
- Anaerobic organisms, **111**
aspiration and, 162
clindamycin for, 175
metronidazole for, 178
pneumonia caused by, 162
- Anal cancer
HIV and, 160
oncogenic microbes and, 231
- Anal fissures, 345
pectinate line and, 345
- Anal pruritus
Enterobius as cause, 145
pinworms as cause, 143
- Anal wink reflex, 476
- Anaphase, 58
- Anaphylaxis, 204
blood transfusion as cause, 206
complement and, 199
epinephrine for, 246
shock caused by, 292
- Anaplasia, 226
- Anaplasma* spp., 130
anaplasmosis caused by, 133
animal transmission of, 132
- Anaplasmosis, **133**
animal transmission of, 132
- Anaplastic thyroid carcinomas, 324
- Anastrozole, 601
reproductive hormones and, 600
- Anatomy
cardiovascular, 265
of coronary artery, **265**
endocrinal, 306–307
gastrointestinal, 339–348
hematologic/oncologic, 378–381
musculoskeletal, 416–424
neurological, 453–475
renal, 532
reproductive, 573–576
respiratory, 608–609
USMLE Step 1 preparation
for, 258
- Ancylostoma* spp.
diseases associated with, 145
infection routes, 142
- Ancylostoma duodenale*, 143
- Androblastomas, 598
- Androgen-binding protein
Sertoli cell secretion of, 576
- Androgen insensitivity
syndrome, **586**
- Androgen-receptor complex
pharmacologic control of, 600
- Androgen receptor defect, 586
- Androgens, **582**
adrenal cortex secretion of, 306
adrenal steroids and, 312
in PCOS, 591
- Androstenedione, 312, 582
pharmacologic control of, 600
- Anemia, **388**
amphotericin B as cause, 182
Ancylostoma and, 145
anorexia nervosa as cause, 520
azathioprine as cause, 212
babesiosis as cause, 141
blood oxygen in, 613
blood transfusion therapy for, 399
chloramphenicol as cause, 175
cirrhosis as cause, 365
cold agglutinin disease as
cause, 632
colorectal cancer as cause, 364
cytarabine as cause, 409
Diphyllobothrium latum as
cause, 144
as drug reaction, 252
epilepsy drugs causing, 500
ESR in, 224
extrinsic hemolytic, **393**
fibroid tumors as cause, 594
hookworms as cause, 143
intrinsic hemolytic, **392**
kwashiorkor as cause, 82
lab values, **394**
macrocytic, **390**
macro-ovalocytes in, 386
malaria as cause, 141
microcytic, hypochromic, **388**
multiple myeloma as cause, 401
nonhemolytic, normocytic, **391**
- nonhomologous end joining
and, 53
- normocytic, normochromic, **391**
- Plummer-Vinson syndrome as
cause, 354, 631
in pregnancy, 580
pure red cell aplasia as cause, 229
recombinant cytokines for, 213
renal failure as cause, 553
ringed sideroblasts in, 387
scurvy as cause, 80
sirolimus as cause, 212
spherocytes in, 387
sulfa drug allergies as cause, 254
thionamides as cause, 335
trimethoprim as cause, 177
tropical sprue as cause, 358
vitamin B₉ deficiency as cause, 79
vitamin B₁₂ deficiency as cause, 80
vitamin E deficiency as cause, 81
Wilson disease as cause, 371
- Anemia of chronic disease, 391
hepcidin in, 198
rheumatoid arthritis as cause, 430
- Anemic infarcts, 219
- Anencephaly, 451
lab findings in, 636
polyhydramnios and, 589
- Energy, **202**
- Anesthetics
general principles, **502**
inhaled, **502**
intravenous, **502**
local, **503**
- Aneuploidy, 585
- Aneurysms, **468**
atherosclerosis as cause, 286
Ehlers-Danlos syndrome and, 63
Marfan syndrome as cause, 71
MI as cause, 288
superior vena cava syndrome
and, 625
- Angelman syndrome, 69
chromosome associated with, 75
- Angina, 287
aortic stenosis as cause, 273
atherosclerosis as cause, 286
calcium channel blockers for, 298
cilostazol/dipyridamole for, 407
cocaine as cause, 522
drug therapy for, **299**
glycoprotein IIb/IIIa inhibitors
for, 407
hydralazine as cause, 298
nitrates for, 299
presentation of, 630
ranolazine for, 299
treatments for, 641
- Angina pectoris
β-blockers for, 249
- Angiodysplasia, 362
- Angioedema
ACE inhibitors as cause, 559
C1 esterase inhibitor deficiency as
cause, 199
scombroid poisoning as cause, 250

- Angiofibromas, 495
- Angiogenesis
 bevacizumab and, 412
 in cancer, 227
 wound healing and, 223
- Angiokeratomas, 100
- Angiomatosis
 von Hippel-Lindau disease as
 cause, 495, 633
- Angiomyolipomas, 495
- Angiosarcomas, 368, 441
 carcinogens causing, 231
 nomenclature for, 228
- Angiotensin II, 312, 540
 ACE inhibitor effects on, 559
 kidney effects, 541
 in nephron physiology, 537
 signaling pathways for, 316
- Angiotensin II receptor
 blockers, 559
 for heart failure, 292
 for hypertension, 298
 naming convention for, 255
 preload/afterload, effect on, 267
- Angiotensinogen, 540
- Angry patients, 42
- Anhedonia, 515
- Anhidrosis
 Horner syndrome as cause, 487,
 633
 Pancoast tumor as cause, 625
- Anidulafungin, 181, 183
- Aniline dyes
 transitional cell carcinoma
 and, 551
- Aniridia
 in WAGR complex, 551
- Anisocytosis, 378
- Anitschkow cells
 in rheumatic fever, 294
- Ankylosing spondylitis, 433
 etanercept for, 448
 HLA-B27 and, 193, 643
 infliximab/adalimumab for, 448
 lab findings in, 635
 therapeutic antibodies for, 214
- Ankyrin
 hereditary spherocytosis and, 71
- Annular pancreas, 339
- Anopheles* mosquito, 141
- Anopia, 489
- Anorectal varices, 344
 cirrhosis as cause, 365
- Anorexia nervosa, 520
 anovulation caused by, 591
 treatments for, 638
- Anorexia (symptom)
 amphetamines as cause, 522
 hypothalamus and, 456
- Anosmia
 zinc deficiency as cause, 82
- ANOVA tests, 39
- Anovulation
 causes of, 591
 endometrial hyperplasia and, 594
- ANP. *See* Atrial natriuretic peptide
 (ANP)
- Antacids, 375
 metabolic alkalosis caused by, 543
- Anterior cerebral artery, 466
 in cavernous sinus, 481
 cingulate herniation and, 498
 in circle of Willis, 466
 stroke, effect on, 467
- Anterior chamber of eye, 482
- Anterior communicating artery
 in circle of Willis, 466
 saccular aneurysm effect on, 468
- Anterior cruciate ligament (ACL)
 injury
 anterior drawer sign in, 416
 presentation of, 630
 in "unhappy triad," 417
- Anterior drawer sign, 416, 630
- Anterior horn, 471
- Anterior hypothalamus, 456
- Anterior inferior cerebellar artery, 467
 in circle of Willis, 466
- Anterior perforated substance, 477
- Anterior pituitary gland, 307
- Anterior spinal artery
 in circle of Willis, 466
 complete occlusion of, 474
 stroke, effect on, 467
- Anterior spinothalamic tract, 472
- Anterior superior
 pancreaticoduodenal
 artery, 343
- Anterior white commissure, 472
- Anterograde amnesia, 512
 brain lesions causing, 464
- Anthracois, 620
 as restrictive lung disease, 619
- Anthracyclines, 251
- Anthrax, 121
 bacteria causing, 114
- Anthrax toxin
Bacillus anthracis and, 121
- Antiandrogens, 603
- Antianginal therapy, 299
- Antiapoptotic molecule
 as oncogene product, 230
- Antiarrhythmic drugs, 302–304
 long QT interval caused by, 277
 torsades de pointes caused by, 251
- Anti- β_2 glycoprotein antibodies
 in antiphospholipid syndrome, 434
- Antibiotics
 for acne, 440
Candida albicans and, 137
Clostridium difficile as cause, 630
 Jarisch-Herxheimer reaction, 131
 long QT interval caused by, 277
 torsades de pointes caused by, 251
- Antibodies
 autoantibodies, 207
 ELISA test for, 67
 to hepatitis viruses, 157
 structure and function, 196
 therapeutic, 214
- Anticardiolipin
 in antiphospholipid syndrome, 434
- Anti-centromere antibodies, 634
 scleroderma and, 437
- Anticholinergic drugs
 toxicity treatment for, 251
- Anticholinesterase drugs, 244
- Anticipation, in genetics, 68
- Anticoagulant drugs, 383
 for acute coronary syndromes, 290
 for antiphospholipid syndrome, 434
 for atrial fibrillation, 278
 osteoporosis and, 426
 warfarin as, 406
- Anticoagulation, in coagulation
 cascade, 384
- Anticodon loop, 56
- Anticonvulsant drugs
 for fibromyalgia, 435
 osteoporosis and, 426
- Antidepressant drugs, 526
 for bulimia nervosa, 520
 for fibromyalgia, 435
 long QT interval caused by, 277
 torsades de pointes caused by, 251
- Anti-desmoglein antibodies, 634
- Anti-digoxin Fab fragments, 251
- Antidiuretic hormone (ADH), 311,
 540
 in diabetes insipidus, 328
 hypothalamus production of, 456
 kidney effects, 541
 in nephron physiology, 537
 pituitary gland and, 307
 SIADH and, 328
 signaling pathways of, 316
- Antidiuretic hormone (ADH)
 antagonists, 336, 556
- Anti-dsDNA antibodies
 in lupus, 434
- Antiemetic drugs
 long QT interval caused by, 277
 marijuana as, 523
 metoclopramide as, 376
 ondansetron as, 376
 torsades de pointes caused by, 251
- Anti-endothelial antibodies, 635
- Antiepileptic drugs
 cytochrome P-450 and, 254
 rash caused by, 253
 as teratogens, 564
- Antifungal drugs, 181
 for tinea versicolor, 136
- Antigen-presenting cells (APCs), 195
 B cells as, 380
 dendritic cells as, 380
 MHC I and II and, 192
 in spleen, 191
- Antigens
 ELISA test for, 67
 type and memory, 197
 variations in, 202
- Anti-gliadin antibodies, 635
- Anti-glomerular basement membrane
 antibodies, 634
- Anti-HBc, 157
- Anti-HBe, 157
- Anti-HBs, 157
- Anthelmintic drugs, 183
 naming convention for, 255
- Antihistamines
 for scromboid poisoning, 250
- Antihistone antibodies, 634
 in lupus, 434
- Antihypertensive drugs
 for eclampsia, 590
 for gestational hypertension, 590
 for preeclampsia, 590
 sexual dysfunction caused by, 520
- Anti-IgE monoclonal antibodies, 628
- Anti-IgG antibodies, 634
- Anti-inflammatory drugs, 446
- Antileukotrienes
 for asthma, 628
- Antimalarial drugs
 G6PD deficiency caused by, 392
- Antimetabolites, 409
 in cell cycle, 408
- Antimicrobial drugs, 170–187
 naming conventions for, 255
 in pregnancy, which to avoid, 187
 as prophylaxis, 181
- Antimitochondrial antibodies, 634
- Antimuscarinic drugs
 for Parkinson disease, 504
 toxicity treatment for, 251
 for urgency incontinence, 551
- Antimuscarinic reaction, 254
- Antimycin A
 in electron transport chain, 89
 as electron transport inhibitor, 89
- Antimycobacterial drugs, 179
- Antineutrophil cytoplasmic
 antibodies, 634
- Antinuclear antibodies (ANA), 635
 in lupus, 434
- Antioxidants
 free radical elimination by, 221
- Antiparasitic drugs
 naming convention for, 255
- Antiphospholipid syndrome, 434
 autoantibody associated with, 207
- Antiplatelet antibodies, 635
 abciximab as, 214
- Antiplatelet drugs
 for acute coronary syndromes, 290
- Antiprogesterin drugs, 602
- Antiprotozoan drugs, 183
- Antipseudomonal drugs, 170
- Antipseudomonal penicillins, 171
- Antipsychotic drugs, 525
 antimuscarinic reaction caused
 by, 254
 dopaminergic pathways and, 458
 galactorrhea caused by, 309
 long QT interval caused by, 277
 naming convention for, 255
 Parkinson-like syndrome caused
 by, 253
 for PCP overdose, 523
 prolactin, effect on, 310
 for schizophrenia, 640
 tardive dyskinesia caused by, 253
 torsades de pointes caused by, 251
 for Tourette syndrome, 511, 524
- Anti-Smith antibodies
 in lupus, 434

- Antisocial personality disorder, 519
conduct disorder as precursor to, 511
- Antithrombin
in coagulation cascade, 384
- Anti-topoisomerase antibodies, 635
- Antitoxins
as passive immunity, 203
- Anti-transglutaminase antibodies, 635
- Antitumor antibiotics, 410
- Anti-UI RNP antibodies, 434
- Antiviral therapy, 184
- Anxiety
barbiturates for, 501
benzodiazepines for, 501
benzodiazepine withdrawal as cause, 522
delirium tremens as cause, 524
hypercalcemia as cause, 542
hyperthyroidism as cause, 321
LSD as cause, 523
MAO inhibitors for, 528
MDMA withdrawal as cause, 523
neurotransmitter changes in, 511
neurotransmitters for, 455
nicotine withdrawal as cause, 522
- Anxiety disorder, 516
atypical antipsychotics for, 525
- Aorta
abdominal, 342
in circle of Willis, 466
coarctation of, 283
in diaphragm, 609
EKG and, 276
in gastrointestinal anatomy, 339
in horseshoe kidney, 531
in syphilitic heart disease, 294
traumatic rupture of, 286
“tree bark” appearance of, 294
- Aortal coarctation
lab findings in, 637
- Aortic aneurysm, 286
Ehlers-Danlos syndrome and, 63
hypertension as cause, 284
key associations, 641
Marfan syndrome as cause, 71, 284
syphilitic heart disease as cause, 294
- Aortic arch derivatives, 568
- Aortic dissection, 287
hypertension as cause, 284
hypertensive emergency and, 284
key associations, 641
Marfan syndrome as cause, 284, 630
- Aortic incompetence
Marfan syndrome as cause, 71
- Aortic insufficiency
syphilitic heart disease as cause, 294
- Aorticopulmonary septum, 263
embryologic derivatives of, 563
- Aortic regurgitation
diastolic murmur in, 272
heart murmurs caused by, 273
Marfan syndrome as cause, 284
presentation of, 630
pulse pressure in, 266
- Aortic root dilation
heart murmur caused by, 273
- Aortic stenosis
ejection click and, 643
heart murmurs caused by, 273
macroangiopathic anemia caused by, 393
paradoxical splitting in, 271
presentation of, 634
pulse pressure in, 266
S4 heart sound and, 645
systolic murmur in, 272
Williams syndrome as cause, 284
- Aortic valve
in cardiac cycle, 270
embryological development of, 262
- Aortic valve sclerosis
systolic murmur in, 272
- Aortitis
syphilis as cause, 131, 167
- APC gene, 230
adenomatous colonic polyps and, 363
colorectal cancer and, 364
familial adenomatous polyposis and, 71, 363
- “Ape hand” (median nerve injury), 419, 421
- Apgar score, 581
- Aphasia, 463
dementia and, 513
frontotemporal dementia as cause, 491
- Aphthous stomatitis
Crohn disease as cause, 359
- Apixaban, 407
as anticoagulant, 383
for long-term anticoagulation, 640
- Aplasia, 563
- Aplasia cutis
methimazole as cause, 335
- Aplasia cutis congenita
fetal methimazole exposure as cause, 564
- Aplastic anemia, 391
in anemia taxonomy, 388
chloramphenicol as cause, 175
as drug reaction, 252
Fanconi anemia as cause, 633
neutropenia caused by, 394
thionamides as cause, 335
- Aplastic crisis
hereditary spherocytosis as cause, 392
sickle cell anemia as cause, 392
- Apolipoproteins, 104
- Aponeurosis of external oblique muscle, 348
- Apoptosis, 216
corticosteroids as cause, 394
evasion of, in cancer, 227
- Appendages, bacterial, 108
- Appendicitis, 360
vs. mittelschmerz, 578
- Appetite regulation, 311
- “Apple core” lesion on X-ray, 364, 635
- Apraxia
dementia and, 513
- Aquaporin
in renin-angiotensin-aldosterone system, 540
- Aqueous humor pathway, 483
- Arabinoglycan synthesis, 179
- Arachidonic acid pathway, 446
- Arachnodactyly
Marfan syndrome as cause, 71, 630
- Arachnoid
in cavernous sinus, 481
- Arachnoid cells
meningiomas in, 496
- Arcuate artery, 532
- Arcuate fasciculus, 462
aphasia and, 463
- Area postrema, 455, 456
- Arenaviruses
characteristics of, 151
as negative-stranded, 152
as segmented, 152
- Arginine, 92
in cystinuria, 96
derivatives of, 94
kidney stones and, 549
- Argininosuccinate
in urea cycle, 93
- Argyll Robertson pupils
presentation of, 633
syphilis as cause, 131, 167
tabes dorsalis and, 474
- Aripiprazole, 525
- Armadillos, as disease vectors, 132
- Aromatase, 582
- Aromatase inhibitors, 601
for breast cancer, 639
- Aromatic amines
as carcinogens, 231
- Arrhythmia
amphotericin B as cause, 182
amyloidosis and, 225
diabetic ketoacidosis as cause, 331
diphtheria as cause, 123
hyperthyroidism as cause, 321
hypokalemia as cause, 542
key associations, 642
local anesthetics as cause, 503
macrolides as cause, 176
McArdle disease as cause, 99
MI as cause, 288
muscular dystrophy as cause, 73
shock caused by, 292
sleep apnea as cause, 621
stimulants as cause, 522
thyroid hormones as cause, 335
treatments for, 638
- Arsenic
angiosarcomas caused by, 368, 441
as carcinogen, 231
glycolysis and, 86
inhalational injuries and, 222
squamous cell carcinomas caused by, 445
toxicity symptoms, 87
toxicity treatment for, 251
- Artemether
for *P. falciparum*, 183
- Arterial oxygen saturation, 613
- Arterial PCO₂, 610, 614
- Arteries, anatomy of, 265
- Arteriolosclerosis, 330
- Arteriosclerosis, 285
pulmonary hypertension as cause, 622
- Arteriovenous malformations (AVMs), 71
- Arteritis, headaches caused by, 494
- Artesunate
for malaria, 141, 183
- Arthralgias
alkapturia as cause, 96
Henoch-Schönlein purpura as cause, 297
rubella as cause, 153
serum sickness as cause, 205
vitamin A toxicity as cause, 77
- Arthritis, 430
AA amyloidosis and, 225
azathioprine for, 409
carpal tunnel syndrome and, 418
celecoxib for, 447
chlamydiae as cause, 134
Crohn disease as cause, 359
gonorrhoea as cause, 167
HLA-B27 and, 193
LMN facial nerve palsy as cause, 634
lupus as cause, 434
Lyme disease as cause, 130
Paget disease of bone as cause, 630
in reactive arthritis, 433
septic, 432
Sjögren syndrome as cause, 631
Takayasu arteritis as cause, 296
ulcerative colitis as cause, 359
Whipple disease as cause, 634
- Arthritis of inflammatory bowel disease
HLA-B27 and, 193
- Arthropathy
hemochromatosis as cause, 371
- Arthus reaction, 205
- Arylcyclohexylamines
as intravenous anesthetics, 502
- Arylsulfatase A
in metachromatic leukodystrophy, 100
- Asbestos
as carcinogen, 231
lung cancer and, 626
- Asbestosis, 620
as restrictive lung disease, 619
- Ascaris* spp., 142
- Ascaris lumbricoides*, 143, 643
- Ascending aorta
embryological development of, 262
- Ascending cholangitis
biliary cirrhosis and, 371
- Ascending colon, 339
- Aschoff bodies, 636
in rheumatic fever, 294

- Ascites
 Budd-Chiari syndrome as
 cause, 368, 630
 cirrhosis as cause, 365
 hepatocellular carcinoma as
 cause, 368
 in Meigs syndrome, 592
- Asenapine, 525
- Aseptic meningitis
 mumps as cause, 155
- Asherman syndrome, 602
- Ashkenazi Jews, disease incidence
 in, 100
- Ash-leaf spots, in tuberous
 sclerosis, 495
- Aspartame, and phenylketonuria, 95
- Aspartate
 in nucleotide synthesis, 49
 in urea cycle, 93
- Aspartate aminotransferase (AST), 366
 in toxic shock syndrome, 119
- Aspartic acid, 92
- Aspart insulin, 334. *See also* Insulin
- Aspergillosis
Aspergillus fumigatus as cause, 137
 bronchiectasis and, 618
 echinocandins for, 183
- Aspergillus* spp.
 as catalase-positive organism, 112
 chronic granulomatous disease
 and, 209, 643
- Aspergillus fumigatus*, 137
 HIV and, 160
- Aspiration, in ARDS, 621
- Aspiration pneumonia, 128
- Aspirin, 447
 for acute coronary syndromes, 290
 arachidonic acid pathway and, 446
 cyclooxygenase, effect on, 385
 hemolysis in G6PD deficiency
 caused by, 252
 for ischemic stroke, 470
 for Kawasaki disease, 296, 640
 for polycythemia vera, 404
 Reye syndrome and, 366
 as uncoupling agent, 89
 as weak acid, 238
 zero-order elimination of, 238
- Asplenia
 Howell-Jolly bodies in, 387
 target cells in, 387
- Asterixis
 cirrhosis as cause, 365
 hepatic encephalopathy as
 cause, 367
 hyperammonemia as cause, 93
- Asthma, 618
 albuterol for, 246
 β -blockers and, 249
 breast milk as risk reduction
 for, 581
 cholinomimetic agents and, 244
 cromolyn sodium for, 379
 drug therapy for, 628
 eczema and, 440
 eosinophilia caused by, 379
 epinephrine for, 246
 gastroesophageal reflux disease
 and, 354
 glucocorticoids for, 336
 lab findings in, 636
 muscarinic antagonists for, 245
 omalizumab for, 214
 pulsus paradoxus in, 294
 salmeterol for, 246
 as type I hypersensitivity
 reaction, 204
- Astigmatism, 483
- Astrocyte foot processes, 455
- Astrocytes, 453
 in glioblastoma multiforme, 496
 origin of, 450
- Astrocytomas, 642
 GFAP stain for, 60
- Ataxia
 amantadine as cause, 504
 Angelman syndrome as cause, 69
 cerebellar hemisphere lesions
 and, 464
 cerebellar vermis lesions and, 464
 epilepsy drugs causing, 500
 hydrocephalus as cause, 471
 Rett syndrome as cause, 511
 streptomycin as cause, 180
 stroke as cause, 467
 tabes dorsalis as cause, 474
 vitamin B₁₂ deficiency as
 cause, 474
 Wernicke-Korsakoff syndrome as
 cause, 77, 464, 523
- Ataxia-telangiectasia, 53, 209
- Atazanavir, 184, 186
- Atelectasis, 622
- Atenolol, 249, 303
- Ateriolosclerosis, 285
- Atherosclerosis, 286, 645
 abdominal aortic aneurysms
 and, 286
 aortic aneurysms and, 641
 diabetes mellitus as cause, 330
 familial hypercholesterolemia as
 cause, 105
 homocystinuria as cause, 96
 stable angina caused by, 287
 transplant rejection as cause, 211
- Athetosis, 461
- ATM gene
 ataxia-telangiectasia and, 209
- Atomoxetine, 511, 638
- Atonic seizures, 494
- Atopic dermatitis, 440
- Atopic reactions, 204
- Atorvastatin, 300
- Atovaquone
 for babesiosis, 141
 for malaria, 141, 640
 for *P. falciparum*, 183
 for *Pneumocystis jirovecii*, 138
- ATPase, 371
- Atracurium, 503
- Atria
 embryological development of, 262
 septation of, 262
- Atrial amyloidosis, 225
- Atrial fibrillation
 arrhythmia and, 642
 β -blockers for, 303
 calcium channel blockers for, 304
 cardiac glycosides for, 301
 ECG tracing of, 278
 embolic stroke and, 470
 hypertension as cause, 284
 jugular venous pulse in, 270
 potassium channel blockers
 for, 303
 sleep apnea as cause, 621
- Atrial flutter
 β -blockers for, 303
 ECG tracing of, 278
 potassium channel blockers
 for, 303
- Atrial natriuretic peptide (ANP), 279,
 540
 amyloidosis and, 225
 kidney effects, 541
 in SIADH, 328
 signaling pathways for, 316
- Atrial septa
 embryological development of, 262
- Atrial septal defect (ASD), 283
 congenital rubella as cause, 284
 cyanosis caused by, 642
 diastolic murmur in, 272
 Down syndrome as cause, 284
 fetal alcohol syndrome as
 cause, 284
- Atrioventricular block
 β -blockers as cause, 249, 303
 calcium channel blockers as
 cause, 298, 304
 ECG tracings for, 278
 Lyme disease as cause, 130
- Atrioventricular canals, 263
- Atrioventricular node, 276
 EKG and, 276
- Atrioventricular septal defect
 (AVSD), 74
- Atrioventricular valves
 embryological development of, 262
- Atrophic gastritis
 gastrin in, 350
 key associations, 642
- Atrophy, 226, 473
- Atropine, 245
 antimuscarinic reaction caused
 by, 254
 for β -blocker overdose, 303
 for cholinesterase inhibitor
 poisoning, 244
 as toxicity treatment, 251
- Attention deficit disorder (ADD)
 amphetamines for, 246
- Attention-deficit hyperactivity disorder
 (ADHD), 511
 CNS stimulants for, 524
 drug therapy for, 524
 smoking as cause, 564
 sympatholytic drugs for, 247
 Tourette syndrome and, 511
 treatments for, 638
- Attributable risk (AR), 34, 646
- Atypical antidepressants, 528
- Atypical antipsychotic drugs, 525
 for bipolar disorder, 515, 524, 638
 for postpartum psychosis, 516
 for schizophrenia, 514, 640
- Atypical depression, 528
- Atypical lymphocytes, 635
- Atypical pneumonias, 624
 chlamydiae as cause, 134
 macrolides for, 176
- Auditory cortex, 462
- Auditory hallucinations, 513
 schizophrenia as cause, 514
- Auditory physiology, 481
- Auer rods, 635
- in acute myelogenous
 leukemia, 402
- Auramine-rhodamine stain, 110
- Auscultation of heart, 272
- Auspitz sign, 440
- Autism spectrum disorder, 511
 double Y males and, 585
 fragile X syndrome as cause, 73
- Autoantibodies, 207
- Autoclave, 187
- Autoclaves, for spore-forming
 bacteria, 114
- Autografts, 210
- Autoimmune anemia, 388
- Autoimmune diseases
 acute pericarditis caused by, 294
 collagen and, 61
 preeclampsia and, 590
 therapeutic antibodies for, 214
- Autoimmune gastritis, 356
- Autoimmune hemolytic anemia, 393
 cephalosporins as cause, 172
 as type II hypersensitivity
 reactions, 204
- Autoimmune hepatitis type I
 autoantibody associated with, 207
- Autoimmune lymphoproliferative
 syndrome, 216
- Autoimmune membranous
 glomerulopathy, 207
- Autoimmune regulator (AIRE), 194
- Autonomic drugs, 241–250, 243
 naming conventions for, 255
- Autonomic insufficiency, 246
- Autonomy, as ethical principle, 39
- Autoregulation of blood flow, 280
- Autosomal dominant hyper-IgE
 syndrome, 208
 presentation of, 633
- Autosomal dominant inheritance, 70
 diseases of, 71
- Autosomal dominant polycystic
 kidney disease
 (ADPKD), 555
 autosomal dominance of, 71
 chromosome associated with, 75
 saccular aneurysms and, 468
- Autosomal recessive inheritance, 70
 diseases of, 72
- Autosomal recessive polycystic kidney
 disease (ARPKD), 555
 Potter sequence caused by, 530

- Autosomal trisomies, **74**
karyotyping for, 67
- Autosplenectomy
key associations, 641
sickle cell anemia as cause, 392
- Avascular necrosis, **427**
glucocorticoids as cause, 212
of scaphoid bone, 418
sickle cell anemia as cause, 392
- Avoidant personality disorder, 519
- Axillary lymph nodes, 190
in breast cancer, 596
- Axillary nerve, 419
- Axonal injury, 220
- Axonemal dynein, 60
- Azathioprine, 409
allopurinol and, 448
in cell cycle, 408
for Crohn disease, 359, 639
as immunosuppressant, 212
pancreatitis caused by, 252
targets of, 213
- Azithromycin, 170, 176
for babesiosis, 141
for chlamydiae, 134
as HIV prophylaxis, 181
for *Legionella pneumophila*, 640
for *Mycobacterium avium-intracellulare*, 124, 179
as *Mycobacterium avium-intracellulare*
prophylaxis, 179
- Azoles, 181, **182**
for *Candida albicans*, 137
- Azotemia
acute interstitial nephritis as
cause, 554
nephritic syndrome and, 546
- Aztreonam, 170, 173
- B**
- B7 protein, cells present on, 202
- B19 virus, 148
- Babesia* spp., 130, **141**
anemia caused by, 393
- Babesiosis, 141
- Babinski reflex, 43, 473, 476
- Babinski sign
presentation of, 634
UMN damage as cause, 632
- Bachmann bundle, 276
- Bacillary angiomatosis, 441
animal transmission of, 132
HIV and, 160
- Bacilli, 109
Gram stain identification of, 118
- Bacillus* spp.
in Gram-positive algorithm, 118
morphology of, 109
- Bacillus anthracis*, **121**
capsule composition, 108
exotoxin produced by, 116
as spore-forming bacteria, 114
- Bacillus cereus*, **122**
food poisoning caused by, 161, 643
as spore-forming bacteria, 114
- Bacitracin
functioning of, 170
as Gram-positive antibiotic
test, 118
organisms sensitive to, 118
Streptococcus pyogenes sensitivity
to, 120
- Bacitracin response, 635
- Back pain, from G6PD
deficiency, 392
- Baclofen, **503**
for multiple sclerosis, 492
- Bacteremia
dapsones for, 178
Staphylococcus gallolyticus
and, 121
tuberculosis and, 124
- Bacteria
 α -hemolytic, 119
 β -hemolytic, 119
encapsulated, 112
genetics of, 114
highly resistant, treating, **181**
hints for, 169
in vivo biofilm-producing, 113
morphology of, 109
normal flora, 161
pigment-producing, 113
special culture requirements, **111**
spore-forming, **114**
stains for, 110
structures of, **108**
taxonomy of, **109**
virulence factors, 113
zoonotic, 132
- Bacterial capsules, 108
- Bacterial endocarditis, **293**
key associations, 643
presentation of, 634
Streptococcus sanguinis as
cause, 120
- Bacterial meningitis, 642
- Bacterial toxins, effect on
immunocytes, **202**
- Bacterial vaginosis
characteristics of, 164
Gardnerella vaginalis as cause, 132
- Bacteroides* spp.
alcoholism and, 162
as anaerobic organism, 111
clindamycin for, 175
lung abscesses caused by, 624
metronidazole for, 178
morphology of, 109
- Bacteroides fragilis*, 161
- “Bag of worms” appearance of
scrotum, 597
- Baker cyst, 417
tibial nerve injury caused by, 422
- BAK protein, 216
- Balancing, as quality
measurement, 46
- “Bamboo spine” on X-ray, 433, 635
- Band cells, 378
- Barbiturates, **501**
intoxication and withdrawal, 522
as intravenous anesthetics, 502
naming convention for, 255
sleep, effect on, 457
- Baroreceptors, **279**
- Barr bodies, 48
- Barrel hoop basement
membrane, 191
- Barrett esophagus, 355
metaplasia and, 226
- Bartonella* spp.
animal transmission of, 132
endocarditis caused by, 293
morphology of, 109
- Bartonella henselae*
bacillary angiomatosis caused
by, 441
granulomatous diseases caused
by, 223
HIV and, 160
- Bartonella quintana*, 145
- Barter syndrome, **538**
markers in, 542
- Basal cell carcinomas
5-fluorouracil for, 409
of skin, 445
sunburn and, 444
- Basal cells, 608
- Basal ganglia, **460**
intraparenchymal hemorrhage
in, 469
lesions in, 464
movement disorders and, 461
- Basal lamina, 61
- Basal metabolic rate, 315
- Basal plate, 450
- Base excision repair, **53**
- Basement membrane
Alport syndrome and, 547
autoantibody to, 207
in blood-brain barrier, 455
collagen in, 61
in filtration, 535
glomerular filtration barrier
and, 533
in glomerulus, 532
- Basal amino acids, 92
- Basilar artery
in circle of Willis, 466
stroke, effect on, 467
- Basilar membrane, 481
- Basiliximab
as immunosuppressant, 212
targets of, 213
- Basophilia, 379
- Basophilic stippling, 386, 635
lead poisoning as cause, 389
in sideroblastic anemia, 389
- Basophils, 378, **379**
IgE antibody and, 197
- BAX protein, 216
- B-cell lymphomas, 646
HIV and, 160
oncogenes and, 230
- B cells, **380**
activation of, **195**
adaptive immunity and, 192
anergy, 202
cell surface proteins, 202
class switching, 195
disorders of, 208, 209
function of, 380
glucocorticoids effect on, 212
in lymph node, 190
major functions of, 193
non-Hodgkin lymphoma and, 399
sirolimus effect on, 212
in spleen, 191
- BCG vaccine, 124, 203
IL-12 receptor deficiency and, 208
- BCL-2* gene, 230
- Bcl-2 protein, 216
- BCR-ABL gene, 230
- Becker muscular dystrophy, **73**
presentation of, 633
as X-linked recessive disorder, 72
- Beck triad of cardiac tamponade, 294, 632
- Beckwith-Wiedemann, 551
- Beclomethasone, 336. *See*
also Glucocorticoids
- Bedwetting. *See* Nocturnal enuresis
- Bell palsy, 480
Lyme disease as cause, 130
sarcoidosis and, 435
- Bell-shaped distribution, 37
- Bence Jones protein, 401
- Benzodiazepines, 143
- Bends, the, 427
- Benevolence, as ethical principle, 39
- Benign prostatic hyperplasia
(BPH), **599**, 644
 α -blockers for, 248
hydronephrosis and, 550
postrenal azotemia caused by, 553
tamsulosin for, 603
treatments for, 638
- Benign tumors, 228
- Benzathine penicillin G, 181
- Benzene
aplastic anemia caused by, 252, 391
myelodysplastic syndromes caused
by, 401
- Benzidine, as carcinogen, 231
- Benzimidazole, 142
- Benzoate, 93
- Benzocaine, 503
methemoglobin and, 612
- Benzodiazepines, **501**
for alcohol withdrawal, 524, 638
for cocaine overdose, 522
for delirium tremens, 524
for epilepsy, 500
for generalized anxiety
disorder, 517
intoxication and withdrawal, 522
as intravenous anesthetics, 502
naming convention for, 255
for panic disorder, 517
for PCP overdose, 523
for phobias, 517
sleep, effect on, 457
toxicity treatment for, 251
- Benzoyl peroxide, for acne, 440
- Benzotropine, 245, 504

- Beriberi
 cardiomyopathy caused by, 291
 vitamin B₁ deficiency as cause, 77
- Berkson bias, 36
- Bernard-Soulier syndrome, 385, 642
- Berylliosis, **620**
 as granulomatous disease, 223
- β₁-blockade, 267
- β₂-agonists
 for asthma, 628
 insulin and, 308
 naming convention for, 255
- β₂-microglobulin
 MHC I and II and, 192
- β-amyloid protein, in Alzheimer disease, 225
- β-blockers, **249**
 for acute coronary syndromes, 290
 for angina, 299
 as antiarrhythmic drugs, **303**
 for aortic dissections, 287
 for cocaine overdose, 246, 522
 diabetes and, 249
 for dilated cardiomyopathy, 291
 for essential tremor, 461
 for glaucoma, 498
 for heart failure, 292
 hydralazine and, 298
 hyperkalemia caused by, 542
 for hypertension, 298
 hypertrophic cardiomyopathy and, 291
 juxtaglomerular apparatus, effect on, 540
 for migraine headaches, 494
 naming convention for, 255
 for pheochromocytomas, 320
 for phobias, 517
 for thyroid storm, 323
 toxicity treatment for, 251
- β cells, 307
 in diabetes mellitus type 1, 331
 in diabetes mellitus type 2, 331
 insulinomas of, 332
 insulin secretion by, 308
- β-dystroglycan, 73
- β-galactosidase, 126
- β-glucan, 183
- β-glucuronidase, 378
- β-hCG
 in Down syndrome, 74
 in Edwards syndrome, 74
 in Patau syndrome, 74
 as tumor marker, 232
- β-hemolysis, 117
- β-hemolytic bacteria, 119
- β-hydroxybutyrate, 102
- β-interferon
 for multiple sclerosis, 492, 640
- β-lactam antibiotics, 170
- β-lactamase inhibitors, **171**
- β-lactams, 443
- Betamethasone, 446
- β-thalassemia, 389
 allelic heterogeneity and, 69
 chromosome associated with, 75
 intron/exon splicing variants and, 55
 lab findings in, 636
- Betaxolol, 249
 for glaucoma, 498
- Bethanechol, 244
- Bevacizumab, 214, **412**
- Bezafibrate, 300
- Bias, in studies, **36**
- Bicarbonate
 carbon dioxide transport and, 615
 for drug overdoses, 238
 as GI secretory product, 351
 in pancreatic insufficiency, 358
 for salicylate toxicity, 251
 for TCA toxicity, 251
- Biceps brachii muscle, in Erb palsy, 420
- Biceps reflex, 476
- Biceps tendon, 417
- Bicornuate uterus, 572
- Bicuspid aortic valve
 aortic dissection and, 287
 coarctation of aorta and, 283
 heart murmur caused by, 273
 thoracic aortic aneurysms and, 286
 Turner syndrome as cause, 284, 585
- Bifurcations, 609
- Biguanide drugs, 334
- Bilaminar disc, 562
- Bilateral acoustic schwannomas, 71, 630
- Bilateral adenopathy, 435
- Bilateral hilar lymphadenopathy, 619
- Bilateral renal agenesis
 oligohydramnios and, 589
 Potter sequence caused by, 530
 pulmonary hypoplasia and, 606
- Bile, **352**
 in hereditary hyperbilirubinemias, 370
 secretin effect on, 350
- Bile acid resins, 300
- Bile acids
 lipid transport and, 104
 reabsorption of, 300
- Bile canaliculus, 346
- Bile duct, 347
- Bile ductule, 346
- Bile salts, 352
 in cholelithiasis, 372
- Biliary cirrhosis, 365, 369, 371
 cystic fibrosis as cause, 72
 lab findings in, 634
 ursodiol for, 376
- Biliary colic, 372
- Biliary structures, **347**
- Biliary tract disease, **371**
Clonorchis sinensis and, 145
- Biliary tract infections, 121
- Bilious vomiting, in Hirschsprung disease, 361
- Bilirubin, **353**
 in bile, 352
 in cholelithiasis, 372
 in hereditary hyperbilirubinemias, 370
 as liver marker, 366
 in toxic shock syndrome, 119
- Bimatoprost, 498
- Bimodal distribution, 37
- Binge eating disorder, 520
- Bioavailability, 237
- Biochemistry, 48–105
 cellular, 58–64
 genetics, 68–77
 laboratory techniques, 64–68
 metabolism, 83–105
 molecular, 48–57
 nutrition, 76–83
- Biofilm-producing bacteria, 113
- Biostatistics/epidemiology, 32–39
- Bipolar disorder, 514, **515**
 antipsychotic drugs for, 525
 atypical antipsychotics for, 525
 drug therapy for, 524
 genetic risk of, 510
 lithium for, 526
 postpartum psychosis and, 516
 treatments for, 638
- Birbeck granules, 638
 in Langerhans cell histiocytosis, 403
- Birds, as disease vectors, 132, 134
- “Bird’s beak” sign on barium swallow, 354
- Bismuth, **375**
- Bisphosphonates, **447**
 esophagitis caused by, 252
 naming convention for, 255
 for osteoporosis, 426, 640
- Bitemporal hemianopia, 489
 hypopituitarism as cause, 329
 Nelson syndrome as cause, 326
- Bitot spots, 77
- Bivalirudin, 405
- BK virus, 148
- Black eschar, caused by cutaneous anthrax, 121
- Blackflies, as disease vectors, 143
- Black liver, 642
- Black lung disease, 620
- Bladder, 574
 bethanechol effect on, 244
 parasympathetic receptors and, 242
 spasms, treating, 245
 transitional cell carcinoma in, 551
- Bladder cancer
 cisplatin/carboplatin for, 411
 hematuria caused by, 544
 hypercalcemia and, 229
 oncogenic microbes and, 231
Schistosoma as cause, 144
Schistosoma haematobium and, 145
- Blast crisis in CML, 642
- Blastocysts, 562
- Blastomyces* spp.
 amphotericin B for, 182
 itraconazole for, 182
- Blastomycosis, **135**
- Bleeding
 direct factor Xa inhibitors as cause, 407
 direct thrombin inhibitors as cause, 405
 essential thrombocythemia as cause, 404
 glycoprotein IIb/IIIa inhibitors as cause, 407
 heparin as cause, 405
 thrombolytics as cause, 407
 warfarin as cause, 406
- Bleomycin, 410
 in cell cycle, 408
 pulmonary fibrosis caused by, 254
 targets of, 408
- Bleomycin toxicity, 413, 619
- Blepharoplasts, 497
- Blepharospasm
 dystonia and, 461
- Blindness
Chlamydia trachomatis as cause, 134
 conversion disorder as cause, 518
 giant cell arteritis as cause, 296
 temporal arteritis as cause, 645
- Blistering skin disorders, **443**
- Blood
 chocolate-colored, 612
 coagulation and kinin pathways, 383
 embryologic derivatives of, 563
 oxygen content of, **613**
 in placenta, 566
 viscosity, in pulmonary vascular resistance, 614
- Blood-brain barrier, **455**
- Blood flow, effect of exercise on, 615
- Blood groups, **382**
- Blood pH, diuretic effect on, 558
- Blood pressure
 α-blocker effect on, 248
 angiotensin II effect on, 540, 541
 antidiuretic hormone regulation of, 311
 cortisol effect on, 313
 fenoldopam and, 298
 in renal disorders, 542
 renin-angiotensin-aldosterone system and, 540
 sympathomimetic effect on, 247
- Blood-testis barrier, 455
- Blood transfusions, **399**
 hemochromatosis and, 643
 key associations, 643
 reactions to, **206–214**
- Blood vessels, collagen in, 61
- Bloody diarrhea
 amebiasis as cause, 139
Campylobacter jejuni as cause, 128
 ulcerative colitis as cause, 359
- Bloody spinal tap, 635
- Bloody stool, 345
- Blotting procedures, **65**
- Blown pupils, in CN III palsy, 489
- “Blue babies,” 282
- Blueberry muffin rash
 cytomegalovirus as cause, 165
 rubella as cause, 153, 165
Toxoplasma gondii as cause, 165

- “Blue kids,” 283
- Blue sclerae
osteogenesis imperfecta as cause, 63, 630
- BNP. *See* Brain natriuretic peptide (BNP)
- Body dysmorphic disorder, 517
- Boerhaave syndrome, 354
- Bombesin, 319
- Bone cancer, 428
key associations, 645
primary bone tumors, 429
- Bone crises
Gaucher disease as cause, 100, 631
- Bone disorders
lab values, 428
osteogenesis imperfecta, 63
Paget disease of bone, 630
- Bone fractures
as child abuse sign, 510
fat emboli as cause, 617
- Bone lesions
adult T-cell lymphoma as cause, 400
Langerhans cell histiocytosis as cause, 403
multiple myeloma and, 401
- Bone marrow suppression, 182
- Bone marrow transplant
for osteopetrosis, 426
for SCID (severe combined immunodeficiency), 209
- Bones
cell biology of, 425
collagen in, 61
cortisol effect on, 313
formation of, 425
as metastasis site, 233
PTH effect on, 314
renal osteodystrophy and, 553
T₃ hormone and, 315
- Bone tumors, 429
- “Boot-shaped” heart, 635
- Borderline personality disorder, 519
dissociative identity disorder and, 512
- Bordetella* spp., 109
- Bordetella pertussis*, 127
culture requirements for, 111
exotoxin produced by, 116
in Gram-negative algorithm, 125
macrolides for, 176
vaccines for, 127
- Bordet-Gengou agar, 111
- Borrelia* spp.
Giemsa stain for, 110
as spirochete, 130
- Borrelia burgdorferi*
animal transmission of, 132
Lyme disease caused by, 130
tetracyclines for, 175
- Borrelia recurrentis*
animal transmission of, 132
as antigenic variation, 202
lice transmission of, 145
- Bosentan, 627
for pulmonary arterial hypertension, 640
- Botulinum toxin, 116, 122, 243
lysogenic phage and, 114
passive antibodies for, 203
- Botulism
bacteria causing, 114
exotoxins as cause, 115
- Bovine spongiform encephalopathy (BSE), 161
- Bowel smooth muscle
activation, 244
- Bowel stenosis, 360
- Bowen disease, 597
- Bowenoid papulosis, 597
- Bowman capsule, 535
- Brachial artery, 423
- Brachial plexus lesions, 420
- Brachiocephalic artery, 466
- Bradycardia
amiodarone as cause, 303
atropine for, 245
β-blockers as cause, 249, 303
cholinesterase inhibitor poisoning as cause, 244
dopamine for, 246
on EKG, 276
hypermagnesemia as cause, 542
hypothyroidism as cause, 321
RCA infarct as cause, 265
sympatholytic drugs as cause, 247
- Bradykinin
ACE inhibitors and, 559
breakdown of, 540
C1 esterase inhibitor deficiency and, 199
- BRAF gene, 230
melanomas and, 445
papillary thyroid carcinoma and, 324
serrated colonic polyps and, 363
vemurafenib and, 413
- Brain
amyloid deposition in, 636
autoregulation of, 280
dopamine receptors and, 242
embryologic derivatives of, 563
embryology of, 450
glucose usage by, 308
ischemia in, 218
as metastasis site, 233
ring-enhancing lesions, 637
T₃ hormone and, 315
- Brain abscesses
HIV and, 160
infections causing, 163
- Brain cysts, 145
- Brain infarcts, 217
- Brain injury
gastritis caused by, 356
hypopituitarism caused by, 329
- Brain lesions, 464
- Brain natriuretic peptide (BNP), 279, 540
in SIADH, 328
signaling pathways for, 316
- Brain stem
dorsal view, 477
ventral view, 477
- Brain tumors, 496, 497
in adults, 496
in children, 497
key associations, 642
metastases as source, 233
nitrosureas for, 410
- Branched-chain ketoacid
dehydrogenase, 77
- Branchial apparatus, 568
- Branchial arch derivatives, 569
- Branchial cleft derivatives, 568
- Branchial pouch derivatives, 570
- Branching enzyme, in glycogen metabolism, 98
- Branching filamentous bacteria, 109
Gram stain identification of, 118
- Branching gram-positive rods with sulfur granules, 635
- BRCA1/BRCA2 genes, 230
breast cancer and, 596
- Breast cancer, 596–597
aromatase inhibitors for, 601
bone metastases in, 644
brain metastases in, 644
breastfeeding and, 581
hormonal contraception
contraindication, 602
hypercalcemia and, 229
incidence/mortality of, 228
key associations, 642
oncogenes and, 230
paclitaxel for, 411
paraneoplastic cerebellar degeneration and, 229
in postmenopausal women, 639
tamoxifen for, 413
trastuzumab for, 214, 413
treatments for, 639
tumor suppressor genes and, 230
- Breast disorders
benign, 595
malignant, 596
- Breastfeeding, 581
mastitis and, 595
ovarian neoplasms and, 592
- Breast milk. *See also* Lactation
dopamine and, 310
IgA antibodies in, 197
prolactin and, 310
- Breast pathology, 595
- Breast trauma, necrosis caused by, 217
- Brenner tumors, 592
- Bretylium, 243
- Bridging vein rupture, 643
- Brief psychotic disorder, 514
- Brimonidine, 498
- Brittle hair, in Menkes disease, 63
- Broad-base budding, in
blastomycosis, 135
- Broad ligament, 574
- Broca aphasia, 463
- Broca area, 462
aphasia and, 463
stroke effects, 467
- Bromocriptine, 504. *See also* Dopamine agonists
prolactin, effect on, 310
for prolactinomas, 640
- Bronchi, 608
- Bronchial asthma, 636
- Bronchial carcinoid tumors, 626
- Bronchiectasis, 618
Aspergillus fumigatus as cause, 137
cystic fibrosis as cause, 72
Kartagener syndrome as cause, 60, 633
- Bronchioalveolar cell carcinomas, 626
- Bronchioles
histamine receptors and, 242
in respiratory tree, 608
- Bronchiolitis obliterans, 211
- Bronchitis
cystic fibrosis as cause, 72
Haemophilus influenzae as cause, 126
- Bronchoconstriction, effect of asthma
drugs on, 628
- Bronchodilation
asthma drugs effect on, 628
sympathetic receptors and, 242
- Bronchogenic apical lung
tumor, 635
- Bronchogenic carcinomas
asbestosis and, 620
carcinogens causing, 231
- Bronchogenic cysts, 606
- Bronchopneumonia, 624
- Bronchopulmonary dysplasia, 221
neonatal respiratory distress syndrome as cause, 607
- Bronchospasm, in carcinoid
syndrome, 631
- “Brown” bone tumor, 635
- Brown-Séquard syndrome, 475
Horner syndrome and, 487
- Brucella* spp.
animal transmission of, 132
in Gram-negative algorithm, 125
as intracellular organism, 112
morphology of, 109
- Brucellosis, 132
- Brugada syndrome, 277
sudden cardiac death caused
by, 287
- Bruising
as child abuse sign, 510
scurvy as cause, 80
- Brunner glands, 341
duodenal ulcers and, 357
- Brushfield spots, 74
- Bruton agammaglobulinemia, 208
as X-linked recessive disorder, 72
- Bruton disease, 632
- Bruxism, 457
- BTK gene, 208
- Budd-Chiari syndrome, 368
hepatocellular carcinoma and, 368
lab findings in, 637
portal hypertension caused by, 365
presentation of, 630
- Budesonide, 628
- Buerger disease, 296, 645
treatments for, 639
- Buffalo hump, in Cushing
syndrome, 317

- Bulbus cordis, 262
- Bulimia nervosa, 520
anovulation caused by, 591
drug therapy for, 524
laxative abuse by, 375
Mallory-Weiss syndrome and, 354
Selective serotonin reuptake inhibitors (SSRIs) for, 527
treatments for, 639
- Bullae, 438
necrotizing fasciitis as cause, 442
Stevens-Johnson syndrome as cause, 443
- Bullous impetigo, 442
- Bullous pemphigoid, 443
autoantibody associated with, 207
as bulla, 438
as type II hypersensitivity reactions, 204
- Bull's-eye rash, in Lyme disease, 632
- Bumetanide, 557
- BUN (blood urea nitrogen)
in acute renal failure, 553
in nephritic syndrome, 545
in ornithine transcarbamylase deficiency, 94
- Bundle of His, 276
- Bunyaviruses
characteristics of, 151
as negative-stranded, 152
as segmented, 152
- Bupivacaine, 503
- Buprenorphine
for heroin addiction, 523
morphine and, 240
for opioid withdrawal, 522
- Bupropion, 528
for major depressive disorder, 515
mechanism of, 526
for nicotine withdrawal, 522
seizures caused by, 253
- Burkholderia cepacia*
as catalase-positive organism, 112
chronic granulomatous disease and, 209
cystic fibrosis and, 162
in immunodeficient patients, 210
morphology of, 109
- Burkitt lymphoma, 400, 645
chromosomal translocations and, 403
EBV and, 149
lab findings in, 637
oncogenes and, 230
oncogenic microbes and, 231
- Burns
as child abuse sign, 510
DIC and, 643
inhalational injuries and, 222
shock caused by, 292
sunburn, 444
testosterone/methyltestosterone for, 603
- Bursitis, prepatellar, 417
- Burton line
in lead poisoning, 389
presentation of, 630
- Buspirone, 526
for generalized anxiety disorder, 517, 639
- Busulfan, 410
pulmonary fibrosis caused by, 254
- Busulfan toxicity, 413
as restrictive lung disease, 619
- Butorphanol, 499
- Butterfly facial rash, 630
- Butterfly gliomas, 496
- C**
- C1 esterase inhibitor deficiency, 199
- C3 deficiency, 199
- C5a receptor, 378
- C5-C9 deficiencies, 199
- CA 15-3/CA27-29, as tumor markers, 232
- CA 19-9, as tumor marker, 232
- CA 125, as tumor marker, 232
- Cabergoline, 640
- Cachexia, 232
TNF- α and, 200
- Café-au-lait spots
aplastic anemia and, 391
causes of, 630
Fanconi anemia as cause, 633
McCune-Albright syndrome as cause, 69
neurofibromatosis type I as cause, 71, 495
- Caffeine intoxication and withdrawal, 522
- Cahill cycle, 93
- Caisson disease, 617
- Calcific aortic stenosis, 220
- Calcification, 220
- Calcineurin
cyclosporine and, 212
tacrolimus and, 212
- Calcinosis, 437
- Calcitonin, 315
medullary thyroid carcinoma production of, 324
for osteoporosis, 426, 640
signaling pathways of, 316
as tumor marker, 232
- Calcium
in bone disorders, 428
calcitonin and, 315
in cardiac muscle, 274
in osteomalacia/rickets, 427
for osteoporosis, 640
in Paget disease of bone, 427
PTH and, 314
Vitamin D and, 313
- Calcium carbonate, 375
- Calcium channel blockers, 298
for angina, 287
as antiarrhythmic drugs, 304
contractility in, 267
cutaneous flushing caused by, 251
gingival hyperplasia caused by, 253
for hypertension, 298
for hypertrophic cardiomyopathy, 291
for migraine headaches, 494
for Raynaud phenomenon, 437
- Calcium channels
autoantibody to, 207
ethosuximide effect on, 500
glucose and, 308
Lambert-Eaton myasthenic syndrome and, 229
myocardial action potential and, 274
opioid effect on, 499
pacemaker action potential and, 275
in smooth muscle contraction, 425
- Calcium homeostasis, 313
- Calcium oxalate nephrolithiasis, 80
- Calcium pyrophosphate deposition disease, 431
- Calcium-sensing receptor (CaSR), 336
- Calf pseudohypertrophy, 630
- Caliciviruses
characteristics of, 151
genomes of, 147
as naked viruses, 147
- California encephalitis, 151
- Call-Exner bodies, 593, 635
- Calluses, as hyperkeratosis, 439
- cAMP (cyclic adenosine monophosphate)
cilostazol/dipyridamole effect on, 407
as endocrine hormone messenger, 316
exotoxin effects on, 116
fructose bisphosphatase-2 and, 87
in glycogen regulation, 97
heat-labile/heat-stable toxin effects on, 116
in hyperparathyroidism, 326
PTH effect on, 314
in *Vibrio cholerae*, 129
- CAMP factor, 121
- Campylobacter* spp.
animal transmission of, 132
bloody diarrhea caused by, 162
morphology of, 109
reactive arthritis and, 433
- Campylobacter jejuni*, 128
in Gram-negative algorithm, 125
Guillain-Barré syndrome and, 493
- Canagliflozin, 335
- Canalicular lung development, 606
- Cancer
as common cause of death, 45
DIC and, 643
ESR in, 224
incidence of, 228
intron/exon splicing variants and, 55
metastases, common, 233
microRNAs and, 55
mortality of, 228
neoplastic progression, 227
pneumoconioses and, 620
splice site mutations as cause, 52
- Cancer drugs
cell cycle, 408
targets, 408
- Cancer epidemiology, 228
- Candesartan, 559
- Candida* spp.
amphotericin B for, 182
azoles for, 182
as catalase-positive organism, 112
chronic granulomatous disease and, 209
echinocandins for, 183
in immunodeficient patients, 210
osteomyelitis and, 644
osteomyelitis caused by, 163
tricuspid valve endocarditis and, 293
vulvovaginitis caused by, 164
- Candida albicans*, 137
HIV and, 160
T cell dysfunction as cause, 208
treatments for, 639
- Candidate identification number (CIN) for USMLE exam, 6
- Candidiasis
Candida albicans as cause, 137
chronic mucocutaneous, 208
cortisol and, 313
nystatin for, 182
- Cannibalism, kuru resulting from, 161
- Capillary fluid exchange, 281, 647
- Capillary lumen, in blood-brain barrier, 455
- Capillary supply in lymph node, 190
- Capitate bone, 418
- Caplan syndrome, 620
- Capsid, viral, 146
- Capsules, bacteria, 108
- Captain's wheel, and paracoccidioidomycosis, 135
- Captopril, 559
- Caput medusae, 344
- Carbachol, 244
for glaucoma, 498
- Carbamazepine
agranulocytosis caused by, 252
aplastic anemia caused by, 252
for bipolar disorder, 515, 638
cytochrome P-450 and, 254
for epilepsy, 500
SIADH caused by, 253
as teratogen, 564
for tonic-clonic seizures, 641
for trigeminal neuralgia, 641
- Carbamoyl phosphate, 93
- Carbamoyl phosphate synthetase I, 84
- Carbamoyl phosphate synthetase II, 84
- Carbapenems, 170, 173
for *Pseudomonas aeruginosa*, 127, 640
- Carbidopa, 505
- Carbohydrate absorption, 352
- Carbon dioxide
exercise and, 615
transport of, 615
- Carbonic anhydrase, 615
- Carbonic anhydrase inhibitors, 544

- Carbon monoxide (CO)
 carboxyhemoglobin and, 612
 as electron transport inhibitor, 89
 inhalational injuries and, 222
 toxicity treatment for, 251
- Carbon monoxide poisoning, 613
- Carbon tetrachloride
 as carcinogen, 231
 free radical injury and, 221
- Carboplatin, **411**
 toxicities of, 413
- Carboxyhemoglobin, 612
- Carboxylases, 84
- Carboxypeptidase, 352
- Carcinoembryonic antigen (CEA), as tumor marker, 232
- Carcinogens, **231**
 griseofulvin as, 183
- Carcinoid syndrome, **332**
 bronchial carcinoid tumors and, 626
 presentation of, 631
 somatostatin for, 336
 treatments for, 639
- Carcinoid tumors
 octreotide for, 375
 of stomach, 356
- Carcinoma in situ, 227
- Carcinomas
 of bone, 428
 colorectal, 364
 hyperparathyroidism and, 645
 invasive, 227
 metastases of, 233
 nomenclature of, 228
 in primary hyperparathyroidism, 325
 of thyroid, 324
- Cardiac arrest, caused by hypermagnesemia, 542
- Cardiac cycle, **270**
- Cardiac death, from cocaine use, 522
- Cardiac depression, 298
- Cardiac function curves, **269**
- Cardiac glycosides, **301**
- Cardiac looping, 262
- Cardiac muscle, in nervous system, 241
- Cardiac output, **266**
 equation for, 647
 exercise and, 615
 in pregnancy, 580
 variables in, 267
 V/Q mismatch and, 614
- Cardiac tamponade, **294**
 jugular venous pulse in, 270
 in MI, 288
 pulse pressure in, 266
 shock caused by, 292
- Cardiac troponin I, 289
- Cardiac tumors, **295**
 key associations, 642
- Cardinal ligament, 574
- Cardinal veins, 262
- Cardiobacterium* spp., 293
- Cardiogenic shock, 292
 MI as cause, 288
 pulse pressure in, 266
- Cardiolipin, 207
- Cardiomegaly, in Pompe disease, 99
- Cardiomegaly with apical trophy, 635
- Cardiomyopathy, **291**
 Chagas disease as cause, 142
 heart failure caused by, 292
 Kussmaul sign in, 295
 S4 heart sound and, 645
 sudden cardiac death caused by, 287
 wet beriberi as cause, 631
- Cardiotoxicity
 doxorubicin as cause, 410
 drugs causing, 413
 methylxanthines as cause, 628
 trastuzumab as cause, 413
- Cardiovascular drugs
 naming conventions for, 255
 reactions to, **251**
- Cardiovascular system, 262–302
 anatomy, 265
 embryology, 262–264
 pathology, 282–296
 pharmacology, 298–304
 physiology, 266–280
 sclerosis of, 437
- Carditis
 Lyme disease as cause, 130
 rheumatic fever as cause, 120, 294
- Carmustine, 410
 in cell cycle, 408
 pulmonary fibrosis caused by, 254
- Carnitine, 101
- Carnitine acyltransferase I, 84
- Carotid artery, 568
 atherosclerosis in, 286, 645
 bifurcation of, 609
 in cavernous sinus, 481
 giant cell arteritis and, 296
- Carotid sinus, 279
- Carpal bones, 418
- Carpal tunnel syndrome, **418**
 lunate dislocation as cause, 418
 median nerve injury as cause, 419
 rheumatoid arthritis as cause, 430
- Carteolol, 498
- Cartilage
 collagen in, 61
 fluoroquinolones, damage caused by, 253
- Carvedilol, 249, 303
- Casal necklace, 78
- Caseating necrosis, 217
 granulomatous diseases and, 223
- Case-control studies, 32, 34
- Caspases, in apoptosis, 216
- Caspofungin, 181, 183
 for *Candida albicans*, 137, 639
- Casts in urine, **544**
- Catabolism, peroxisome and, 59
- Catalase, 221
- Catalase-positive organisms, **112**
- Cataracts, **483**
 diabetes mellitus as cause, 330
 galactosemia as cause, 91
 glucocorticoids as cause, 212, 336
 muscular dystrophy as cause, 73
 prednisone as cause, 412
 rubella as cause, 165
 sorbitol as cause, 92
- Catecholamines
 adrenal medulla secretion of, 306
 amphetamines and, 246
 contractility, effect on, 267
 ephedrine and, 246
 pacemaker action potential and, 275
 pheochromocytoma effect on, 320
 synthesis of, **95**
- Cats, as disease vectors, 140, 163, 136, 169
- Cat scratch disease, 132
 as granulomatous disease, 223
- Caudal fold closure defects, 338
- Caudal medulla, effects of stroke on, 467
- Caudal regression system, 564
- Caudate, effect of Huntington disease on, 71, 462, 630
- Cause-and-effect diagram, 46
- Cavernous hemangiomas, 368
- Cavernous sinus, 470, **481**
- CCR5 protein
 HIV and, 158
 maraviroc and, 186
 as receptor, 150
- CD3 protein
 cells present on, 202
 regulatory T cells and, 194
- CD4 protein
 cells present on, 202
 helper T cells and, 194
 as receptor, 150
 regulatory T cells and, 194
- CD4+ T cells, 193
 in HIV, 159
- CD5 protein, 402
- CD8 protein
 cells present on, 202
 cytotoxic T cells and, 194
- CD8+ T cells, 193
- CD14 protein, 202
- CD16 protein, 202
- CD18 protein, 209
- CD19 protein, 202
- CD20 protein
 cells present on, 202
 in chronic lymphocytic leukemia, 402
- CD21 protein
 cells present on, 202
 as receptor, 150
- CD25 protein
 cells present on, 202
 regulatory T cells and, 194
- CD28 protein, 202
- CD34 protein
 cells present on, 202
 in leukocyte extravasation, 221
- CD40L protein, 202
- CD40 protein, 202
- CDKN2A gene, 230
- CEA tumor marker, 364
- Cefaclor, 172
- Cefazolin, 170
 characteristics of, 172
 as prophylaxis, 181
- Cefepime, 170
 characteristics of, 172
 for *Pseudomonas aeruginosa*, 127
- Cefotaxime, 172
- Cefoxitin, 170
 characteristics of, 172
- Ceftaroline, 170
 characteristics of, 172
 for MRSA, 181
 for *Staphylococcus aureus*, 641
- Ceftazidime
 characteristics of, 172
 for *Pseudomonas aeruginosa*, 127
- Ceftriaxone, 170
 characteristics of, 172
 for gonococci, 126
 for *Haemophilus influenzae*, 126
 for meningitis, 163
 for meningococci, 126
 for *Neisseria gonorrhoeae*, 640
 for *Neisseria meningitidis*, 640
 as prophylaxis, 181
 for typhoid fever, 129
- Cefuroxime, 172
- Celecoxib, 254, **447**
 arachidonic acid pathway and, 446
- Celiac artery, in chronic mesenteric ischemia, 362
- Celiac disease, 358
 autoantibody associated with, 207
 biliary cirrhosis and, 371
 dermatitis herpetiformis and, 443
 HLA genes and, 193
 lab findings in, 635
- Celiac lymph nodes, 190
- Celiac trunk, 342, **343**
- Cell cycle phases, **58**
- Cell envelope, bacterial, 108
- Cell injury, **218**
- Cell lysis, 542
- Cell membrane
 in apoptosis, 216
 blebbing, in cell injury, 218
- Cell surface proteins, **202**
- Cell trafficking, **59**
- Cellular biochemistry, 58–64
- Cellular crescents in Bowman capsule, 635
- Cellular inflammation, 219
- Cellulitis, 442
Streptococcus pyogenes as cause, 120
- Cell walls
 bacterial, **108**
 bacteria lacking, 109
 as bacterial structure, 108
- Central canal of spinal cord, 472
- Central clearing, caused by tinea corporis, 136
- Central diabetes insipidus, 328
- Central nervous system (CNS), **241**
 anesthetic principles for, 502
 injury to, as cause of shock, 292
 nitrosoureas, effect on, 410
 origins of, **450**

- Central nervous system (CNS)
depression
barbiturates as cause, 501
- Central pontine myelinolysis.
See Osmotic demyelination syndrome
- Central post-stroke pain syndrome, **468**
- Central retinal artery occlusion, **486**
presentation of, 630
- Central sleep apnea, 621
- Central sulcus, 462
- Central tendon, 609
- Central vein, 218
- Central vertigo, 495
- Centriacinar emphysema, 618
- Centrilobular necrosis, 231
- Centromeres, 207
- Cephalexin, 172
- Cephalosporins, 170, **172**
disulfiram-like reaction caused by, 254
for enterococci, 639
organisms not covered by, 172
pseudomembranous colitis caused by, 252
for *Pseudomonas aeruginosa*, 127
for *Streptococcus pneumoniae*, 641
- Ceramide, 100
- Ceramide trihexoside, 100
- Cerebellar hemisphere lesions, 464
- Cerebellar tonsillar herniation, 642
- Cerebellar vermis lesions, 464
- Cerebellum, **459**
development of, 450
- Cerebral aqueduct of Sylvius, 471
- Cerebral arteries, **466**
in cavernous sinus, 481
- Cerebral cortex
functions of, **462**
motor and sensory areas in, 465
- Cerebral edema
diabetic ketoacidosis as cause, 331
hyperammonemia as cause, 93
therapeutic hyperventilation for, 465
- Cerebral hemispheres, 450
- Cerebral infarct, 513
- Cerebral peduncle, 477
- Cerebral perfusion, **465**
- Cerebral perfusion pressure, 465
- Cerebrospinal fluid (CSF), 471
Guillain-Barré syndrome as cause, 493
in poliomyelitis, 475
yellowish tint, 638
- Cerebrovascular disease, in diabetes mellitus, 330
- Certolizumab, 214
- Ceruloplasmin
free radical elimination by, 221
in Wilson disease, 637
- Cervical cancer, 591, 643
carcinogens causing, 231
epidemiology of, 590
HIV and, 160
- hydronephrosis caused by, 550
oncogenic microbes and, 231
papillomaviruses as cause, 148
- Cervical dysplasia, 591
- Cervical lymphadenopathy, 630
- Cervical lymph nodes, 190
- Cervical rib, 420
- Cervicitis
chlamydia as cause, 167
gonorrhea as cause, 167
- Cervix
anatomy of, 574
lymphatic drainage of, 573
pathology of, **591**
- Cestodes, **144**
- Cetirizine, 627
- Cetuximab, 214, **412**
- CFTR* gene
chronic pancreatitis and, 373
cystic fibrosis and, 72
- cGMP (cyclic guanosine monophosphate)
atrial natriuretic peptide and, 279
as endocrine hormone messenger, 316
hydralazine and, 298
in male sexual response, 575
PDE-5 inhibitors, effect on, 603
in smooth muscle contraction, 425
- Chagas disease, 142
achalasia caused by, 354
cardiomyopathy caused by, 291
lab findings in, 635
- Chancroids, 167
- Chandelier sign, 167
- Chaperone protein, **57**
- Charcoal yeast extract culture, 111
for *Legionella pneumophila*, 127
- Charcot-Bouchard
microaneurysms, 468
- Charcot joints
in syphilis, 131
tabes dorsalis and, 474
- Charcot-Leyden crystals, 618
- Charcot-Marie-Tooth disease, 493
- Charcot triad, 492
- Charging, tRNA, 56
- Chédiak-Higashi syndrome, 209
lab findings in, 636
- Cheilosis, 78
- Chelation
for hemochromatosis, 371
for iron poisoning, 396
- Chemical tracheobronchitis, 222
- Chemokines, 200
- Chemoreceptors, **279**
- Chemotherapy
acute myelogenous leukemia and, 402
for Ewing sarcomas, 429
myelodysplastic syndromes caused by, 401
neutropenia caused by, 394
for osteosarcomas, 429
for pancreatic cancer, 373
readmissions caused by, 45
- Chemotoxicities, **413**
- Cherry hemangiomas, 441
- Cherry-red spot on macula, **486**
Niemann-Pick disease as cause, 100, 632
Tay-Sachs disease as cause, 100, 630
- Chest pain
angina as cause, 630
Dressler syndrome as cause, 630
panic disorder as cause, 517
pneumothorax as cause, 623
pulmonary embolism as cause, 617
unstable angina as cause, 630
- Chest wall, **611**
- Chest X-rays
aortic dissections on, 287
asthma on, 618
balloon heart on, 291
lung abscesses on, 624
notched ribs on, 283
Wegener granulomatosis on, 296
- Chiari I malformation, 452
- Chiari II malformation, 451, 642
- Chickenpox
live attenuated vaccine for, 146
rash caused by, 166
VZV as cause, 149
- Child abuse, **510**
confidentiality exceptions and, 41
osteogenesis imperfecta and, 63
- Childbirth
Budd-Chiari syndrome and, 368
butorphanol for pain relief in, 499
contraction frequency reduction in, 602
- C-section, neonatal flora after, 161
- endometritis after, 594
- Graves disease and, 323
- low birth weight, 581
- misoprostol for inducing, 375
- oxytocin for induction of, 336
- postpartum mood disturbances, **516**
- preterm, as common cause of death, 45
- progesterone levels after, 577
- pudendal block during, 422
- Sheehan syndrome after, 329
- stress incontinence and, 551
- Childhood disorders, **511**
- Child neglect, **510**
- Children
developmental milestones in, 43
- Chimeric monoclonal A_b, 255
- Chipmunk facies, 389
- Chi-square tests, 39
- Chlamydia* spp., **134**
as atypical organism, 162
Giemsa stain for, 110
as intracellular organism, 112
macrolides for, 176
morphology of, 109
pneumonia caused by, 624
reactive arthritis and, 433
sulfonamides for, 177
tetracyclines for, 175
- Chlamydia, 167
- Chlamydia trachomatis*, 134
pelvic inflammatory disease caused by, 167, 644
pneumonia caused by, 162
serotypes, **134**
STDs caused by, 645
as STI, 167
treatments for, 639
UTIs caused by, 552
- Chlamydomydia pneumoniae*, 134
pneumonia caused by, 162
- Chlamydomydia psittaci*, 134
animal transmission of, 132
- Chloasma, 439
- Chloramphenicol, 170, **175**
aplastic anemia caused by, 252, 391
gray baby syndrome caused by, 252
in pregnancy, avoiding, 187
as protein synthesis inhibitors, 174
for *Rickettsia rickettsii*, 640
- Chlordiazepoxide, 501
for alcohol withdrawal, 524
- Chlorhexidine, 187
- Chloride channels, in cystic fibrosis, 72
- Chloroquine, **183**
for malaria, 141, 640
- Chlorpheniramine, **627**
- Chlorpromazine, 525
- Chlorpropamide, 334
- Chlorthalidone, 558
- Chocolate agar, 111
Haemophilus influenzae culture on, 126
- Chocolate-colored blood, 612
- Chocolate cysts, 592, 594, 635
- Cholangiocarcinomas
Clonorchis sinensis and, 144, 145
hyperbilirubinemia caused by, 369
oncogenic microbes and, 231
sclerosing cholangitis and, 371
- Cholangitis, 372
- Cholecalciferol, **313**. *See* also Vitamin D
- Cholecystectomy, 372
for porcelain gallbladder, 372
- Cholecystitis, 372
- Cholecystokinin (CCK), 350
location of, 351
- Cholelithiasis, 347, **372**
acute pancreatitis caused by, 373
biliary cirrhosis and, 371
Crohn disease as cause, 359
hyperbilirubinemia caused by, 369
octreotide and, 375
pancreatitis and, 644
presentation of, 631
somatostatinomas as cause, 332
ursodiol for, 376
- Cholera toxin, 116
lysogenic phage and, 114
- Cholestasis serum markers, 366
- Cholesteatomas, **482**

- Cholesterol
 absorption of, 300
 in bile, 352
 in cholelithiasis, 372
 synthesis of, **84, 103**
 vitamin B₃ effect on, 78
- Cholesterol desmolase, 312
- Cholesterol ester transfer protein (CETP), 104
- Cholestyramine, 300
- Choline, 243
- Cholinergic agonists, 255
- Cholinergic drugs, 243
- Cholinergic effects, 301
- Cholinesterase inhibitors
 diarrhea caused by, 252
 poisoning from, **244**
- Cholinomimetic agents, **244, 498**
- Chondrocalcinosis, 431
- Chondrocytes
 in achondroplasia, 426
 bone formation and, 425
 in osteoarthritis, 430
- Chondrosarcomas, 429
- Chordae rupture, heart murmur caused by, 273
- Chorea, 461
 Huntington disease as cause, 630
- Choreiform movements
 Huntington disease as cause, 71
- Choriocarcinomas, **587**
 hCG in, 580
 lab findings in, 636
 methotrexate for, 409
 of testicles, 598
 theca-lutein cysts and, 592
- Chorionic plate, 566
- Chorionic villi
 in hydatidiform moles, 587
 in placenta, 566
- Chorioretinitis
 congenital toxoplasmosis as cause, 630
Toxoplasma gondii as cause, 165
 in toxoplasmosis, 140
- Choristomas, 228
- Choroid, 482
- Choroiditis, 484
- Chromaffin cells, 306
 embryologic derivatives of, 563
 pheochromocytomas and, 320
- Chromatin, in multiple myeloma, 401
- Chromatin structure, **48**
- Chromatolysis, **220**
- Chromogranin A, 626
- Chromosomal disorders, **75**
 karyotyping for, 67
- Chromosomal translocations, 75, **403**
- Chronic adrenal insufficiency, 379
- Chronic atrophic gastritis, 642
- Chronic bronchitis, 618
 presentation of, 632
- Chronic closure, 484
- Chronic gastritis, 356
- Chronic gout, 639
- Chronic granulomatous disease, 209, 223
 IFN- γ for, 187
 key associations, 643
 recombinant cytokines for, 213
 respiratory burst in, 201
- Chronic inflammation, 219
- Chronic ischemic heart disease, 287
- Chronic kidney disease
 in anemia taxonomy, 388
 erythropoietin in, 541
 focal segmental glomerulosclerosis and, 548
 hypertension as cause, 284
- Chronic lymphocytic leukemia (CLL), 402
 key associations, 644
 lab findings in, 638
 prednisone for, 412
 rituximab for, 214, 412
- Chronic mesenteric ischemia, 362
- Chronic mucocutaneous candidiasis, 208
- Chronic myelogenous leukemia (CML), 402
 basophilia caused by, 379
 busulfan for, 410
 chromosomal translocations and, 403
 death caused by, 642
 hydroxyurea for, 411
 imatinib for, 412
 key associations, 644
 oncogenes and, 230
 Philadelphia chromosome and, 644
 treatments for, 639
- Chronic myeloproliferative disorders, **404**
- Chronic obstructive pulmonary disease (COPD)
 albuterol for, 246
 β -blockers and, 249
 cholinomimetic agents and, 244
 muscarinic antagonists for, 245
 pulmonary hypertension and, 645
 salmeterol for, 246
- Chronic pancreatitis, **373**
 key associations, 644
 pancreatic cancer and, 373
 pancreatic insufficiency caused by, 358
- Chronic placental insufficiency, 530
- Chronic pyelonephritis, 552
 lab findings in, 638
- Chronic renal disease, 590
- Chronic renal failure, 325, 553
- Chronic respiratory disease, as common cause of death, 45
- Chronic thromboembolic pulmonary hypertension, 622
- Chronic transplant rejection, 211
- Churg-Strauss syndrome, **297**
 autoantibody associated with, 207
 as granulomatous disease, 223
 lab findings in, 634
- Chvostek sign, 542, 631
 in hypoparathyroidism, 325
- Chylomicrons, 105
 lipid transport and, 104
- Chylothorax, 623
- Chymotrypsin, 352
- Cidofovir, **185**
 for CMV, 639
- Cigarette smoke, as carcinogen, 231
- Ciguatoxin, 250
- Cilastatin
 imipenem and, 173
 seizures caused by, 253
- Ciliary body, 482
- Ciliary ganglia, in pupillary contraction, 487
- Cilia structure, **60**
- Ciliated cells, 608
- Cilostazol, **407**
- Cimetidine, 374
 cytochrome P-450 and, 254
 gynecomastia caused by, 595
- Cinacalcet, **336**
- Cinchonism
 Class IA antiarrhythmic as cause, 302
 as drug reaction, 253
- Cingulate gyrus, 458
- Cingulate herniation, 498
- Ciprofloxacin, 170, 178
 for Crohn disease, 359
 cytochrome P-450 and, 254
 for *Mycobacterium avium-intracellulare*, 179
 as prophylaxis, 181
 for *Pseudomonas aeruginosa*, 127
- Circadian rhythm
 hypothalamus control of, 456
 sleep physiology and, 457
- Circle of Willis, **466**
 saccular aneurysms and, 468
- Circulatory system
 fetal, **264**
 in kidneys, 532
- Circumcision, and penile cancer, 597
- Cirrhosis, **365**
 α_1 -antitrypsin deficiency as cause, 369
 alcoholic, 367
 autoantibody associated with, 207
 cholelithiasis and, 372
 cystic fibrosis as cause, 72
 esophageal varices and, 354
 fresh frozen plasma for, 399
 fructose intolerance as cause, 91
 as granulomatous disease, 223
 gynecomastia caused by, 595
 hemochromatosis as cause, 371
 hepatocellular carcinomas and, 368
 liver cancer and, 645
 loop diuretics for, 557
 non-alcoholic fatty liver disease and, 367
 pleural effusion caused by, 623
 portal hypertension caused by, 365
 Wilson disease as cause, 371
- Cirrhotic liver, 643
- Cisplatin, **411**
 acute tubular necrosis caused by, 554
- in cell cycle, 408
- Fanconi syndrome caused by, 538
- targets of, 408
- toxicities of, 413
- toxicity caused by, 254
- Citalopram, 527
- Citrate synthase, in metabolic pathways, 85
- Citrobacter* spp.
 in Gram-negative algorithm, 125
 lactose fermentation by, 126
- Citrulline, in urea cycle, 93
- c-KIT gene, 230
- CKK hormone, 319
- CK-MB
 in myocardial infarction, 287, 289
- Cladribine, 409
 in cell cycle, 408
 for hairy cell leukemia, 402
- Clara cells, 607
 in respiratory tree, 608
- Clarithromycin, 170, 176
 for *Helicobacter pylori*, 130
 as HIV prophylaxis, 181
 for *Mycobacterium avium-intracellulare*, 179
 in pregnancy, avoiding, 187
- Clasp knife spasticity, 473
- Classical conditioning, **508**
- Clathrin, 59
- Claudication
 atherosclerosis as cause, 286
 Buerger disease as cause, 296
 cilostazol/dipyridamole for, 407
 giant cell arteritis as cause, 296
- Clavulanate, 126
- Clavulanic acid, 171
- Claw hand, 421
 Klumpke palsy as cause, 420
- Clearance of drugs, 237, 646
- Clear cell adenocarcinomas, 591
 DES and, 601
 of vagina, 642
- Cleft lip, 570
- Cleft palate, **570**
 22q11 deletion syndromes as cause, 76
 Patau syndrome as cause, 74, 632
 Pierre Robin sequence as cause, 569
 as teratogenic effect, 564
 vitamin A overdose as cause, 564
- Clevidipine, 298
 for hypertensive emergency, 298
- Clindamycin, 170, **175**
 for bacterial vaginosis, 132
Clostridium difficile and, 122
 for endometritis, 594
 for lung abscesses, 624
 vs. metronidazole, 175
 as protein synthesis inhibitors, 174
 pseudomembranous colitis caused by, 252
- Clinical reflexes, **476**
- Clinical trials, **32**
- Clinical vignette strategies for USMLE Step 1 exam, 20

- Clitoris, 572
 “Clock-face” chromatin, 401
 Clofazimine
 for Hansen disease, 125
 for *Mycobacterium leprae*, 179
 Clomiphene, 601
 hot flashes caused by, 252
 for infertility, 640
 reproductive hormones and, 600
 Clomiphene citrate, 591
 Clomipramine, 527
 for obsessive-compulsive disorder, 517
 Clonidine, 247
 for Tourette syndrome, 511
 Cloning methods, as laboratory techniques, 67
Clonorchis sinensis, 144
 diseases associated with, 145
 as oncogenic microbe, 231
 Clonus, 527
 Clopidogrel, 407
 for acute coronary syndromes, 290
 for ischemic stroke, 470
 thrombogenesis and, 385
 Closed-angle glaucoma, 484
 pilocarpine for, 244
Clostridium spp., 122
 as anaerobic organism, 111
 in Gram-positive algorithm, 118
 morphology of, 109
Clostridium botulinum, 122
 exotoxin produced by, 116
 food poisoning caused by, 161
 as spore-forming bacteria, 114
 therapeutic uses of, 122
 treatments for, 639
Clostridium difficile, 122
 antibiotic use and, 122
 metronidazole for, 178
 as nosocomial infection, 168
 presentation of, 630
 proton pump inhibitors and, 374
 as spore-forming bacteria, 114
 treatments for, 639
 vancomycin and, 173
 watery diarrhea caused by, 162
Clostridium perfringens, 122
 clindamycin for, 175
 exotoxin produced by, 117
 food poisoning caused by, 161
 as spore-forming bacteria, 114
 watery diarrhea caused by, 162
Clostridium tetani, 122
 exotoxin produced by, 116
 as spore-forming bacteria, 114
 treatments for, 639
 Clotrimazole, 181, 182
 Clotting factors, 81
 Clozapine, 525
 agranulocytosis caused by, 252
 Clubbing
 bronchiectasis as cause, 618
 Eisenmenger syndrome as cause, 283
 Clubbing of nails, in cystic fibrosis, 72
 Club cells, 607
 Clue cells, 638
 in bacterial vaginosis, 132, 164
 Cluster A personality disorders, 519
 Cluster B personality disorders, 519
 Cluster C personality disorders, 519
 Cluster headaches, 494
 triptans for, 505
c-MYC gene, 230
 CNS lymphomas
 HIV and, 160
 oncogenic microbes and, 231
 CNS stimulants, 524
 Coagulation, 81
 Coagulation cascade, 384
 Coagulation disorders, 396
 Coagulation pathways, 383
 Coagulative necrosis, 217
 MI as cause, 288
 Coagulopathy
 postpartum hemorrhage as cause, 589
 preeclampsia as cause, 590
 Coal workers’ pneumoconiosis, 620
 CoA production, 78, 83
 Coarctation of aorta, 283, 284, 585
 Cobblestone mucosa, in Crohn disease, 359
 Cocaine, 246
 angina caused by, 287
 β -blockers and, 249
 cardiomyopathy caused by, 291
 coronary vasospasm caused by, 251
 intoxication and withdrawal, 522
 liver processing of, 346
 as local anesthetic, 503
 as noradrenergic drug, 243
 placental abruption and, 588
 pulmonary arterial hypertension caused by, 622
 as teratogen, 564
Coccidioides spp.
 amphotericin B for, 182
 itraconazole for, 182
 silver stain for, 110
 Coccidioidomycosis, 135
 erythema nodosum and, 444
 Cocciobacilli, 125
 Coccus bacteria, 109
 antibiotic tests for, 118
 Gram stain identification of, 118
 Cochlea, 481
 Codeine, 499
 Codman triangle, 429, 637
 Codominance, 68
 Codons, start and stop, 53
 “Coffee bean” nuclei of Brenner tumors, 592
 Cognitive behavioral therapy (CBT)
 for acute stress disorder, 517
 for ADHD, 511, 638
 for adjustment disorder, 517
 for anxiety disorders, 516
 for atypical depression, 515
 for binge eating disorder, 520
 for body dysmorphic disorder, 517
 for conduct disorder, 511
 for generalized anxiety disorder, 517
 for major depressive disorder, 515
 for obsessive-compulsive disorder, 517
 for oppositional defiant disorder, 511
 for panic disorder, 517
 for phobias, 517
 for postpartum depression, 516
 for PTSD, 517
 for separation anxiety disorder, 511
 Cohort studies, 32
 relative risk and, 34
 Coin lesion on CXR, 626
 Colchicine
 for acute gout attack, 638
 agranulocytosis caused by, 252
 for calcium pyrophosphate deposition disease, 431
 diarrhea caused by, 252
 for gout, 431, 448
 microtubules and, 60
 myopathy caused by, 253
 Cold agglutinin disease, 632
 Cold agglutinins, 134
 Cold autoimmune hemolytic anemia, 393
 Cold intolerance
 hypothyroidism as cause, 631
 Sheehan syndrome as cause, 632
 Colectomy, for ulcerative colitis, 359
 Colesevelam, 300
 Colestipol, 300
 Colistin B, 127
 Colitis, 160
 Collagen, 61
 osteoblasts and, 425
 in scar formation, 222
 synthesis and structure, 62
 in wound healing, 223
 Collagenase, in neutrophils, 378
 Collapsing pressure, 607
 Collecting tubules
 defects in, 538
 diuretics and, 556
 in nephron physiology, 537
 potassium-sparing diuretics and, 558
 Colles fracture, 426
 Colliculi, 477
 Colon
 histology of, 341
 ischemia in, 218
 Colon cancer
 5-fluorouracil for, 409
 familial adenomatous polyposis and, 71
 irinotecan/topotecan for, 411
 lab findings in, 638
 liver metastases in, 644
 metastases of, 233
 oncogenes and, 230
 Staphylococcus gallolyticus and, 121
 tumor suppressor genes and, 230
 Colonic ischemia, 362
 Colonic polyps, 363
 Colorado tick fever, 151

- Color blindness, 180
 Colorectal cancer, 364
 bevacizumab for, 214, 412
 cetuximab for, 214, 412
 familial adenomatous polyposis and, 363
 incidence/mortality of, 228
 juvenile polyposis syndrome as cause, 363
 lab findings in, 635
 Lynch syndrome, 53
 molecular pathogenesis of, 364
 tumor suppressor genes and, 230
 Colovesical fistulas, 360
 Coltivirus, 151
 Coma
 brain lesions causing, 464
 hepatic encephalopathy caused by, 367
 hyperosmolar hyperglycemia nonketotic syndrome as cause, 332
 hyponatremia as cause, 542
 medium-chain acyl-CoA dehydrogenase deficiency as cause, 101
 rabies as cause, 155
 Reye syndrome as cause, 366
 thyroid storm as cause, 323
 Trypanosoma brucei as cause, 140
 Combined pathway for coagulation, 383
 Comedocarcinomas, 596
 Commales, nonoverlapping genetic code, 50
 Comma-shaped rods, 125
 Common bile duct, 340, 347
 Common cold, 152
 Common peroneal nerve, 422
 Common variable immunodeficiency (CVID), 208
 Communicating hydrocephalus, 471
 Competence, in bacterial genetics, 114
 Competitive agonists, 240
 Competitive inhibitors, 236
 Complement, 199
 binding of, 196
 disorders of, 199
 innate immunity and, 192
 Complement activation, 199
 by antibodies, 196
 Arthus reaction as cause, 205
 Complementation, viral, 146
 Complex renal cysts, 555
 Compliance (lungs), 611
 Complications of pregnancy, 588–589
 Comprehensive Basic Science Examination (CBSE), 10
 Comprehensive Basic Science Self-Assessment (CBSSA), 11
 Computer-Based Test (CBT)
 exam schedule for, 7–8
 simulation test for, 5
 structure of, 3
 walkthrough of, 3

- COMT inhibitors, 504
 Conditioning, psychological, 508
 Conduct disorder, 511
 as antisocial personality disorder precursor, 519
 Conducting zone of respiratory tree, 608
 Conduction aphasia, 463
 Conductive hearing loss, 481
 Condylomata acuminata, 440
 IFN- α for, 187
 as STI, 167
 Condylomata lata
 presentation of, 634
 syphilis as cause, 131, 167
 Confidence intervals, **38**
 Confidentiality, **41**
 Confluence of the sinuses, 470
 Confounding bias, in studies, 36
 Congenital adrenal hyperplasia, 642
 Congenital adrenal hyperplasias, **312**
 Congenital conjugated hyperbilirubinemia, 642
 Congenital heart disease, 282–283
 disorders associated with, **284**
 Down syndrome as cause, 74
 Edwards syndrome as cause, 74
 key associations, 642
 maternal phenylketonuria as cause, 95
 Patau syndrome as cause, 74
 pulmonary arterial hypertension caused by, 622
 rubella as cause, 165
 Turner syndrome as cause, 634
 Congenital hydroceles, 598
 Congenital hypothyroidism, 322
 cretinism and, 642
 Congenital long QT syndrome, **277**
 Congenital lung malformations, **606**
 Congenital nevus, 438
 Congenital rubella
 cardiac defects associated with, 284
 heart murmur caused by, 273
 Congenital solitary functioning kidney, **531**
 Congenital syphilis, 131
 Congenital toxoplasmosis, 140
 presentation of, 630
 Congo red stain, 225
 Conivaptan, 336
 for SIADH, 328, 640
 Conjoined tendon, 348
 Conjugate vaccines, 112
 Conjugation
 in bacterial genetics, 114
 Conjunctival infections
 Kawasaki disease as cause, 296
 Conjunctivitis, **484**
 adenoviridae as cause, 148
 antimicrobial prophylaxis for, 181
 chlamydia as cause, 167
 chlamydiae as cause, 134
 gonococci as cause, 126
 Haemophilus influenzae as cause, 126
 LMN facial nerve palsy as cause, 634
 measles as cause, 631
 in reactive arthritis, 433
 Connective tissue diseases
 aortic dissection and, 287
 pulmonary arterial hypertension caused by, 622
 thoracic aortic aneurysms and, 286
 Connective tissue drug reactions, **253**
 Conn syndrome, 318
 lab findings in, 636
 Consent, **40**
 Consolidation (lung finding), 622
 Constipation
 aluminum hydroxide as cause, 375
 anal fissures caused by, 345
 antipsychotic drugs as cause, 525
 calcium channel blockers as cause, 298
 Hirschsprung disease as cause, 361
 hypothyroidism as cause, 321
 irritable bowel syndrome as cause, 360
 loperamide as cause, 376
 ondansetron as cause, 376
 opioids as cause, 499
 osmotic laxatives for, 375
 ranolazine as cause, 299
 vincristine as cause, 411
 Constrictive pericarditis
 jugular venous pulse in, 270
 key associations, 642
 Contact activation pathway for coagulation, 383
 Contact dermatitis, 205
 Contemplation stage of overcoming addiction, 521
 Continuous heart murmurs, 273
 Contraception
 combined, **602**
 copper intrauterine device for, 602
 emergency, 602
 parental consent for minors and, 40
 progestins for, 602
 Contractility, in cardiac output, 267
 Contraction alkalosis, 72
 Conversion disorder, 518
 Convulsions, vitamin B₆ deficiency as cause, 78
 Coombs hemolysis, 247
 Coombs-positive hemolytic anemia, 393
 as drug reaction, 252
 Coombs test, 204, 393
 COPI/COPII, in cell trafficking, 59
 Copper deficiency, 389
 Copper intrauterine device, **602**
 Copper toxicity, 251
 Copy number variations (CNV), 66
 Cord factor, in mycobacteria, 124
 Cori cycle, 93
 Cori disease, 99
 presentation of, 632
 Cornea, 482
 collagen in, 61
 Kayser-Fleischer rings in, 631
 Corneal arcus
 familial hypercholesterolemia as cause, 71, 105
 hyperlipidemia as cause, 285
 Corneal reflex, 479
 Corneal vascularization, 78
 Corniculate cartilage, 569
 Coronary aneurysms, 630
 Coronary artery
 anatomy of, **265**
 atherosclerosis in, 286, 645
 occlusion of, 265
 Coronary artery disease
 atrial fibrillation and, 278
 diabetes mellitus as cause, 330
 HMG-CoA reductase inhibitors for, 300
 hormonal contraception contraindication, 602
 hypertension as cause, 284
 menopause as cause, 582
 sudden cardiac death caused by, 287
 Coronary sinus, development of, 262
 Coronary steal syndrome, 287
 Coronary vasospasm, 251
 Coronaviruses
 characteristics of, 151
 genomes of, 147
 Cor pulmonale, 613, 645
 bronchitis as cause, 618
 heart failure and, 292
 pneumoconioses and, 620
 Corpus albicans, 579
 Corpus cavernosum
 female homolog of, 572
 lymphatic drainage of, 573
 Corpus luteum, 579
 hCG and, 580
 progesterone production in, 577
 Corpus spongiosum, 572
 Correct results, in statistical hypothesis testing, 38
 Corticobulbar tract, 467
 Corticospinal tract, 467
 Corticosteroids
 for asthma, 628
 cataracts and, 483
 for Crohn disease, 359, 639
 Cushing syndrome caused by, 317, 642
 for facial nerve palsy, 480
 for giant cell arteritis, 296
 hyperglycemia caused by, 252
 for hypopituitarism, 329
 as immunosuppressants, 212
 lymphopenia caused by, 394
 for microscopic polyangiitis, 296
 for minimal change disease, 548
 neutrophilia caused by, 394
 osteonecrosis caused by, 427
 osteoporosis caused by, 253
 pancreatitis caused by, 252
 for polyarteritis nodosa, 296
 for polymyalgia rheumatica, 435
 for syndrome of apparent mineralocorticoid excess, 538
 for Takayasu arteritis, 296
 targets of, 213
 for thyroid storm, 323
 for Wegener granulomatosis, 296, 639
 Corticotroph hyperplasia, 496
 Corticotropin-releasing hormone (CRH), 309
 adrenal cortex regulation of, 306
 cortisol regulation, 313
 Cushing syndrome and, 317
 signaling pathways of, 316
 Cortisol, **313**
 adrenal cortex secretion of, 306
 congenital adrenal hyperplasias and, 312
 in Cushing syndrome, 317
 in primary adrenal insufficiency, 318
 signaling pathways for, 316
 Cortisone, 446
Corynebacterium spp.
 in Gram-positive algorithm, 118
 morphology of, 109
Corynebacterium diphtheriae, **123**
 culture requirements for, 111
 exotoxin produced by, 116
 in unvaccinated children, 169
 Coryza, in measles, 631
 Cough
 ACE inhibitors as cause, 254, 559
 asthma as cause, 618
 bronchitis as cause, 618
 gastroesophageal reflux disease as cause, 354
 lung cancer as cause, 626
 opioids for, 499
 Wegener granulomatosis as cause, 296
 Councilman bodies, 636
 yellow fever as cause, 152
 Countertransference, **508**
 Courvoisier sign, 632
 pancreatic cancer as cause, 373
 Cowdry type A bodies, 636
 Cowper gland, 575
 Cowpox, 148
Coxiella spp., 112
Coxiella burnetii
 animal transmission of, 132
 endocarditis caused by, 293
 Q fever caused by, 133
 as spore-forming bacteria, 114
 Coxsackievirus, 151
 acute pericarditis caused by, 294
 as picornavirus, 152
 Coxsackievirus type A, 166
 rash in, 133
 Coxsackievirus type B
 cardiomyopathy caused by, 291
 myocarditis and, 644
 C-peptide
 insulin and, 308
 in insulinomas, 332

- Cranial nerves, **479**
 1st (olfactory), **479**
 location in brain stem, 477
 2nd (optic), **479**
 embryologic derivatives of, 563
 in eye anatomy, 482
 location in brain stem, 477
 Marcus Gunn pupils and, 487
 3rd (oculomotor), **479**
 in cavernous sinus, 481
 location in brain stem, 477
 ocular motility and, 488
 palsy of, 469, 489
 in pupillary contraction, 487
 4th (trochlear), **479**
 in cavernous sinus, 481
 location in brain stem, 477
 ocular motility and, 488
 palsy of, 489
 5th (trigeminal), **479**
 as branchial arch derivative, 569
 lesion in, 480
 location in brain stem, 477
 migraine headaches and, 494
 neuralgia of, 494
 in tongue, 452
 6th (abducens), **479**
 location in brain stem, 477
 ocular motility and, 488
 palsy of, 489
 7th (facial), **479**
 as branchial arch derivative, 569
 lesions in, **480**
 location in brain stem, 477
 in tongue, 452
 8th (vestibulocochlear), **479**
 acoustic neuromas and, 453
 location in brain stem, 477
 schwannomas and, 496
 9th (glossopharyngeal), 279, **479**
 as branchial arch derivative, 569
 location in brain stem, 477
 in tongue, 452
 10th (vagus), 279, **479**
 as branchial arch derivative, 569
 lesion in, 480
 location in brain stem, 477
 in tongue, 452
 11th (accessory), **479**
 lesion in, 480
 location in brain stem, 477
 12th (hypoglossal), **479**
 lesion in, 480
 location in brain stem, 477
 in tongue, 452
 impingement of, 426
 lesions of, **480**
 nuclei of, **478**
 pathways for, **478**
 reflexes, afferent/efferent for, 479
 Craniopharyngiomas, 497, 563, 642
 hypopituitarism caused by, 329
 Craniotabes, 427
 C-reactive protein (CRP)
 as acute-phase reactants, 198
 innate immunity and, 192
 in osteomyelitis, 163
 Creatine, 94
 Creatine kinase, 186
 Creatine phosphate, 103
 Creatinine
 ACE inhibitor effect on, 559
 in acute renal failure, 553
 glomerular filtration rate and, 534
 in nephritic syndrome, 545
 in proximal convoluted tubules, 539
 Creatinine clearance, 534
 Cre-lox system, 68
 Cremasteric muscle and fascia, 348
 Cremaster reflex, 476
 Crepitus, in necrotizing fasciitis, 442
 Crescentic glomerulonephritis, 635
 CREST syndrome, 437
 autoantibody associated with, 207
 biliary cirrhosis and, 371
 Raynaud phenomenon and, 437
 Cretinism, 322
 key associations, 642
 Creutzfeldt-Jakob disease, 161, 491
 dementia caused by, 513
 “Crew cut” on skull X-ray, 389, 392, 636
 CRH. *See* Corticotropin-releasing hormone (CRH)
 Cribriform plate, 478
 Cricoid cartilage, 569
 Cricothyroid muscle, 569
 Cri-du-chat syndrome, **75**
 chromosome associated with, 75
 Crigler-Najjar syndrome, 369, 370
 presentation of, 633
 Crimean-Congo hemorrhagic fever, 151
 Crohn disease, 359, 641
 azathioprine for, 212
 B₁₂ deficiency caused by, 390
 cholelithiasis and, 372
 as granulomatous disease, 223
 lab findings in, 637
 natalizumab for, 214
 spondyloarthritis and, 433
 sulfasalazine for, 375
 treatments for, 639
 vitamin B₁₂ deficiency caused by, 80
 Crossover studies, 36
 Cross-sectional studies, 32
 Croup, **154**
 lab findings in, 638
 paramyxoviruses as cause, 153
 pulsus paradoxus in, 294
 CRP, and ESR, 224
 Crust, skin, 438
 Cryoprecipitate, 399
 Crypt hyperplasia, 358
 Cryptococcal meningitis, 182
 Cryptococcosis, 137
Cryptococcus spp.
 amphotericin B for, 182
 meningitis caused by, 163
 as urease-positive organism, 112
Cryptococcus neoformans, **137**
 HIV and, 160
 stains for, 110
 treatments for, 639
 Cryptorchidism, **597**
 hypospadias and, 573
 Sertoli cells and, 576
 testicular tumors and, 598
Cryptosporidium spp., **139**
 HIV and, 160
 hyper-IgM syndrome and, 209
 watery diarrhea caused by, 162
 Ziehl-Neelsen stain for, 110
 Crypts of Lieberkühn, 341
 C-section deliveries
 neonatal flora and, 161
 neonatal respiratory distress syndrome and, 607
 Cuneiform cartilage, 569
 Curling ulcers
 gastritis caused by, 356
 Currant jelly sputum, 128, 169
Klebsiella pneumoniae as cause, 633
 “Currant jelly” stools, 362, 633
 Curschmann spirals, 618, 635
 Cushing disease, 317
 Cushing-like symptoms
 prednisone as cause, 412
 protease inhibitors as cause, 186
 Cushing reaction, 279
 Cushing syndrome, **317**
 acanthosis nigricans and, 444
 anovulation caused by, 591
 glucocorticoids as cause, 212, 336
 key associations, 642
 as paraneoplastic syndrome, 229
 small cell lung cancer as cause, 626
 Cushing ulcers, 641
 gastritis caused by, 356
 Cutaneous anthrax, **121**
 edema toxin and, 116
 Cutaneous flushing
 carcinoid syndrome as cause, 332
 as drug reaction, 251
 Cutaneous larva migrans, 143
 Cutaneous leishmaniasis, 142
 Cutaneous mycoses, **136**
 Cutaneous neurofibromas, 71
 Cutaneous paraneoplastic syndromes, 229
 Cutis aplasia
 Patau syndrome as cause, 74, 632
 CXCR4
 as receptor, 150
 CXCR4/CCR5 protein
 cells present on, 202
 Cyanide
 in electron transport chain, 89
 as electron transport inhibitor, 89
 methemoglobin affinity for, 612
 methemoglobinemia as treatment, 612
 Cyanide poisoning
 nitroprusside as cause, 298
 treatment for, 251
 Cyanopsia, 603
 Cyanosis
 “blue babies,” 282
 “blue kids,” 283
 bronchitis as cause, 618
 Eisenmenger syndrome as cause, 283
 esophageal atresia as cause, 338
 key associations, 642
 methemoglobinemia as cause, 612
 patent ductus arteriosus as cause, 283
 pulmonary hypertension as cause, 622
 tetralogy of Fallot as cause, 282
 Cyanotic shunt, 644
 Cyclin-CDK complexes, 58
 Cyclin-dependent kinases (CDKs), 58
 Cyclins, 58
 Cyclobenzaprine, **503**
 Cyclooxygenase
 acetaminophen and, 446
 aspirin effect on, 385, 447
 celecoxib and, 447
 NSAID effect on, 447
 Cyclophilin targets, 213
 Cyclophosphamide, 410
 hemorrhagic cystitis caused by, 553
 for microscopic polyangiitis, 296
 for polyarteritis nodosa, 296
 SIADH caused by, 253, 328
 toxicities of, 413
 transitional cell carcinoma and, 551
 for Wegener granulomatosis, 296, 639
 Cycloplegia
 atropine as cause, 245
 muscarinic antagonists for, 245
 Cyclosporine
 gingival hyperplasia caused by, 253
 gout caused by, 253
 as immunosuppressant, 212
 targets of, 213
 Cyclothymic disorder, 514, 515
 Cyproheptadine, 527
 Cyproterone, 600
 Cystathionine, 78
 Cystathionine synthase deficiency, 96
 Cysteine, 96
 Cystic duct, 347
 Cysticercosis, 144
 Cystic fibrosis, **72**
Aspergillus fumigatus and, 137
 bronchiectasis and, 618
 chromosome associated with, 75
 common organisms with, 162
 fat-soluble vitamin deficiencies and, 76
 lab findings in, 635
 meconium ileus in, 362
 N-acetylcysteine for, 627
 pancreatic insufficiency caused by, 358
 pancreatitis and, 644
Pseudomonas aeruginosa and, 113, 127
 Cystic hygromas, 441
 Turner syndrome as cause, 585, 634
 Cystine, 549
 Cystinosis, 538
 Cystinuria, **96**
 Cystitis, 551, 552

- Cytarabine, 409
in cell cycle, 408
- Cytochrome C, 216
- Cytochrome P-450
azoles and, 182
barbiturates and, 501
cimetidine and, 374
epilepsy drug effects on, 500
griseofulvin and, 183
interactions with, **254**
macrolides and, 176
phenobarbital effect on, 500
porphyria caused by, 395
rifamycins and, 179
ritonavir and, 186
- Cytokeratin
as cytoskeletal element, 60
in epithelial cells, 438
as stain, 60
- Cytokine receptor, 230
- Cytokines, **200**
in Graves disease, 323
recombinant, **213**
- Cytokinesis, 58
- Cytomegalovirus (CMV), 149
calcification and, 220
cholecystitis and, 372
cidofovir for, 185
esophagitis and, 354
foscarnet for, 185
ganciclovir for, 185
HIV and, 160
hyper-IgM syndrome and, 209
in immunodeficient patients, 210
lab findings in, 636
pneumonia caused by, 624
receptors for, 150
retinitis and, 486
as ToRCHeS infection, 165
treatments for, 639
- Cytoplasmic membrane
in bacterial cell walls, 108
as bacterial structure, 108
- Cytoplasmic processing bodies
(P-bodies), 54
- Cytoplasm, metabolism in, 83
- Cytosine methylation, 48
- Cytoskeletal elements, **60**
- Cytosol, 424
- Cytotoxic T cells, **194**
cell surface proteins, 202
- Cytotrophoblasts, 566
choriocarcinomas and, 587
- D**
- D₂ antagonists, 525
- Dabigatran, 640
- Daclizumab
as immunosuppressant, 212
targets of, 213
- Dacryocytes, 386
- Dactinomycin, 410
RNA polymerase inhibition by, 54
targets of, 408
- Dactylitis
seronegative spondyloarthritis as
cause, 433
sickle cell anemia as cause, 392
- DAF (GPI-anchored enzyme)
deficiency, 199
- Dalfopristin, 170
for VRE, 181
- Dalteparin, 405
- Danazol, **602**
for endometriosis, 594
pseudotumor cerebri and, 471
reproductive hormones and, 600
- Dandy-Walker syndrome, 451
- Dantrolene, **503**
for malignant hyperthermia, 502,
640
for neuroleptic malignant
syndrome, 525
- Dapagliflozin, 335
- Dapsone, **177**
for dermatitis herpetiformis, 443
for Hansen disease, 125
hemolysis in G6PD deficiency
caused by, 252
for *Mycobacterium leprae*, 179
for *Pneumocystis jirovecii*, 138
- Daptomycin, **178**
for MRSA, 181
for *Staphylococcus aureus*, 641
- Dark-field microscopy, 130
- Darunavir, 184
for HIV, 186
- Datura*, 245
- Daunorubicin, 410
dilated cardiomyopathy caused
by, 251
- DCC gene, 230
- D-dimer lab, 616
- Deafness
Alport syndrome as cause, 547
congenital long QT syndrome as
cause, 277
congenital syphilis as cause, 131
rubella as cause, 165
syphilis as cause, 165
- Deamination, and base excision
repair, 53
- Death
aortic dissection as cause, 287
causes of, common, **45**
children, explaining to, 42
eclampsia as cause, 590
hyperosmolar hyperglycemia
nonketotic syndrome as
cause, 332
pulmonary embolism as
cause, 617
pulmonary hypertension as
cause, 622
rabies as cause, 155
sleep apnea as cause, 621
sudden cardiac death as cause, 287
thyroid storm as cause, 323
- Debranching enzyme
in Cori disease, 99
in glycogen metabolism, 98
- Decay-accelerating factor (DAF), 199
- Deceleration injury, 286
- Decidua basalis, 566
- Decision-making capacity, **40**
- Decompression sickness, 617
- Deep brachial artery, 423
- Deep inguinal ring, 348
- Deep venous thrombosis (DVT), **616**
direct factor Xa inhibitors for, 407
embolic stroke and, 470
glucagonomas as cause, 332
heparin for, 405
lab findings in, 636
tamoxifen/taloxifene and, 413
- Deer flies, as disease vectors, 143
- Defensins, 192
- Deferasirox
for hemochromatosis, 371
for iron poisoning, 251, 396
- Deferiprone
for hemochromatosis, 371
for iron poisoning, 251
- Deferoxamine
for hemochromatosis, 371
for iron poisoning, 251, 396
- Deformation, 563
- Degenerate/redundant genetic
code, **50**
- Degmacytes, 386
in G6PD deficiency, 90, 392
- Dehydration
filtration effects of, 535
loop diuretics as cause, 557
mannitol as cause, 557
osmotic laxatives as cause, 375
SGLT-2 inhibitors as cause, 335
shock caused by, 292
- Dehydrogenases, 84
- Deiodinase, 315
- Delavirdine, 184
for HIV, 186
- Delirium, **512**
antipsychotic drugs for, 525
barbiturate withdrawal as
cause, 522
dementia and, 513
diabetic ketoacidosis as cause, 331
PCP as cause, 523
thyroid storm as cause, 323
- Delirium tremens (DTs), **524**
alcohol withdrawal as cause, 522,
523
- Δ cells, 307
somatostatinomas of, 332
somatostatin produced by, 350
- Δ-dimers, 636
- Delta virus, 151
- “Delta wave” on EKG, 635
- Delta wave sleep, 457
- Deltoid muscle
axillary nerve injury and, 419
in Erb palsy, 420
- Delusional disorder, **514**
- Delusions, 513
mesolimbic pathway and, 458
schizophrenia as cause, 514
- Demeclocycline, **336**. *See*
also Tetracyclines
diabetes insipidus caused by, 253,
328
for SIADH, 328, 640
- Dementia, **491, 513**
Creutzfeldt-Jakob disease as
cause, 161
HIV and, 160
Huntington disease as cause, 71,
462, 630
key associations, 643
metachromatic leukodystrophy as
cause, 100, 493
pellagra as cause, 78, 631
splice site mutations as cause, 52
- Demyelinating disease, 643
- Demyelination
diseases of, **493**
in vitamin B₁₂ deficiency, 474
- Dendritic cells, **380**
innate immunity and, 192
Langerhans cell histiocytosis
and, 403
in T- and B-cell activation, 194
- Dengue, 151
- Denial, as ego defense, 508
- Denosumab, 214
for osteoporosis, 426, 640
- De novo pyrimidine and purine
synthesis, **49**
rate-determining enzyme for, 84
- Dense deposit disease, 547
- Dental caries, 120
- Dental plaque
bacteria producing, 113
normal flora on, 161
- Dentate nucleus, 459
- Dentin
collagen in, 61
in osteogenesis imperfecta, 63
- Dentinogenesis imperfecta, 63
- Denys-Drash syndrome, 551
- Dependent personality disorder, 519
- Depersonalization/derealization
disorder, 512
panic disorder as cause, 517
- Depression
anorexia nervosa and, 520
atypical antipsychotics for, 525
atypical features in, **515**
benzodiazepine withdrawal as
cause, 522
dementia caused by, 513
dissociative identity disorder
and, 512
drug therapy for, 524
electroconvulsive therapy for, 516
glucagonomas as cause, 332
Huntington disease as cause, 71,
462
hyperparathyroidism as cause, 326
marijuana withdrawal as cause, 523
MDMA withdrawal as cause, 523
metoclopramide as cause, 376
mirtazapine for, 248
neurotransmitter changes in, 511
neurotransmitters for, 455
postpartum, 516
Selective serotonin reuptake
inhibitors (SSRIs) for, 527
serotonin-norepinephrine reuptake
inhibitors (SNRIs) for, 527

- sexual dysfunction caused by, 520
stimulant withdrawal as cause, 522
suicide and, 516
treatments for, 639
- Deprivation effects on infants, **510**
- De Quervain thyroiditis, 322
- Dermacentor* tick, as disease
vector, 132
- Dermatitis
B-complex deficiency as cause, 76
glucagonomas as cause, 332
pellagra as cause, 78, 631
as type IV hypersensitivity
reaction, 205
vitamin B₅ deficiency as cause, 78
vitamin B₇ deficiency as cause, 79
- Dermatitis herpetiformis, 443
celiac disease and, 358
- Dermatology, 437-445
macroscopic terms, **438**
microscopic terms, **439**
- Dermatomes, landmark, **476**
- Dermatomyositis, **436**
autoantibody associated with, 207
- Dermatophytes, 136
- Dermatophytoses, 182
- Dermis, 437
- Dermoid cysts, 592
- Descending colon, 339
- Desert bumps/desert rheumatism, 135
- Desflurane, 502
- Desipramine, 527
- Desloratadine, 627
- Desmin
as cytoskeletal element, 60
as stain, 60
- Desmoplakin, 438
- Desmopressin
for diabetes insipidus, 639
for hemophilia, 396
- Desmopressin acetate, 311, 336
for diabetes insipidus, 328
- Desmosome, 438
autoantibody to, 207
- Desquamated epithelium casts in
sputum, 635
- Desvenlafaxine, 527
- Detached retina, **485**
- Detemir insulin, 334. *See also* Insulin
- Developmental delays, caused by
renal failure, 553
- Developmental milestones, **43**
- Dexamethasone, 336. *See also* Glucocorticoids
arachidonic acid pathway and, 446
- Dexlansoprazole, 374
- Dextrazoxane, 410
- Dilated cardiomyopathy prevention
with, 251
- Dextroamphetamine, 524
- Dextrocardia, 262
- Dextromethorphan, 499, **627**
- Diabetes insipidus, **328**
antidiuretic hormone in, 311
demeclocycline as cause, 336
desmopressin acetate for, 336
as drug reaction, 253
- lithium as cause, 526
potassium-sparing diuretics for, 558
thiazides for, 558
treatments for, 639
- Diabetes mellitus, **330-331**. *See also* Hyperglycemia
acanthosis nigricans and, 444
atherosclerosis and, 286
atypical antipsychotics as
cause, 525
 β -blockers and, 249
binge eating disorder as cause, 520
breast milk as risk reduction
for, 581
Candida albicans and, 137
carpal tunnel syndrome and, 418
cataracts and, 483
chronic renal failure and, 553
CN III damage caused by, 489
diabetic ketoacidosis caused by, 331
diabetic retinopathy caused by, 485
drug therapy for, **334-335**
endometrial cancer and, 594
facial nerve palsy caused by, 480
Friedreich ataxia as cause, 475
fungal infections and, 169
glaucoma and, 484
glucagonomas as cause, 332
glucocorticoids as cause, 336
glucosuria in, 536
hemochromatosis as cause, 371
hypertension and, 284, 298
Klebsiella and, 128
mucormycosis and, 137
neonatal respiratory distress
syndrome and, 607
pancreatic cancer and, 373
polyhydramnios and, 589
preeclampsia and, 590
in pregnancy, cardiac defects
associated with, 284
Pseudomonas aeruginosa and, 127
pyelonephritis and, 552
readmissions caused by, 45
renal papillary necrosis and, 554
sexual dysfunction caused by, 520
tacrolimus and, 212
teratogenic effects of, 564
type 1 vs. type 2, 331
urinary tract infections in, 164
UTIs and, 552
- Diabetes mellitus type 1, **331**
anencephaly and, 451
autoantibody associated with, 207
HLA-DR3 and, 193, 643
HLA-DR4 and, 193, 643
treatments for, 334, 639
- Diabetes mellitus type 2, **331**
hyperosmolar hyperglycemia
nonketotic syndrome
and, 332
treatments for, 334, 639
- Diabetic glomerulonephropathy, 548
- Diabetic ketoacidosis
black eschar and, 630
ketone bodies in, 102
metabolic acidosis as cause, 543
- presentation of, 631
treatments for, 639
- Diabetic ketoacidosis (DKA), **331**
diabetes mellitus type 1 as
cause, 330
- Diabetic nephropathy
ACE inhibitors for, 559
angiotensin II receptor blockers
for, 559
- Diabetic neuropathy, 527
- Diabetic retinopathy, **485**
- Diagnosis errors, 46
- Diagnosis of parathyroid disease, **325**
- Diagnostic test evaluation, **33**
- Dialectical behavior therapy for
borderline personality
disorder, 519
- Dialysis-related amyloidosis, 225
- Diamond-Blackfan anemia, 390
- Diapedesis, 221
- Diaper rash
Candida albicans as cause, 137
nystatin for, 182
- Diaphoresis
acromegaly as cause, 327
MI as cause, 288
serotonin syndrome as cause, 527
- Diaphragmatic hernias, 349
- Diaphragm structures, **609**
- Diaphysis, 429
- Diarrhea
amebiasis as cause, 139
Bacillus cereus as cause, 122
B-complex deficiency as cause, 76
bismuth/sucralfate for, 375
bronchial carcinoid tumor as
cause, 626
Campylobacter jejuni as cause, 128
carcinoid syndrome as cause, 631
cholera toxin as cause, 116
cholinesterase inhibitor poisoning
as cause, 244
clindamycin as cause, 175
Clostridium difficile as cause, 122,
630
Cryptosporidium as cause, 139
as drug reaction, 252
ezetimibe as cause, 300
giardiasis as cause, 139
graft-versus-host disease as
cause, 211
HIV and, 160
hyperthyroidism as cause, 321
inflammatory bowel diseases as
cause, 359
irritable bowel syndrome as
cause, 360
lactase deficiency as cause, 92
lactose intolerance as cause, 358
leflunomide as cause, 447
loperamide for, 376
magnesium deficiency caused
by, 314
magnesium hydroxide as cause, 375
malabsorption syndromes as
cause, 358
metabolic acidosis caused by, 543
metoclopramide as cause, 376
- misoprostol as cause, 375
opioids for, 499
opioid withdrawal as cause, 522
organisms causing, **162**
osmotic laxatives as cause, 375
pellagra as cause, 78, 631
rotavirus as cause, 152
Salmonella as cause, 129
SCID as cause, 209
serotonin syndrome as cause, 527
Shigella as cause, 129
threadworms as cause, 143
thyroid storm as cause, 323
Vibrio cholerae as cause, 129
VIPomas as cause, 350
vitamin C toxicity as cause, 80
Whipple disease as cause, 634
Yersinia enterocolitica as cause, 129
- Diastole, 270
heart failure and, 292
heart murmurs of, 272, 273
heart sounds of, 272
- Diastolic pressure, 266
- Diazepam, 501
for alcohol withdrawal, 524
flumazenil and, 240
for tetanus, 122
- Diclofenac, 447
arachidonic acid pathway and, 446
- Dicloxacillin, 170
characteristics of, 171
for *Staphylococcus aureus*, 641
- Dicrotic notch, in cardiac cycle, 270
- Dicyclomine, 245
- Didanosine, 184
for HIV, 186
pancreatitis caused by, 252
- Diencephalon, 450
- Diethylcarbamazine, 183
for nematode infections, 143
- Diethylstilbestrol (DES), 601
clear cell adenocarcinoma of
vagina and, 591, 642
as teratogen, 564
- Differential media, 110
- Differential tables for USMLE Step 1
exam, 13
- Differentiation, tumor, 226
- Diffuse cortical necrosis, **552**
- Diffuse glomerular disorders, 544
- Diffuse hemorrhage, 156
- Diffuse large B-cell lymphoma
(DLBCL), 400, 402
- Diffuse proliferative
glomerulonephritis
(DPGN), 546, 638
- Diffuse scleroderma, 437
- Diffuse stomach cancer, 356
- Diffuse systemic scleroderma, 635
- Diffusion-limited gas exchange, 613
- Digestion
bile function in, 352
carbohydrate absorption, 352
malabsorption syndromes, 358
pancreatic secretions for, 352
ulcerative colitis and, 359
vitamin/mineral absorption, 352

- Digestive tract
 anatomy of, **341**
 histology of, **341**
- Digitalis
 contractility, effect on, 267
 hyperkalemia caused by, 542
 toxicity treatment for, 251
- Digitoxin, 61
- Digoxin, 301
 antidote for, 214
 for dilated cardiomyopathy, 291
 sodium-potassium pump inhibition, 61
 therapeutic index value of, 240
- Digoxin immune Fab, 214
- Digoxin poisoning
 magnesium for, 304
- Dihydroergotamine, 494
- Dihydrofolate reductase, 49
- Dihydrofolic acid, 177
- Dihydroorotate dehydrogenase
 leflunomide effect on, 49, 447
- Dihydropyridine calcium channel blockers, 255
- Dihydropyridine receptor, 424
- Dihydrorhodamine test, 209
- Dihydrotestosterone (DHT), 582
 in genital development, 572
 pharmacologic control of, 600
- Dihydroxyacetone-P in fructose metabolism, 91
- Dilated cardiomyopathy, 291
 doxorubicin as cause, 410
 as drug reaction, 251
 heart failure caused by, 292
 hemochromatosis as cause, 371
 muscular dystrophy as cause, 73
 wet beriberi as cause, 77, 631
- Diltiazem, 298, 304
- Dimenhydrinate, **627**
- Dimercaprol
 for arsenic toxicity, 251
 for gold poisoning, 251
 for lead poisoning, 251, 389
 for mercury poisoning, 251
- Dinitrophenol, 89
- Dipalmitoylphosphatidylcholine, 607
- Diphenhydramine, **627**
- Diphenoxylate, 499
- Diphtheria
Corynebacterium diphtheriae as cause, 123
 exotoxins as cause, 115
 vaccine for, 123
- Diphtheria toxin, 116
 lysogenic phage and, 114
- Diphyllobothrium latum*, 144
 B₁₂ deficiency caused by, 390
 diseases associated with, 145
 vitamin B₁₂ deficiency caused by, 80
- Diplococci, 125
- Diplopia, 631
 myasthenia gravis as cause, 436
 osmotic demyelination syndrome as cause, 492
 pseudotumor cerebri as cause, 471
 vertigo caused by, 495
- Dipyridamole, **407**
 for coronary steal syndrome, 287
- Direct factor Xa inhibitors, **407**
- Direct hernias, 348
- Direct inguinal hernias, 349
- Direct thrombin inhibitors, **405**
- Disc herniation, 423
- Disease prevention, **44**
- Disopyramide, 302
- Disorganized speech, in schizophrenia, 514
- Disorganized thought, 513
- Displacement, as ego defense, 508
- Disruption, in organogenesis, 563
- Disseminated candidiasis, 137
- Disseminated intravascular coagulation (DIC)
 acute myelogenous leukemia as cause, 402
 amniotic fluid emboli as cause, 617
 Ebola as cause, 156
 endotoxins as cause, 117
 fresh frozen plasma for, 399
 key associations, 643
 lab findings in, 636
 microangiopathic anemia caused by, 393
 placental abruption as cause, 588
 schistocytes in, 387
 Waterhouse-Friderichsen syndrome as cause, 318, 630
- Dissociation, as ego defense, 508
- Dissociative amnesia, 512
- Dissociative disorders, **512**
- Dissociative fugue, 512
- Dissociative identity disorder, 512
- Distal convoluted tubules, 532
 defects in, 538
 diuretics and, 556
 in filtration, 535
 in nephron physiology, 537
 renal tubular acidosis of, 544
- Distal humerus, 423
- Distal interphalangeal (DIP) joints, 421
- Distal vagina, lymphatic drainage of, 573
- Distortions of hand, **421**
- Distribution, statistical, 37
- Distributive shock, 292
- Disulfiram
 for alcoholism, 523, 638
 ethanol metabolism and, 83
- Disulfiram-like reaction, 254
- Diuresis, for shock, 292
- Diuretics
 acute interstitial nephritis caused by, 554
 for dilated cardiomyopathy, 291
 electrolyte changes, **558**
 for glaucoma, 498
 in gout, 448
 magnesium levels and, 314
 pancreatitis caused by, 252
 for SIADH, 328
 site of action, **556**
- Diverticula, 645
- Diverticula of GI tract, **360**
- Diverticulitis, 360
 vs. appendicitis, 360
- Diverticulosis, 360
- Diverticulum, 360
- Diverticulum in pharynx, 643
- Dizziness, 495
 calcium channel blockers as cause, 298
- DMPK gene, 73
- DNA
 cloning methods, 67
 free radical effect on, 221
 introns vs. exons, **55**
 methylation of, **48**
 mutations in, **52**
 protein synthesis direction, **53**
 repair of, **53**
 replication of, **51**
- DNA laddering in apoptosis, 216
- DNA ligase, **51**
- DNA polymerase inhibitors, 255
- DNA polymerases, **51**
- DNA topoisomerases, **51**
- DNA viruses, **148**
 characteristics of, 147
 genomes of, **147**
 replication of, 147
- Dobutamine, 246
- Dofetilide, 303
- Dogs, as disease vectors, 144, 163, 136, 169
- Dominant inheritance, 70
- Dominant negative mutations, 68
- Dominant parietal cortex lesions, 464
- Donepezil, 244
 for Alzheimer disease, 505
- DOPA, in tyrosine catabolism, 95
- Dopamine, 246, 309, 455
 atypical antipsychotic effects on, 525
 bupropion effect on, 528
 in depression, 511
 as derivative, 94
 in Huntington disease, 71, 462, 511
 kidney functions, 541
 lactation and, 310
 MAO inhibitor effect on, 528
 in noradrenergic drugs, 243
 in Parkinson disease, 504, 511
 pheochromocytoma secretion of, 320
 prolactin and, 310
 in schizophrenia, 511
 in tyrosine catabolism, 95
 vitamin B₆ and, 78
- Dopamine agonists
 for Parkinson disease, 504
 prolactin, effect on, 310
 for prolactinomas, 326, 640
- Dopamine antagonists, 310
- Dopamine receptors, 242, 460
- Dopaminergic pathways, **458**
- Doripenem, 170, 173
- Dornase alfa (DNAse), 72
- Dorsal column of spinal cord, 472, 473
- Dorsal interossei muscle, 421
- Dorsal motor nucleus, 479
- Dorsal optic radiation, 489
- Dorsal pancreatic bud, 339
- Dosage calculations, **237**
- Double-blinded studies, 32
- “Double bubble” sign on X-ray, 338
- Double stranded viruses, 147
- Double Y males, 585
- Down syndrome, **74**
 acute lymphoblastic leukemia and, 402
 acute myelogenous leukemia and, 402
 Alzheimer disease and, 491
 cardiac defects associated with, 284
 cataracts and, 483
 chromosome associated with, 75
 duodenal atresia and, 338
 hCG in, 580
 Hirschsprung disease and, 361
 horseshoe kidney and, 531
 intellectual disability caused by, 643
 lab findings in, 635
 presentation of, 633
- Doxazosin, 248
- Doxepin, 527
- Doxorubicin, 410
 cardiomyopathy caused by, 291
 dilated cardiomyopathy caused by, 251
 targets of, 408
 toxicities of, 413
- Doxycycline, 170, 175
 for chlamydiae, 134
 for *Chlamydia trachomatis*, 639
 for lymphogranuloma venereum, 134
 for *Mycoplasma pneumoniae*, 134
 for *Rickettsia rickettsii*, 640
- DPC4/SMAD4 gene, 230
- DPP-4 inhibitors, 335
- Dressler syndrome
 MI as cause, 288
 presentation of, 630
- DRESS syndrome, 500
- Droling, treatment for, 245
- Drug clearance, 646
- Drug-induced lupus, 207
- Drugs
 autonomic, **243**
 cholinomimetic agents, 244
 dosage calculations, 237
 efficacy vs. potency, **239**
 elimination of, 238
 errors in, 46
 interactions, 237
 metabolism of, **238**
 patient difficulty with, 42
 reactions to, **251–254**
 therapeutic index, **240**
 toxic dose, 240
 toxicities, **251**
- Drug trials, 32
- Dry beriberi, 77
- Dry cough, caused by ACE inhibitors, 254

- Dry mouth
Lambert-Eaton myasthenic syndrome as cause, 436
tricyclic antidepressants as cause, 527
- Dry skin, caused by Vitamin A toxicity, 77
- Dubin-Johnson syndrome, 369, 370, 642
- Duchenne muscular dystrophy, **73**
frameshift mutation as cause, 52
presentation of, 630
as X-linked recessive disorder, 72
- Ductal adenocarcinomas, 347
- Ductal carcinoma in situ (DCIS), 596
- Ductal carcinomas, 595
- Ductal lumen, 596
- Ductus arteriosus, 568
in fetal circulation, 264
postnatal derivative of, 264
- Ductus deferens
embryology of, 571
ureter and, 532
- Ductus venosus
in fetal circulation, 264
postnatal derivative of, 264
- Duloxetine, 527
- Duodenal atresia, **338**
Down syndrome as cause, 74
- Duodenal ulcers, 357
- Duodenum, 339
biliary structures and, 347
histology of, 341
location of, 351
- Duplex collecting system, **531**
- Dural venous sinuses, **470**
- Duret hemorrhage, 498
- Dwarfism, 327
achondroplasia as cause, 426
- D-xylose test, 358
- Dynein, 60
- Dysarthria, 463
cerebellar vermis lesions and, 464
Friedreich ataxia as cause, 475
osmotic demyelination syndrome as cause, 492
- Dyschezia
endometriosis as cause, 594
- Dysentery
amebiasis as cause, 139
Escherichia coli as cause, 128
Shigella spp. and, 116
- Dysgerminomas, 593
- Dysgeusia, 82
- Dyslipidemia, **105**
β-blockers as cause, 249
metoprolol as cause, 303
renal failure as cause, 553
vitamin B₃ for, 78
- Dysmenorrhea, 579
adenomyosis as cause, 594
copper IUD as cause, 602
endometriomas as cause, 592
endometriosis as cause, 594
- Dysmetria
stroke as cause, 467
vertigo caused by, 495
- Dysmyelinating diseases, **493**
- Dyspareunia, 520
endometriomas as cause, 592
endometriosis as cause, 594
- Dyspepsia, 603
- Dysphagia
achalasia as cause, 354
esophageal cancer as cause, 355
gastroesophageal reflux disease as cause, 354
heart enlargement as cause, 265
osmotic demyelination syndrome as cause, 492
Plummer-Vinson syndrome as cause, 354, 388, 631
sclerodermal esophageal dysmotility as cause, 354
stroke as cause, 467
Zenker diverticulum as cause, 361
- Dysplasia, 226, 227
- Dyspnea
aortic stenosis as cause, 273
asthma as cause, 618
bronchitis as cause, 618
emphysema as cause, 633
heart failure as cause, 292
hypersensitivity pneumonitis as cause, 619
hypothyroidism as cause, 321
pneumothorax as cause, 623
pulmonary embolism and, 617
Wegener granulomatosis as cause, 296
- Dysthymia, 514, 515
- Dystonia, 461
benztropine for, 245
Lesch-Nyhan syndrome as cause, 50
nigrostriatal pathway and, 458
- Dystrophic calcification, 220
- Dystrophin gene, 73
- Dysuria
BPH as cause, 599
prostatitis as cause, 599
UTIs as cause, 164, 552
- E**
- Eardrum, 481
- Early-onset Alzheimer disease, 74
- Ear physiology, **481**
- Earthquakes, coccidioidomycosis incidence after, 135
- Eastern equine encephalitis, 151
- Eating disorders, **520**
- Eaton agar, 111
for *Mycoplasma pneumoniae*, 134
- Ebola, **156**
as filovirus, 151
Ebstein anomaly, 263, 282
fetal lithium exposure as cause, 564
lithium as cause, 284, 526
- Eburnation, 637
- E-cadherin, 438
in neoplastic progression, 227
- Echinocandins, 181, **183**
cutaneous flushing caused by, 251
- Echinococcus granulosus*, 144
diseases associated with, 145
- Echinocytes, 386
- Echothiophate, 498
- Echovirus, 151
as picornavirus, 152
- Eclampsia, 590
benzodiazepines for, 501
hypertensive emergency and, 284
- Ecthyma gangrenosum, 127
Pseudomonas aeruginosa and, 127
- Ectocervix, 574
- Ectoderm
branchial clefts derived from, 568
derivatives of, 563
- Ectoparasites, **145**
- Ectopic pregnancy, **589**
vs. appendicitis, 360
Chlamydia trachomatis as cause, 134
hCG in, 580
Kartagener syndrome as cause, 60
methotrexate for, 409
salpingitis and, 167
- Eculizumab, 214
for paroxysmal nocturnal hemoglobinuria, 392
- Eczema, 440
hyper-IgE syndrome as cause, 208, 633
phenylketonuria as cause, 95
skin scales in, 438
as type I hypersensitivity reaction, 204
Wiskott-Aldrich syndrome as cause, 209
- Eczematous dermatitis, 439
- Edema
acute poststreptococcal glomerulonephritis as cause, 546
Arthus reaction as cause, 205
calcium channel blockers as cause, 298
capillary fluid exchange and, 281
cirrhosis as cause, 365
danazol as cause, 602
diabetic ketoacidosis as cause, 331
endotoxins as cause, 117
fludrocortisone as cause, 336
glitazone/thiazolidinediones as cause, 334
glomerular filtration barrier and, 533
heart failure as cause, 292
immunosuppressants as cause, 212
as inhalational injury, 222
Kawasaki disease as cause, 296
kwashiorkor as cause, 82
loop diuretics for, 557
myxedema as cause, 631
nephrotic syndrome as cause, 548, 633
pseudoephedrine/phenylephrine for, 627
pulmonary hypertension as cause, 613
Trichinella spiralis and, 145
trichinosis as cause, 143
wet beriberi as cause, 77, 631
- Edema toxin, 116
- Edinger-Westphal nuclei, 487
- EDRF. See Endothelium-derived relaxing factor (EDRF)
- Edrophonium, 244, 503
- Edwards syndrome, **74**
cataracts and, 483
chromosome associated with, 75
hCG in, 580
horseshoe kidney and, 531
presentation of, 632
- Efavirenz, 184
for HIV, 186
- Effective refractory period
Class IA antiarrhythmic effect on, 302
Class IC antiarrhythmic effect on, 302
myocardial action potential and, 274
- Effective renal plasma flow, **534, 647**
- Effects analysis for medical errors, 46
- Efferent arteriole, 532
angiotensin II, effect on, 541
ANP/BNP effect on, 540
constriction of, 535
dopamine, effect on, 541
in filtration, 535
- Efferent nerves, 279
- Efficacy of drugs, vs. potency, 239
- EGF. See Epidermal growth factor (EGF)
- EGFR* gene, 626
- Ego defenses, **508**
- Ehlers-Danlos syndrome, **63**
collagen and, 62
collagen deficiency in, 61
heart murmur caused by, 273
presentation of, 631
saccular aneurysms and, 468
- Ehrlichia chaffeensis*, 132
- Ehrlhiosis, **133**
animal transmission of, 132
- Eikenella* spp., 293
- Eisenmenger syndrome, 283
cyanotic shunt and, 644
- Ejaculation
innervation of, 575
sperm pathway in, 575
- Ejaculatory ducts, 575
embryology of, 571
- Ejection click, 643
- Ejection fraction, 267, 647
- Ejection murmur, 634
- Elastase, 352
in emphysema, 618
- Elastic recoil, 611
- Elastin, **64**
- Elbow injuries, **417**
- Elder abuse, 41
- Electrocardiograms (ECGs), **276**
acute pericarditis on, 294
cardiac tamponade on, 294
MI diagnosis with, 289
tracings of, **278**
- Electroconvulsive therapy, **516**
for major depressive disorder, 515
for postpartum psychosis, 516

- Electrolyte disturbances, **542**
- Electron transport chain, **89**
- Electron transport inhibitors, **89**
- Elek test, **123**
- Elementary bodies in chlamydiae, **134**
- Elephantiasis, **143**
- 11 β -hydroxylase, **312**
- 11 β -hydroxysteroid dehydrogenase, **538**
- 11-deoxycorticosterone, **312**
- 11-deoxycortisol, **312**
- metyrapone and, **318**
- Elfin facies, in Williams syndrome, **75**
- Elimination of drugs, **238**
- urine pH and, **238**
- ELISA (enzyme-linked immunosorbent assay), **67**
- HIV diagnosis with, **158**
- Elliptocytes, **386**
- Elliptocytosis, **386**
- Elongation of protein synthesis, **57**
- Eltrombopag, **213**
- Emancipated minors, **40**
- EMB agar, **111**
- Escherichia coli* on, **164**
- lactose-fermenting enteric bacteria on, **126**
- Emboli, caused by
- atherosclerosis, **286**
- Embolic stroke, **470**
- Emboliform nucleus, **459**
- Embryogenesis
- genes involved in, **562**
- intrinsic pathway and, **216**
- Embryology
- cardiovascular, **262–264**
- derivatives of, **563**
- endocrinal, **306**
- erythropoiesis, **381**
- gastrointestinal, **338–339**
- genital, **571**
- neurological, **450–452**
- pancreatic, **339**
- renal, **530–531**
- reproductive, **562–573**
- respiratory, **606–607**
- splenic, **339**
- USMLE Step 1 preparation for, **258**
- Embryonal carcinomas, **598**
- Emotionally distraught patients, **42**
- Empagliflozin, **335**
- Emphysema, **618**
- α_1 -antitrypsin deficiency as cause, **369**
- compliance in, **611**
- diffusion in, **613**
- diffusion-limited gas exchange in, **613**
- elastin and, **64**
- presentation of, **633**
- Empty sella syndrome, **329**
- Emtricitabine, **184**
- for HIV, **186**
- Enalapril, **559**
- Encapsulated bacteria, **112**
- vaccines for, **112**
- Encephalitis
- Cryptococcus neoformans* as cause, **137**
- guanosine analogs for, **184**
- HIV and, **160**
- HSV-2 as cause, **165**
- measles as cause, **154**
- small cell lung cancer as cause, **626**
- VZV as cause, **149**
- Encephalopathy
- hypertensive emergency and, **284**
- lead poisoning as cause, **389**
- Lyme disease as cause, **130**
- neuroleptic malignant syndrome as cause, **525**
- End-diastolic volume, **266**
- Endemic typhus, **132**
- Endocannabinoids, **311**
- Endocardial cushion, **262**
- Endocardial fibroelastosis, **291**
- Endocarditis
- antimicrobial prophylaxis for, **181**
- bacteria causing, **113**
- bacterial, **293**
- Candida albicans* as cause, **137**
- dapsone for, **178**
- heart murmur caused by, **273**
- heroin addiction and, **523**
- Staphylococcus aureus* as cause, **119**
- Endocervix, **574**
- Endochondral ossification, **425**
- Endocrinal drug reactions, **252**
- Endocrinal paraneoplastic syndromes, **229**
- Endocrine hormone signaling pathways, **316**
- Endocrine pancreas cell types, **307**
- Endocrine system, **306–336**
- anatomy, **306–307**
- embryology, **306**
- pathology, **317–333**
- pharmacology, **334–336**
- physiology, **308–316**
- Endoderm
- branchial pouches derived from, **568**
- derivatives of, **563**
- endodermal tubules, **606**
- Endometrial artery, **566**
- Endometrial cancer, **594, 643**
- epidemiology of, **590**
- estrogens and, **601**
- lab findings in, **637**
- Lynch syndrome and, **363**
- PCOS and, **591**
- progestins for, **602**
- tamoxifen and, **413**
- tumor suppressor genes and, **230**
- Endometrial hyperplasia, **594**
- follicular cysts as cause, **592**
- progesterone and, **577**
- Endometrial vein, **566**
- Endometriomas, **592**
- Endometriosis, **594**
- danazol for, **602**
- endometriomas and, **592**
- lab findings in, **635**
- ovarian neoplasms and, **592**
- Endometritis, **594**
- pelvic inflammatory disease as cause, **167**
- Endometrium, **574**
- conditions of, **594**
- Endoneurium, **454**
- Endoplasmic reticulum, **58, 59**
- Endosomes, **59**
- Endothelial cells
- in filtration, **535**
- in glomerulus, **532**
- in wound healing, **223**
- Endothelium-derived relaxing factor (EDRF), **316**
- Endothelium, in leukocyte extravasation, **221**
- Endotoxins, **115, 117**
- End-stage renal disease findings, **638**
- End-systolic volume, **266**
- Enflurane, **502**
- seizures caused by, **253**
- Enfuvirtide, **184, 186**
- Enhancers, in gene expression, **54**
- Enoxacin, **178**
- Enoxaparin, **405**
- for deep venous thrombosis, **616**
- Entacapone, **504**
- Entamoeba* spp., **178**
- Entamoeba histolytica*, **139**
- bloody diarrhea caused by, **162**
- Enteritis
- vitamin B₅ deficiency as cause, **78**
- vitamin B₇ deficiency as cause, **79**
- vitamin B₁₂ deficiency caused by, **80**
- Enterobacter* spp.
- lactose fermentation by, **126**
- morphology of, **109**
- as nosocomial infection, **168**
- Enterobacter aerogenes*, **172**
- Enterobius* spp.
- diseases associated with, **145**
- infection routes, **142**
- Enterobius vermicularis*, **143, 643**
- Enterochromaffin-like cells, **319**
- Enterococci, **121**
- penicillinase-sensitive penicillins for, **171**
- treatments for, **639**
- vancomycin for, **173**
- vancomycin-resistant (VRE), **121**
- Enterococcus* spp.
- in Gram-positive algorithm, **118**
- UTIs caused by, **164**
- Enterococcus faecalis*, **121**
- Enterococcus faecium*, **121**
- Enterohemorrhagic *Escherichia coli* (EHEC), **128**
- bloody diarrhea caused by, **162**
- exotoxin produced by, **116**
- Enteroinvasive *Escherichia coli* (EIEC), **128, 162**
- Enterokinase/enteropeptidase, **352**
- Enterotoxigenic *Escherichia coli* (ETEC), **128**
- exotoxin produced by, **116**
- watery diarrhea caused by, **162**
- Enteroviruses, meningitis caused by, **163**
- Enveloped viruses, **146**
- Envelopes, viral, **147**
- env* gene, **158**
- Enzyme kinetics, **236**
- Enzymes
- rate-determining, **84**
- terminology for, **84**
- Eosinopenias, **394**
- Eosinophilia, **379**
- Aspergillus fumigatus* as cause, **137**
- macrolides as cause, **176**
- Eosinophilic esophagitis, **354**
- Eosinophilic inclusions, **636**
- Eosinophils, **378, 379**
- corticosteroid effect on, **394**
- cortisol effect on, **313**
- in esophagus, **354**
- as immune response to helminths, **142**
- Ependymomas, **497**
- neurofibromatosis type 2 as cause, **71**
- Ephedrine, **246**
- as noradrenergic drug, **243**
- Epicanthal folds, in cri-du-chat syndrome, **75**
- Epidemics, **153**
- Epidemic typhus, **132**
- Epidemiology/biostatistics, **32–39**
- Epidermal growth factor (EGF) signaling pathways for, **316**
- in wound healing, **223**
- Epidermis, **437**
- embryologic derivatives of, **563**
- Epidermophyton*, **136**
- Epididymis, **575**
- embryology of, **571**
- Epididymitis, **167**
- Epidural hematomas, **469**
- key associations, **643**
- presentation of, **632**
- Epigastric veins, **344**
- Epiglottitis
- Haemophilus influenzae* as cause, **126**
- lab findings in, **638**
- in unvaccinated children, **169**
- Epilepsy, **494**
- drug therapy for, **500**
- gustatory hallucinations in, **513**
- lung abscesses and, **624**
- splice site mutations as cause, **52**
- Sturge-Weber syndrome as cause, **495**
- Epinephrine, **246**. See also Catecholamines
- adrenal medulla secretion of, **306**
- α -blockade of, **248**
- for anaphylactic reaction, **206**
- diabetes mellitus caused by, **330**
- for glaucoma, **498**
- glycogen regulation and, **97**
- in nervous system, **241**
- pheochromocytoma secretion of, **320**

- in tyrosine catabolism, 95
- vitamin B₆ and, 78
- Epineurium, 454
- Epiphysis, tumors in, 429
- Epiploic foramen of Winslow, 340
- Episcleritis
 - Crohn disease as cause, 359
 - ulcerative colitis as cause, 359
- Epsipadias, 573
- Epistaxis, **616**
 - hereditary hemorrhagic telangiectasia as cause, 71
 - Osler-Weber-Rendu syndrome as cause, 634
- Epithelial cell junctions, **438**
- Epithelial cells, tumor nomenclature, 228
- Epithelial hyperplasia, 595
- Epithelial tumors, 60
- Epithelium, 341
- Eplerenone, 558
- Epoetin alfa, 213
- Epoprostenol
 - for pulmonary arterial hypertension, 640
 - for pulmonary hypertension, 627
- Epstein-Barr virus (EBV), 149
 - aplastic anemia caused by, 391
 - Burkitt lymphoma and, 400
 - hairy leukoplakia and, 442
 - head and neck cancer and, 616
 - HIV and, 160
 - Hodgkin lymphoma and, 399
 - in immunodeficient patients, 210
 - lab findings in, 635, 636
 - as oncogenic microbe, 231
 - receptors for, 150
- Eptifibatid, 407
 - thrombogenesis and, 385
- Erb palsy, 420
 - presentation of, 632
- Erectile dysfunction, 520
 - β -blockers as cause, 249, 303
 - cimetidine as cause, 374
 - Lambert-Eaton myasthenic syndrome as cause, 436
 - PDE-5 inhibitors for, 603
 - Peyronie disease and, 597
 - sildenafil for, 627
 - treatments for, 639
- Erection, innervation of, 575
- Ergosterol synthesis, 181
- Ergosterol synthesis inhibitors, 255
- Ergot alkaloids, 251
- Erlotinib, **412**
- Errors, medical, 46
- Ertapenem, 170, 173
- Erysipelas, 442
 - Streptococcus pyogenes* as cause, 120
- Erythema
 - hernias as cause, 349
 - Kawasaki disease as cause, 296
- Erythema marginatum, 120, 294
- Erythema migrans, 130, 632
- Erythema multiforme, 443
- Erythema nodosum, 444
 - Crohn disease as cause, 359
 - sarcoidosis and, 435
 - ulcerative colitis as cause, 359
- Erythroblastosis fetalis, 382
 - as type II hypersensitivity reactions, 204
- Erythrocytes, **378**
 - blood types of, 382
 - Coombs test, 393
 - DAF deficiency and, 199
 - erythropoietin and, 541
 - glucose usage by, 308
 - in hereditary spherocytosis, 392
 - macrophages and, 379
 - in multiple myeloma, 401
 - in myeloproliferative disorders, 404
 - pathologic forms of, **386–387**
 - spheroid, in spherocytosis, 71
 - stacked, 638
 - in urine, 544, 637
- Erythrocyte sedimentation rate (ESR), **224**
 - in osteomyelitis, 163
 - in subacute granulomatous thyroiditis, 322
- Erythrocytosis, 378
 - oxygen-hemoglobin dissociation curve and, 612
- Erythroderma, 631
- Erythrotoxic toxin (Group A strep), 114
- Erythromelalgia
 - essential thrombocythemia as cause, 404
 - polycythemia vera as cause, 404
- Erythromycin, 170, 176
 - diarrhea caused by, 252
 - as prophylaxis, 181
 - as protein synthesis inhibitor, 174
 - reactions to, 252
- Erythroplasia of Queyrat, 597
- Erythropoiesis, 621
- Erythropoietin
 - for anemia of chronic disease, 391
 - in aplastic anemia, 391
 - hemangioblastoma production of, 496
 - high altitude and, 615
 - kidney functions, 541
 - in polycythemia vera, 404
 - signaling pathways for, 316
- Escherichia coli*, **128**
 - as catalase-positive organism, 112
 - cephalosporins for, 172
 - chronic granulomatous disease and, 209, 643
 - culture requirements for, 111
 - on EMB agar, 126
 - as encapsulated bacteria, 112
 - galactosemia as cause, 91
 - in Gram-negative algorithm, 125
 - in immunodeficient patients, 210
 - lactose fermentation by, 126
 - meningitis caused by, 163
 - morphology of, 109
 - in neonates, 165
 - as nosocomial infection, 168
 - penicillinase-sensitive penicillins for, 171
 - pneumonia caused by, 162
 - prostatitis caused by, 599
 - splenic dysfunction and, 191
 - type III secretion system of, 113
 - urinary tract infections caused by, 552, 646
 - UTIs caused by, 164
- Escherichia coli* O157:H7, 161
- E-selectin, in leukocyte extravasation, 221
- Esmolol, 249, 303
- Esomeprazole, 374
- Esophageal atresia, 338
- Esophageal cancer, **355**
 - achalasia and, 354
 - key associations, 643
- Esophageal dysmotility in CREST syndrome, 437
- Esophageal squamous cell carcinomas, 354
- Esophageal strictures, 354
- Esophageal varices, 344, 354
- Esophageal veins, 344
- Esophageal webs, 354, 388
- Esophagitis, 354
 - bisphosphonates as cause, 447
 - as drug reaction, 252
 - HIV and, 160
- Esophagus
 - anastomosis at, 344
 - blood supply and innervation of, 342
 - in diaphragm, 609
 - histology of, 341
 - pathologies of, **354**
- Essential amino acids, 92
- Essential fructosuria, 91
- Essential hypertension, 298
- Essential thrombocythemia, 404
- Essential tremor, 461
- Esters, as local anesthetics, 503
- Estradiol, 600
- Estril
 - in Down syndrome, 74
 - in Edwards syndrome, 74
 - pharmacologic control of, 600
- Estrogen, **577, 601**
 - in androgen insensitivity syndrome, 586
 - in bone formation, 425
 - breast cancer and, 596
 - endometrial cancer caused by, 594
 - in fibroadenomas, 595
 - in genital development, 572
 - Granulosa cell tumors and, 593
 - in Klinefelter syndrome, 585
 - lactation and, 581
 - in menopause, 582
 - in menstrual cycle, 579
 - osteoporosis and, 426
 - in ovulation, 578
 - in pregnancy, 580
 - in premature ovarian failure, 591
 - prolactin, effect on, 310
 - signaling pathways for, 316
 - thecoma production of, 592
 - in Turner syndrome, 585
- Estrone, 600
- Eszopiclone, 501
- Etanercept, 448
 - lupus-like syndrome caused by, 253
- Ethacrynic acid, **557**
- Ethambutol, **180**
 - for *Mycobacterium tuberculosis*, 179, 640
- Ethanol
 - as carcinogen, 231
 - metabolism of, **83**
 - zero-order elimination of, 238
- Ethics, 39–42
 - confidentiality, 41
 - consent, 40
 - core principles of, **39**
 - directives, 41
 - situations in, **42**
- Ethinyl estradiol, 601
 - for contraception, 602
- Ethosuximide, 500
 - for absence seizures, 638
- Ethylenediaminetetraacetic (EDTA), 389
- Ethylene glycol
 - metabolic acidosis caused by, 543
 - toxicity treatment for, 251, 639
- Etonogestrel, 602
- Etoposide, **411**
 - in cell cycle, 408
 - targets of, 408
 - as topoisomerase inhibitors, 51
- Euchromatin, **48**
- Eukaryotes
 - DNA replication in, 51
 - functional gene organization in, **54**
 - ribosomes in, 57
 - RNA polymerases in, 54
 - RNA processing, **54**
- Eustachian tubes, 570
- Ewing sarcoma, 429, 637
 - dactinomycin for, 410
 - lab findings in, 637
- Exanthem subitum, 149
- Excitatory pathway, 460
- Executioner caspases, 216
- Exemestane, 601
- Exenatide, 335
- Exercise
 - pulse pressure in, 266
 - respiratory response to, 615
- Exocrine glands, 242
- Exons, vs. introns, **55**
- Exophytic mass in colorectal cancer, 364
- Exotoxin A, 116, 117
 - Pseudomonas aeruginosa* and, 127
- Exotoxins, **115**
 - organisms with, 116–117
- Expectorants, **627**
- Expiratory reserve volume (ERV), 610
- External hemorrhoids, 345

- External iliac arteries, 342
 External inguinal ring, 349
 External spermatic fascia, 348
 Extinction, in conditioning, 508
 Extracellular fluid (ECF), 533
 Extragonadal germ cell tumors, **598**
 Extraperitoneal tissue, 348
 Extravascular hemolysis, 391
 Extrinsic hemolytic anemia, **393**
 Extrinsic pathway, **216**
 for coagulation, 383
 warfarin and, 406
 Exudate, vs. transudate, **224**
 Exudative pleural effusion, 623
 Ex vacuo ventriculomegaly, 471
 Eyes
 anatomy of, **482**
 aqueous humor pathway, 483
 bilateral movement of, 490
 motility of, 488
 Ezetimibe, 300
 diarrhea caused by, 252
- F**
- Fab region of antibodies, 196
 Fabry disease, 100
 as X-linked recessive disorder, 72
 Facial dysmorphism as teratogenic effect, 564
 Facial nerve (7th cranial nerve), **479**
 as branchial arch derivative, 569
 lesions in, **480**
 location in brain stem, 477
 pathway for, 478
 in tongue, 452
 Facial nerve palsy, 480
 Borrelia burgdorferi as cause, 169
 Lyme disease as cause, 130
 Factitious disorder, **518**
 vs. malingering, 518
 Factor IX concentrate, 396
 Factor VIII concentrate, 396
 Factor V Leiden mutation, 384
 Factor Xa
 direct inhibitors of, 407
 heparin effect on, 405
 Factor Xa inhibitors, 383
 Factor XI concentrate, 396
 Facultative intracellular organisms, 112
 FADH (flavin adenine dinucleotide), 88
 Failing the USMLE Step 1 exam, 21–22
 Failure mode analysis for medical errors, 46
 Failure to thrive
 as child neglect sign, 510
 deprivation as cause, 510
 galactosemia as cause, 91
 orotic aciduria as cause, 390
 SCID as cause, 209
 Falciform ligament, 340
 Fallopiian tubes
 anatomy of, 574
 epithelial histology of, 574
 fertilization in, 580
- False-negative rate, 33
 False-positive rate, 33
 Falx cerebri, **498**
 Famiciclovir, **184**
 Familial adenomatous polyposis, 363
 APC gene and, 364
 autosomal dominance of, 71
 chromosome associated with, 75
 lab findings in, 638
 Familial dyslipidemias, **105**
 Familial hypercholesterolemia, 105
 autosomal dominance of, 71
 presentation of, 630
 Familial hypocalciuric hypercalcemia, 325
 Family therapy for separation anxiety disorder, 511
 Famotidine, 374
 Fanconi anemia, 391
 nonhomologous end joining and, 53
 presentation of, 633
 Fanconi syndrome, **538**
 as drug reaction, 253
 presentation of, 633
 renal tubular acidosis as cause, 544
 Wilson disease as cause, 371
 Fascia, collagen in, 61
 Fasciculations, as motor neuron sign, 473
 Fasciculations, LMN damage as cause, 632
 Fastigial nucleus, 459
 Fasting plasma glucose test, 330
 Fasting state, 87, 103
 Fast twitch muscle fibers, 424
 Fat emboli, 617
 Fatigue
 adrenal insufficiency as cause, 318
 adrenocortical insufficiency as cause, 633
 heart failure as cause, 292
 hypothyroidism as cause, 321
 Fat necrosis, 217, 595
 calcification and, 220
 Fat redistribution, as drug reaction, 253
 Fat-soluble vitamins, **76**
 Fatty acids
 in gluconeogenesis, 89
 metabolism of, **101**
 oxidation of, 83, 84
 Fatty acid synthase, 78
 Fatty acid synthesis
 location of in cell, 83
 rate-determining enzyme for, 84
 Fatty casts, 544
 in nephrotic syndrome, 548
 Fatty liver disease
 hepatocellular carcinoma and, 368
 lab findings in, 638
 Fatty liver, in Reye syndrome, 366
 Fava beans, as cause of G6PD deficiency, 392
FBNI gene, 71
 Fc region of antibodies, 196
- Febrile nonhemolytic transfusion reaction, 206
 Febrile pharyngitis, 148
 Febuxostat
 for gout, 431, 448, 639
 for Lesch-Nyhan syndrome, 50
 Fecal elastase, 358
 Fecalith obstruction, in appendicitis, 360
 Fecal microbiota transplant, 122
 Fecal retention, 512
 Feces, and bilirubin, 353
 Federation of State Medical Boards (FSMB), 2
 Fed state, 87, 103
 Felty syndrome, 430
 Female genital embryology, 571
 Female reproductive anatomy, **574**
 Female reproductive epithelial histology, **574**
 Femoral artery, 347
 Femoral hernias, 349
 Femoral nerve, 347, 422
 Femoral region, **347**
 Femoral ring, 347
 Femoral sheath, 347
 Femoral triangle, 347
 Femoral vein, 347
 Fenofibrate, 300
 Fenoldopam, 246, 298
 for hypertensive emergency, 298
 Fentanyl, 499
 Ferritin
 as acute-phase reactant, 198
 in anemia, 394
 in anemia of chronic disease, 391
 in iron deficiency anemia, 388
 lab values in anemia, 394
 in sideroblastic anemia, 389
 Ferrochelatase, 395
 Ferruginous bodies, 636
 Fertility
 GnRH and, 309
 Fertilization, 578, 580
 Fetal. *See also* Pregnancy
 Fetal alcohol syndrome, 284, 564, **565**
 holoprosencephaly and, 451
 Fetal circulation, **264**
 Fetal death, from parvovirus, 148
 Fetal development, early, **562**
 Fetal distress
 placental abruption as cause, 588
 vasa previa as cause, 589
 Fetal erythropoiesis, **381**
 Fetal hemoglobin, 611
 Fetal hemorrhage, 564
 Fetal hypothyroidism, 322
 Fetal lung maturity, 607
 Fetal-postnatal derivatives, **264**
 Fetal respiration, 606
 Fetal tissue, collagen in, 61
 Fetus hepaticus, 365
 Fever
 bacterial endocarditis as cause, 293
 Kawasaki disease as cause, 296
 thyroid storm as cause, 323
 tuberculosis as cause, 124
- Fexofenadine, 627
 FGF. *See* Fibroblast growth factor (FGF)
FGF gene, 562
 Fibrates, 300
 hepatitis caused by, 252
 for hypertriglyceridemia, 640
 myopathy caused by, 253
 Fibrinogen
 as acute-phase reactant, 198
 in cryoprecipitate, 399
 ESR and, 224
 in platelet plug formation, 385
 receptor for, 378
 in thrombocytes, 378
 in thrombogenesis, 385
 Fibrinoid necrosis, 217
 Fibrinolysis, in coagulation cascade, 384
 Fibrinolytic system, 383
 Fibrinous pericarditis, 288
 Fibroadenomas, 595, 642
 location of, 595
 Fibroblast growth factor (FGF)
 signaling pathways for, 316
 in wound healing, 223
 Fibroblast growth factor receptor (FGFR3), 426
 Fibroblasts
 cortisol and, 313
 in wound healing, 223
 Fibrocystic changes of breast, 595, 637
 Fibroid tumors, 594
 leuprolide for, 601
 Fibromas, 592
 nomenclature for, 228
 Fibromuscular dysplasia, 284
 Fibromyalgia, **435**
 Fibronectin
 in cryoprecipitate, 399
 in thrombocytes, 378
 Fibrosarcomas, 228
 Fibrosis
 diffusion-limited gas exchange in, 613
 silicosis as cause, 620
 Fibrous plaque in atherosclerosis, 286
 Fick principle, 266
 Fidaxomicin, 122
 Fiduciary duty to patients, 39
 Fifth disease
 B19 virus as cause, 148
 presentation of, 630
 rash caused by, 166
 50S inhibitors, 174
 Filgrastim, 213
 Filoviruses
 characteristics of, 151
 Ebola as, 156
 as negative-stranded, 152
 Filtration, **535**
 Filtration fraction, 647
 glomerular dynamics, effect on, 535
 Fimbria, 108
 anatomy of, 574

- Financial considerations in treatment, 42
- Finasteride, 603
reproductive hormones and, 600
- Fingernails, glomus tumors under, 441
- First-order elimination, 238
- Fishbone diagram, 46
- Fishy smell, in *Gardnerella vaginalis*, 132
- Fitz-Hugh-Curtis syndrome, 167
gonococci as cause, 126
- 5-aminosalicylic drugs, 359, 375
- 5 α -reductase
testosterone and, 582
- 5 α -reductase deficiency, 571, 586
- 5 α -reductase inhibitors
for benign prostatic hyperplasia, 638
for BPH, 599
- 5-fluorouracil, 409
in cell cycle, 408
photosensitivity caused by, 253
pyrimidine synthesis and, 49
targets of, 408
toxicities of, 413
- 5-HT
in anxiety, 511
in depression, 511
MAO inhibitor effect on, 528
mechanism of, 526
opioid effect on, 499
serotonin syndrome and, 527
tramadol effect on, 499
trazodone effect on, 528
tricyclic antidepressant effect on, 527
- 5-HT_{1B/1D} agonists
naming convention for, 255
- 5-HT agonists, 505
- 5-hydroxyindoleacetic acid (5-HIAA), 319
in carcinoid syndrome, 332
- Fixation, as ego defense, 508
- Fixed splitting, 271
- Flaccid paralysis, 473
botulinum toxin as cause, 116
LMN lesion as cause, 475
- Flagellin, 192
- Flagellum
as bacterial structure, 108
in cell walls, 108
- Flash cards for USMLE Step 1 exam, 13
- Flat affect, 458
- Flat facies in Down syndrome, 74
- Flavin nucleotides, 86
- Flaviviruses
characteristics of, 151
genomes of, 147
- Fleas, as disease vectors, 132, 133
- Flecainide, 302
- Flexor digiti minimi muscle, 421
- Flexor pollicis brevis muscle, 421
- Flies, as disease vectors, 143
- Floppy baby syndrome
botulinum toxin as cause, 116
- Clostridium botulinum* as cause, 122
spinal cord lesions causing, 474
- Flow cytometry, 66
- Flow volume loops, 619
- Fluconazole, 181, 182
for *Candida albicans*, 137, 639
for *Cryptococcus neoformans*, 639
for systemic mycoses, 135
- Flucytosine, 182
- Fludrocortisone, 336. *See* also Glucocorticoids
- Fluid compartments, 533
- Flumazenil
for benzodiazepine overdose, 251, 501, 522
diazepam and, 240
nonbenzodiazepine hypnotics and, 501
- Fluorescence in situ hybridization, 67
- Fluorescent antibody stain, 110
- Fluoroquinolones, 170, 178
for *Mycoplasma pneumoniae*, 134
in pregnancy, avoiding, 187
for *Pseudomonas aeruginosa*, 127
tendonitis/cartilage damage caused by, 253
as topoisomerase inhibitors, 51
for typhoid fever, 129
- Fluoxetine, 527
- Fluphenazine, 525
for Tourette syndrome, 511, 524
- Flutamide, 603
for prostate cancer, 640
reproductive hormones and, 600
- Fluticasone, 628
- FMRI gene, 73
- Foam cells
in atherosclerosis, 286
Niemann-Pick disease as cause, 100
- Focal glomerular disorders, 544
- Focal hepatic necrosis, 252
- Focal necrotizing vasculitis, 296
- Focal neurological signs
hyperosmolar hyperglycemia nonketotic syndrome as cause, 332
meningiomas as cause, 496
vertigo and, 495
- Focal segmental
glomerulosclerosis, 548
nephrotic syndrome and, 644
- Focal seizures, 494
- Folate antagonists, 564
- Folate synthesis
sulfonamides and, 177
trimethoprim and, 177
- Folic acid
anencephaly and, 451
for neural tube defect prevention, 640
neural tube defects and, 451
in pregnancy, 79
synthesis and reduction of, 170
- Follicles, lymph, 190
- Follicle-stimulating hormone (FSH)
clomiphene effect on, 601
in cryptorchidism, 597
in Kallmann syndrome, 586
in Klinefelter syndrome, 585
in menopause, 582
ovulation/spermatogenesis and, 310
in PCOS, 591
pharmacologic control of, 600
in premature ovarian failure, 591
progesterone and, 577
secretion of, 307
signaling pathways of, 316
in spermatogenesis, 576
in Turner syndrome, 585
- Follicular conjunctivitis, 134
- Follicular cysts, 592
- Follicular lumen, 315
- Follicular lymphomas, 216, 400, 645
chromosomal translocations and, 403
- Follicular phase of menstrual cycle, 579
- Follicular thyroid carcinomas, 324
- Fomepizole
ethanol metabolism and, 83
for ethylene glycol/methanol intoxication, 639
as toxicity treatment, 251
- Fondaparinux, 383
- Food allergies, and eczema, 440
- Food poisoning
Bacillus cereus as cause, 122
bacteria causing, 114
key associations, 643
organisms causing, 161
Staphylococcus aureus as cause, 119
toxic shock syndrome toxin as cause, 117
- Food toxins, 250
- Foot drop, from lead poisoning, 389
- Foramen cecum, 306
- Foramen magnum, 478
- Foramen of Magendie, 471
- Foramen of Monro, 471
- Foramen ovale, 262, 478
in fetal circulation, 264
postnatal derivative of, 264
- Foramen primum, 262
- Foramen rotundum, 478
- Foramen secundum, 262
- Foramen spinosum, 478
- Foramina of Luschka, 471
- Forebrain, 450
anomalies of, 451
- Foregut
blood supply/innervation of, 342
development of, 338
- Formoterol, 628
- Fornix, 458, 574
- 46,XX/46,XY DSD, 586
- Fosamprenavir, 184
for HIV, 186
- Foscarnet, 185
for CMV, 639
- Fosphenytoin, 500
- Fossa ovalis, 264
- Fovea, 482
cherry-red spot at, 486
- FOXP3 protein, 194
- Fragile X syndrome, 73
chromosome associated with, 75
intellectual disability caused by, 643
as trinucleotide repeat expansion disease, 73
X-linked dominant inheritance of, 70
- Frameshift mutations, 52
muscular dystrophy and, 73
- Francisella* spp.
as intracellular organism, 112
morphology of, 109
- Francisella tularensis*
animal transmission of, 132
in Gram-negative algorithm, 125
- Frataxin, 475
- Free fatty acids
in diabetic ketoacidosis, 331
in fast/starvation states, 103
lipid transport and, 104
- Free nerve endings, 454
- Free radical injury, 219, 221
- Fresh frozen plasma, 399
for warfarin toxicity, 251, 641
- “Fried egg” cells in ovarian tumors, 593
- Friedreich ataxia, 475
chromosome associated with, 75
hypertrophic cardiomyopathy and, 291
as trinucleotide repeat expansion disease, 73
- Frontal eye fields, 462
lesions in, 464
- Frontal lobe
lesions in, 464
stroke effects, 467
- Frontotemporal dementia, 491
ex vacuo ventriculomegaly caused by, 471
- Fructokinase
essential fructosuria and, 91
in fructose metabolism, 91
in metabolic pathways, 85
- Fructose-1,6-bisphosphatase, 84
in gluconeogenesis, 89
in metabolic pathways, 85
- Fructose-2,6-bisphosphate, 87
- Fructose intolerance, 91
- Fructose metabolism
diagram of, 85
disorders of, 91
- Fructosuria, 91
- FSH. *See* Follicle-stimulating hormone (FSH);
See Follicle-stimulating hormone (FSH)
- FTA-ABS test for syphilis, 131
- Fumarate, in urea cycle, 93
- Functional residual capacity (FRC), 610
chest wall and, 611
in flow volume loops, 619
- Fundus, 574

- Fungal infections
 IL-12 receptor deficiency as cause, 208
 thymic aplasia as cause, 208
- Fungi
 culture requirements for, 111
 immunocompromised patients and, 162
 necrosis and, 217
 opportunistic infections, 137
 silver stain for, 110
 topical infections, treatment of, 182
- Funny current, 275
- Furosemide, 254, **557**
 gout caused by, 253
 interstitial nephritis caused by, 253
 pancreatitis caused by, 252
- Fusion inhibitors, 186
- Fusobacterium* spp.
 alcoholism and, 162
 as anaerobic organism, 111
 lung abscesses caused by, 624
- G**
- G6PD
 HMP shunt and, 84
 in respiratory burst, 201
- G6PD deficiency, **90**, 392
 in anemia taxonomy, 388
 degmacytes in, 386
 Heinz bodies in, 387
 as X-linked recessive disorder, 72
- GABA, 455
 in anxiety, 511
 barbiturate effect on, 501
 basal ganglia and, 460
 benzodiazepine effect on, 501
 as derivative, 94
 epilepsy drug effect on, 500
 in Huntington disease, 462, 511
 in Huntington disease, 71
 vitamin B₆ and, 78
- GABA channels, 183
- Gabapentin, 500
- GABA_B receptor agonists, 492
- gag* gene, 158
- Gag reflex, 479
- Gait problems
 muscular dystrophy as cause, 73
 Parkinson disease as cause, 461, 633
- Galactocerebrosidase, 100
 in Krabbe disease, 493
- Galactocerebroside, 100
- Galactokinase, 85
- Galactokinase deficiency, 91
 cataracts and, 483
- Galactorrhea
 antipsychotic drugs as cause, 309, 525
 pituitary prolactinomas as cause, 309
 tuberoinfundibular pathway and, 458
- Galactose-1-phosphate, 85
- Galactose-1-phosphate uridylyltransferase, 91
- Galactose metabolism
 diagram of, 85
 disorders of, **91**
- Galactosemia, 91
 cataracts and, 483
- Galantamine, 244
 for Alzheimer disease, 505
- Galant reflex, 476
- Gallbladder, 347
 blood supply and innervation of, 342
 cholecystokinin effect on, 350
- Gallbladder cancer
 porcelain gallbladder and, 372
 sclerosing cholangitis and, 371
- Gallstone ileus, 372
- Gallstones. *See* Cholelithiasis
- γ -glutamyltransferase (GGT)
 in alcohol use, 522
- γ -glutamyl transpeptidase (GGT), 366
- γ -interferon, 379
- Ganciclovir, **185**
 agranulocytosis caused by, 252
 for CMV, 639
- Ganglioneuromatosis, 634
- Gangrene
 Buerger disease as cause, 296
 diabetes mellitus as cause, 330
- Gangrenous necrosis, 217
- Gap junctions, 438
- Gardener's pupil, 245
- Gardnerella* spp., 109
- Gardnerella vaginalis*, **132**
 lab findings in, 638
 metronidazole for, 178
- Gardner syndrome, 363
 presentation of, 632
- Gargoylism, 100
- Garlic breath, in arsenic toxicity, 87
- Gas gangrene
 alpha toxin as cause, 117
 bacteria causing, 114
Clostridium perfringens as cause, 122, 162
- Gastrorectomy, 390
- Gastric acid, 351
 histamine receptors and, 242
 somatostatin and, 350
- Gastric adenocarcinomas
 acanthosis nigricans and, 444
Helicobacter pylori as cause, 130
- Gastric arteries, 343
 ligaments containing, 340
- Gastric bypass surgery
 ghrelin and, 350
 vitamin B₁₂ deficiency caused by, 80
- Gastric cancer, **356**
 brain metastases in, 644
 carcinogens causing, 231
 chronic atrophic gastritis and, 642
 chronic gastritis and, 356
 key associations, 642, 645
 lab findings in, 637
 liver metastases in, 644
 metastases of, 233
 oncogenes and, 230
 oncogenic microbes and, 231
 sign of Leser-Trélat and, 229
 trastuzumab for, 413
- Gastric obstruction, 357
- Gastric sclerosis, 437
- Gastric ulcers, 357
 key associations, 641
 NSAID toxicity as cause, 447
- Gastric vessels, 340
- Gastrin, 350
 location of, 351
 signaling pathways for, 316
 somatostatinomas and, 332
- Gastrinomas, 336
- Gastritis, **356**
 gastrin in, 350
 H₂ blockers for, 374
Helicobacter pylori as cause, 130
 key associations, 642
 proton pump inhibitors for, 374
 stomach cancer and, 356
- Gastrocolic ligament, 340
- Gastroduodenal artery, 343
- Gastroenteritis
Listeria monocytogenes as cause, 123
 rotavirus as cause, 152
- Gastroepiploic arteries, 343
 ligament containing, 340
- Gastroesophageal reflux disease (GERD), 354
 esophageal cancer and, 355
- Gastrohepatic ligament, 340
- Gastrointestinal bleeding
 hereditary hemorrhagic telangiectasia as cause, 71
 iron poisoning as cause, 396
 Osler-Weber-Rendu syndrome as cause, 634
- Gastrointestinal drug reactions, **252**
- Gastrointestinal ligaments, **340**
- Gastrointestinal stromal tumors (GISTs), 230
- Gastrointestinal system, 338–377
 anatomy, 339–348
 blood supply to, **342**
 embryology, **338**, 338–339
 innervation of, **342**
 pathology, 353–374
 pharmacology, 374–376
 physiology, 350–354
 regulatory substances, **350**
 secretory products, **351**
- Gastroschisis, 338
- Gastrosplenic ligament, 340
- Gaucher disease, 100, 644
 osteonecrosis caused by, 427
 presentation of, 631
- Gaussian distribution, 37
- G-CSF. *See* Granulocyte-colony stimulating factor (G-CSF)
- Gemfibrozil, 300
- Gemifloxacin, 178
- Gender dysphoria, **520**
- Gender identity, 43
- Gene expression modifications, **68**
- Gene expression regulation, **54**
- Gene inheritance modes, 70
- General anesthetic, 255
- Generalized anxiety disorder (GAD), 516, **517**
 buspirone for, 526
 drug therapy for, 524
 Selective serotonin reuptake inhibitors (SSRIs) for, 527
 serotonin-norepinephrine reuptake inhibitors (SNRIs) for, 527
 treatments for, 639
- Generalized seizures, 494
- Genetics, 68–77
 22q11 deletion syndromes, 76
 autosomal dominant diseases, 71
 autosomal recessive diseases, 72
 autosomal trisomies, 74
 bacterial, 114
 chromosomes, and disorders, 75
 code features, **50**
 genetic terms, 68–69
 modes of inheritance, 70
 muscular dystrophies, 73
 trinucleotide repeat expansion diseases, 73
 X-linked recessive disorders, 72
- Genetic shift/drift in influenza viruses, 153
- Genital herpes, 167
- Genitalia
 ambiguous, 571, 585, 586
 embryology of, **571**
 estrogen and, 577
 male/female homologs, **572**
- Genital lesions, 632, 634
- Genital tubercles, 572
- Genital ulcers, 167
- Genital warts, 167
- Genitourinary cancer, 644
- Genitourinary drug reactions, **253**
- Genotyping microarrays, 66
- Gentamicin, 170, 174
 for endometritis, 594
- Geriatric patients
 Alzheimer disease in, 491
 amyloidosis in, 225
 angiosarcomas in, 441
 atropine in, 245
 changes in, **44**
 cherry hemangiomas in, 441
 colonic ischemia and, 362
 drug metabolism in, 238
 lipofuscin in, 225
 Medicare for, 44
 nosocomial infections in, 168
 osteoporosis in, 426
 volvulus in, 362
 Zenker diverticulum in, 361
- Germinal center, in spleen, 191
- Germinal centers of lymph nodes, 190
- Gerstmann syndrome, 464
- Gestational diabetes mellitus, 334
 cardiac defects associated with, 284
- Gestational hypertension, 590
- GFAP (glial fibrillary acid proteins)
 as astrocyte marker, 453
 as cytoskeletal element, 60

- in pilocytic astrocytomas, 497
- as stain, 60
- GH. *See* Growth hormone (GH)
- Ghon complex, 636
 - in tuberculosis, 124
- Ghon focus, 124
- Ghrelin, 311, 350
 - hunger and, 456
- GHRH. *See* Growth-hormone-releasing hormone (GHRH)
- Giant cell arteritis, **296**
- Giant cell pneumonia, 154
- Giant cells
 - in chronic inflammation, 219
- Giant cell tumors, 429
- Giant cell tumors of bone, 638
- Giardia* spp.
 - metronidazole for, 178
 - watery diarrhea caused by, 162
- Giardia lamblia*, **139**
- Giardiasis, 139
- Giemsa stain, 110
 - for *Borrelia*, 130
 - chlamydiae on, 134
- Gigantism, 311, 327
- Gilbert syndrome, 369, 370, 643
- Gingiva, blue line on, 630
- Gingival hyperplasia
 - calcium channel blockers as cause, 298
 - cyclosporine as cause, 212
 - as drug reaction, 253
 - epilepsy drugs causing, 500
- Gingivostomatitis, 149
- Gitelman syndrome, **538**
 - markers in, 542
- Glans penis, 575
 - cancer of, 597
 - lymphatic drainage of, 573
- Glanzmann thrombasthenia, 385
 - presentation of, 632
- Largine insulin, 334. *See also* Insulin
- Glaucoma, **484**
 - acetazolamide for, 557
 - atropine as cause, 245
 - β -blockers for, 249
 - carbachol for, 244
 - diabetes mellitus as cause, 330
 - diagnosing, 244
 - drug therapy for, **498**
 - epinephrine for, 246
 - pilocarpine for, 244
 - Sturge-Weber syndrome as cause, 495
- Glimepiride, 334
- Glioblastoma multiforme, 496, 642
 - lab findings in, 637
 - nitrosoureas for, 410
- Glioblastomas, 60
- Glipizide, 334
- Glitazones, 334
- Global aphasia, 463
- Globoid cells
 - Krabbe disease as cause, 100, 493
- Globose nucleus, 459
- Globus pallidus externus, 460
- Glomerular diseases, **545**
 - nomenclature of, **544**
- Glomerular filtration barrier, **533**
- Glomerular filtration rate, **534, 647**
 - ACE inhibitor effect on, 559
 - ANP effect on, 541
 - glomerular dynamics, effect on, 535
 - juxtaglomerular apparatus and, 540
 - in prerenal azotemia, 553
- Glomerulonephritis
 - Alport syndrome as cause, 547
 - azathioprine for, 212
 - bacterial endocarditis as cause, 293
 - intrinsic renal failure caused by, 553
 - key associations, 643
 - lab findings in, 635, 637, 638
 - pharyngitis and, 120
 - RBC casts in, 544
 - Streptococcus pyogenes* as cause, 120
 - Wegener granulomatosis as cause, 296
- Glomerulus
 - anatomy of, 532
 - changes in dynamics, **535**
 - nodular hyaline deposits in, 637
- Glomus tumors, 441
- Glossitis
 - B-complex deficiency as cause, 76
 - megaloblastic anemia as cause, 390
 - Plummer-Vinson syndrome as cause, 354, 631
 - vitamin B₃ deficiency as cause, 78
 - vitamin B₉ deficiency as cause, 79
- Glossopharyngeal nerve (9th cranial nerve), **479**
 - as branchial arch derivative, 569
 - location in brain stem, 477
 - pathway for, 478
 - receptor transmission by, 279
 - in tongue, 452
- Glossoptosis, 569
- GLP-1 analogs, 335
- Glucagon, **309**
 - for β -blocker toxicity, 251, 303
 - catabolic effects of, 309
 - DPP-4 inhibitor effect on, 335
 - fructose biphosphatase-2 and, 87
 - GLP-1 analog effect on, 335
 - glucagonomas and, 332
 - glycogen regulation and, **97**
 - insulin and, 308, 309
 - production of, 307
 - signaling pathways of, 316
 - somatostatin and, 350
 - somatostatinomas and, 332
- Glucagon-like peptide 1, 308
- Glucagonomas, **332**
 - MEN 1 syndrome as cause, 333
 - somatostatin for, 336
- Glucocerebrosidase
 - in Gaucher disease, 100
- Glucocerebroside, 100
- Glucocorticoids, **336**
 - for acute gout attack, 638
- in adrenal insufficiency, 318
- adrenal steroids and, 312
- arachidonic acid pathway and, 446
- for calcium pyrophosphate deposition disease, 431
- diabetes mellitus caused by, 330
- fat redistribution caused by, 253
- for gout, 431, 448
- myopathy caused by, 253
- for rheumatoid arthritis, 430
- Glucokinase
 - vs. hexokinase, **86**
 - in metabolic pathways, 85
- Gluconeogenesis, **89**
 - cortisol and, 313
 - diagram of, 85
 - ethanol metabolism and, 83
 - glucagon and, 309
 - in insulin deficiency, 330
 - location of in cell, 83
 - metformin effect on, 334
 - pyruvate metabolism and, 88
 - rate-determining enzyme for, 84
 - thyroid hormones and, 315
- Glucose
 - ATP production and, 86
 - blood-brain barrier and, 455
 - clearance of, **536**
 - for diabetic ketoacidosis, 331
 - GH secretion and, 311
 - in glycogen metabolism, 98
 - insulin and, 308
 - metabolism of, 52
 - Neisseria* fermentation of, 126
 - for porphyria, 395
 - transporters, 308
- Glucose-6-phosphatase
 - in gluconeogenesis, 89
 - in HMP shunt, 90
 - in Von Gierke disease, 99
- Glucose-dependent insulinotropic peptide (GIP), 350
- Glucosuria
 - glucose clearance and, 536
 - in pregnancy, 536
 - SGLT-2 inhibitors as cause, 335
- Glulisine insulin, 334. *See also* Insulin
- Glutamate
 - in Alzheimer disease, 511
 - ammonia transport by, 93
 - derivatives of, 94
 - opioid effect on, 499
- Glutamic acid, 92
- Glutamic acid decarboxylase (GAD-65), 207
- Glutamine, 49
- Glutathione
 - acetaminophen and, 446
 - as derivative, 94
 - in G6PD deficiency, 392
 - Glutathione peroxidase, 201
 - free radical elimination by, 221
 - Glutathione reductase, 201
 - NADPH and, 86
- Gluteus maximus muscle, 422
- Gluteus medius muscle, 422
- Gluteus minimus muscle, 422
- GLUT transporters, 308
- Glyburide, 334
- Glyceraldehyde, 91
- Glycerol, 91
- Glycine
 - derivatives of, 94
 - in nucleotide synthesis, 49
- Glycocalyx, 108
- Glycogen, **98**
 - in cell injury, 218
 - insulin and, 308
 - periodic acid-Schiff stain for, 110
 - regulation of, **97**
- Glycogenesis
 - diagram of, 85
 - rate-determining enzyme for, 84
- Glycogenolysis
 - diagram of, 85
 - glucagon and, 309
 - in insulin deficiency, 330
 - rate-determining enzyme for, 84
 - thyroid hormones and, 315
- Glycogen phosphorylase, 84
 - in glycogen metabolism, 98
- Glycogen phosphorylase kinase, 97
- Glycogen storage diseases, **99, 538**
- Glycogen synthase, 84
 - in glycogen metabolism, 98
 - in glycogen regulation, 97
- Glycolysis
 - arsenic and, 86
 - diagram of, 85
 - hexokinase/glucokinase in, 86
 - location of in cell, 83
 - metformin effect on, 334
 - pyruvate metabolism and, 88
 - rate-determining enzyme for, 84
 - regulation of, **87**
 - type 2 muscle fibers and, 424
- Glycopeptides, 170
- Glycoprotein IIb/IIIa inhibitors, **407**
- Glycoproteins, in HIV, 158
- Glycopyrrolate, 245
- Glycosylation, 57
- Glycyrrhetic acid, 538
- GNAQ gene, 495
- GnRH. *See* Gonadotropin-releasing hormone (GnRH)
- Goblet cells, 341
 - in respiratory tree, 608
- Goiter, **321**
 - congenital hypothyroidism caused by, 322
 - lack of maternal iodine as cause, 564
 - in Riedel thyroiditis, 322
- Gold toxicity, 251
- Golfer's elbow, 417
- Golgi apparatus, 59
 - in plasma cells, 381
- Gonadal drainage, **573**
- Gonadal mosaicism, 69
- Gonadotroph hyperplasia, 496
- Gonadotropin, 592

- Gonadotropin-releasing hormone (GnRH), 309
 estrogen and, 577
 for infertility, 640
 in Kallmann syndrome, 586
 in menopause, 582
 in menstrual cycle, 579
 in ovulation, 578
 prolactin and, 310
 for prostate cancer, 640
 signaling pathways for, 316
 in spermatogenesis, 576
- Gonadotropin-releasing hormone (GnRH) agonists
 for adenomyosis, 594
 for endometriosis, 594
 reproductive hormones and, 600
- Gonadotropin-releasing hormone (GnRH) antagonists, 600
- Gonococcal arthritis, 432
- Gonococci, vs. meningococci, 126
- Gonorrhea
 antimicrobial prophylaxis for, 181
 ceftriaxone for, 172
 gonococci as cause, 126
 as STI, 167
- Goodpasture syndrome, 546
 autoantibody associated with, 207
 collagen deficiency in, 61
 HLA-DR2 and, 193
 lab findings in, 634, 636, 637
 as restrictive lung disease, 619
 as type II hypersensitivity reactions, 204
- Good syndrome, 229
- Gottron papules, 436
- Gout, 431
 as drug reaction, 253
 drug therapy for, 448
 kidney stones and, 549
 lab findings in, 636, 637
 Lesch-Nyhan syndrome as cause, 50, 631
 loop diuretics as cause, 557
 presentation of, 634
 treatments for, 638, 639
 Von Gierke disease as cause, 99
- Gower maneuver, 73
- Gowers sign, 630
- Gp41, 186
- G-protein-linked 2nd messengers, 242
- Grafts, 210
- Graft-versus-host disease, 211
 as type IV hypersensitivity reaction, 205
- Gram-negative organisms
 cell wall structure in, 108
 cephalosporins for, 172
 examples of, 109
 lab algorithm for, 125
- Gram-positive cocci antibiotic tests, 118
- Gram-positive organisms
 cell wall structure in, 108
 cephalosporins for, 172
 examples of, 109
 lab algorithm for, 118
 vancomycin for, 173
- Gram stain, 110
- Granular casts, 544
 in acute tubular necrosis, 554
- Granulocyte-colony stimulating factor (G-CSF), 316
- Granulocytes, 378
 morulae in, 133
- Granulocytopenia, 177
- Granulomas, 219
 macrophages and, 379
- Granulomatosis infantiseptica
 as granulomatous disease, 223
Listeria monocytogenes as cause, 123
- Granulomatous disease, 223
 hypervitaminosis D caused by, 428
 vitamin D toxicity in, 81
- Granulosa cells, 577
- Granulosa cell tumors, 593
 endometrial hyperplasia and, 594
- Granzyme B
 cytotoxic T cells and, 194
 extrinsic pathway and, 216
- Granzymes, 193
- Grapefruit juice, and cytochrome P-450, 254
- Graves disease, 323
 autoantibody associated with, 207
 goiter caused by, 321
 HLA-DR3 and, 193, 643
 presentation of, 631
 as type II hypersensitivity reactions, 204
- Gray baby syndrome
 chloramphenicol as cause, 175, 187
 as drug reaction, 252
- Great cerebral vein of Galen, 470
- Greater sac, 340
- Grief, 516
- Griseofulvin, 183
 cytochrome P-450 and, 254
 disulfiram-like reaction caused by, 254
 microtubules and, 60
 in pregnancy, avoiding, 187
- Ground-glass appearance on lung X-ray, 160, 607
- Growth hormone (GH), 311, 336
 acromegaly caused by, 327
 diabetes mellitus caused by, 330
 ghrelin and, 311
 for hypopituitarism, 329
 insulin resistance caused by, 308, 311
 in Laron syndrome, 327
 secretion of, 307
 signaling pathways for, 316
 thyroid hormones and, 315
- Growth hormone (GH) deficiency, 336
- Growth-hormone-releasing hormone (GHRH), 309
 GH and, 311
 signaling pathways of, 316
- Growth media properties, 110
- Growth signal in cancer, 227
- GTPase, 230
- GTP (guanosine triphosphate)
 in smooth muscle contraction, 425
 in TCA cycle, 88
- Guaifenesin, 627
- Guanethidine, 243
- Guanfacine, 247
- Guanine synthesis, 187
- Gubernaculum, 571, 573
- Guessing during USMLE Step 1 exam, 20
- Guillain-Barré syndrome, 493
Campylobacter jejuni as cause, 128
 endoneurium in, 454
 presentation of, 633
 as restrictive lung disease, 619
 Schwann cells in, 453
 as type II hypersensitivity reactions, 204
- Gummas
 syphilis as cause, 131, 167
- Gustatory hallucinations, 513
- Guyon canal syndrome, 418
- Gynecologic tumor
 epidemiology, 590
- Gynecomastia, 595
 antiandrogens for, 603
 antipsychotics as cause, 525
 azoles as cause, 182
 choriocarcinomas as cause, 598
 cimetidine as cause, 374
 cirrhosis as cause, 365
 Klinefelter syndrome as cause, 585
 potassium-sparing diuretics as cause, 558
 SHBG and, 316
 tuberoinfundibular pathway and, 458
- Gyrase, 170
- Gyri, in Alzheimer disease, 491
- H**
- H₁ blockers, 254, 627
- H₂-antagonists, 255
- H₂ blockers, 374
- Haemophilus* spp.
 endocarditis caused by, 293
 morphology of, 109
- Haemophilus ducreyi*
 presentation of, 632
 as STI, 167
- Haemophilus influenzae*, 126
 biofilm produced by, 113
 cephalosporins for, 172
 chloramphenicol for, 175
 culture requirements for, 111
 in Gram-negative algorithm, 125
 influenza and, 153
 penicillinase-sensitive penicillins for, 171
 pneumonia caused by, 162
 as postviral infection, 162
 rhinosinusitis caused by, 616
 vaccine for, 163
- Haemophilus influenzae* type B
 as encapsulated bacteria, 112
 IgA protease and, 113
 in immunodeficient patients, 210
- meningitis caused by, 163
 rifamycins for, 179
 splenic dysfunction and, 191
 transformation in, 114
 treatments for, 639
 in unvaccinated children, 169
 vaccine for, 112
- Hairy cell leukemia, 402
 cladribine for, 409
 IFN- α for, 187
- Hairy leukoplakia, 442
 HIV and, 160
- Half-life equation, 237, 646
- Halitosis, in Zenker diverticulum, 361
- Hallucinations, 513
 cocaine as cause, 522
 delirium and, 512
 Lewy body dementia as cause, 491
 memantine as cause, 505
 mesolimbic pathway and, 458
 pellagra as cause, 78
 postpartum psychosis as cause, 516
 schizophrenia as cause, 514
 tricyclic antidepressants as cause, 527
- Hallucinogen intoxication and withdrawal, 523
- Haloperidol, 525
 for delirium, 512
 for Huntington disease, 505
 torsades de pointes caused by, 251
- Haloethane, 502
 necrosis caused by, 252
- Hamartin protein, 230
- Hamartomas, 228
 tuberous sclerosis as cause, 71, 495
- Hamartomatous colonic polyps, 363
- Hamate bone, 418
- Hammer toes, 475
- Hand
 distortions of, 421
 muscles of, 421
- Hand-foot-mouth disease, 166
- Hand grip, effect on auscultation, 272
- Hand tremors, 321
- Hand-wringing, in Rett syndrome, 511
- Hansen disease, 125
 animal transmission of, 132
 dapsone for, 177
 erythema nodosum and, 444
 as granulomatous disease, 223
- Hantavirus, 151
- “Happy puppet” symptoms, in Angelman syndrome, 69
- Haptens
 acute interstitial nephritis caused by, 554
 amiodarone as, 303
- Haptoglobin, 391
- Hardy-Weinberg equilibrium, 646
- Hardy-Weinberg population genetics, 69
- Hartnup disease, 78
 vitamin B₃ deficiency as cause, 78
- Hashimoto thyroiditis, 322
 autoantibody associated with, 207
 biliary cirrhosis and, 371

- goiter caused by, 321
 HLA-DR3 and, 193, 643
 HLA-DR5 and, 193
 thyroid lymphoma and, 324
- Hassall corpuscles, 191
- Hay fever
 HLA-DR2 and, 193
 as type I hypersensitivity reaction, 204
- HbA_{1c} test, 330
- HBcAg (hepatitis B core antigen), 157
- HbC disease, 392
 in anemia taxonomy, 388
 target cells in, 387
- HBeAg (hepatitis B extracellular antigen), 157
- HbH disease, 388
- HBsAg (hepatitis B surface antigen), 157
- hCG. *See* Human chorionic gonadotropin (hCG)
- HCTZ. *See* Hydrochlorothiazide (HCTZ)
- HDL (high-density lipoprotein), 105
- Headaches, **494**
alpha-blockers as cause, 248
 caffeine withdrawal as cause, 522
 Chiari I malformation as cause, 452
 cilostazol/dipyridamole as cause, 407
 cimetidine as cause, 374
 ethosuximide as cause, 500
 fluoroquinolones as cause, 178
 giant cell arteritis as cause, 296
 griseofulvin as cause, 183
 hydralazine as cause, 298
 hypersensitivity pneumonitis as cause, 619
 Jarisch-Herxheimer reaction as cause, 631
 Nelson syndrome as cause, 326
 nitrates as cause, 299
 nonbenzodiazepine hypnotics as cause, 501
 ondansetron as cause, 376
 PDE-5 inhibitors as cause, 603
 pituitary adenomas as cause, 326
 pituitary apoplexy as cause, 329
 polyarteritis nodosa as cause, 296
 pseudotumor cerebri as cause, 471
 ranolazine as cause, 299
 sofosbuvir as cause, 187
 subarachnoid hemorrhage as cause, 468
 superior vena cava syndrome and, 625
 terbinafine as cause, 182
 triptans for, 505
- Head and neck cancer, **616**
 cetuximab for, 214, 412
- Head trauma, 512
- Healing, wound, **223**
- Healthy worker effect, 36
- Hearing loss, **481**
 cholesteatoma as cause, 482
 cytomegalovirus as cause, 165
 Meniere disease as cause, 631
 osteogenesis imperfecta as cause, 63
 Paget disease of bone as cause, 427
 presbycusis as cause, 44
- Heart
 autoregulation of, 280
 electrocardiograms, **276**
 embryology, **262**
 in fetal development, 562
 ischemia in, 218
 morphogenesis of, **262–263**
 in nervous system, 241
 normal pressures in, **280**
 sclerosis of, 437
- Heart auscultation, **272**
- Heart block, 265
- Heartburn, 354
- Heart disease
 as common cause of death, 45
 congenital, 282–283
 Fabry disease as cause, 100
- Heart failure, **292**
 ACE inhibitors for, 559
 acromegaly as cause, 327
 acute tubular necrosis caused by, 554
 amiodarone as cause, 303
 angiotensin II receptor blockers for, 559
 aortic regurgitation as precursor, 273
 atrial septal defect as cause, 283
 β -blockers as cause, 249, 303
 β -blockers for, 249
 B-type natriuretic peptide in, 279
 calcium channel blockers as cause, 304
 cardiac glycosides for, 301
 chronic ischemic heart disease as cause, 287
 contractility in, 267
 diabetic ketoacidosis as cause, 331
 disopyramide as cause, 302
 dobutamine for, 246
 dopamine for, 246
 Ebstein anomaly and, 282
 ejection fraction in, 267
 ESR in, 224
 fludrocortisone and, 336
 glitazone/thiazolidinediones as cause, 334
 hydralazine for, 298
 hypertension as cause, 284
 hypertension with, treatment for, 298
 hypertensive emergency and, 284
 jugular venous pulse in, 270
 key associations, 645
 lab findings in, 637
 loop diuretics for, 557
 MI as cause, 288
 pleural effusion caused by, 623
 potassium-sparing diuretics for, 558
 pulse pressure in, 266
 readmissions caused by, 45
 renal failure as cause, 553
 S3 heart sound and, 645
 shock caused by, 292
 sleep apnea as cause, 621
 systolic vs. diastolic, 267
 thiazides for, 558
 ventricular septal defect as cause, 283
- Heart murmurs, **273**
 aortic regurgitation as cause, 630
 auscultation of, 272
 bacterial endocarditis as cause, 293
 bedside maneuvers and, 272
 key associations, 643
 PDA as cause, 631
- Heart nodules, 636
- Heart rate, 247
- Heart sounds, **270**
 auscultation of, 272
 in cardiac cycle, 270
 in cardiac tamponade, 294, 632
 key associations, 645
 splitting in, **271**
- Heart transplant, for dilated cardiomyopathy, 291
- Heart valve development, 263
- Heat-labile toxin, 116
- Heat shock proteins, 57
- Heat-stable toxin, 116
- Heinz bodies, 90, 387, 392
- Helicase, **51**
- Helicobacter* spp., 109
- Helicobacter pylori*, **130**
 as catalase-positive organism, 112
 chronic granulomatous disease and, 209
 diseases associated with, 642
 gastritis caused by, 356
 in Gram-negative algorithm, 125
 metronidazole for, 178
 as oncogenic microbe, 231
 penicillinase-sensitive penicillins for, 171
 silver stain for, 110
 stomach cancer and, 356
 as urease-positive organism, 112
- Heliotrope rash, 436
- HELLP syndrome, 590
 schistocytes in, 387
- Helminthic infections
 eosinophils and, 379
 key associations, 643
- Helminths, 142
- Helper T cells, **194**
 cell surface proteins, 202
 cytokines secreted by, 200
 in granulomatous diseases, 223
- Hemagglutinin, in influenza viruses, 153
- Hemangioblastomas, 496
 polycythemia and, 229
 von Hippel-Lindau disease as cause, 495, 633
- Hemangiomas, 228
- Hemarthroses, 396
- Hemarthrosis, 80
- Hematemesis
 esophageal varices as cause, 354
 Mallory-Weiss syndrome as cause, 354, 523, 634
- Hematochezia
 angiodysplasia as cause, 362
 colonic ischemia as cause, 362
 colorectal cancer as cause, 364
 diverticulosis as cause, 360
 Meckel diverticulum as cause, 567
- Hematocrit
 high altitude and, 615
 in polycythemia vera, 404
- Hematologic drug reactions, **252**
- Hematology/oncology, 378–415
 anatomy, 378–381
 pathology, 386–406
 pharmacology, 405–413
 physiology, 381–385
- Hematomas, 643
- Hematopoiesis, 401
- Hematopoietic stem cells, 202
- Hematuria
 bladder cancer as cause, 551
 Henoch-Schönlein purpura as cause, 633
 hereditary hemorrhagic telangiectasia as cause, 71
 IgA nephropathy as cause, 546
 kidney stones as cause, 549
 nephritic syndrome as cause, 546
 Osler-Weber-Rendu syndrome as cause, 634
 protease inhibitors as cause, 186
 renal cell carcinoma as cause, 550
 renal cyst disorders as cause, 555
 renal oncocytomas as cause, 550
 RPGN as cause, 546
Schistosoma haematobium and, 145
 Wegener granulomatosis as cause, 296
 Wilms tumor as cause, 551
- Heme
 bilirubin and, 353
 chloroquine and, 183
 for porphyria, 395
 sideroblastic anemia and, 389
 synthesis of, 83, **395**
 vitamin B₆ and, 78
- Hemianopia, 489
 in pituitary adenomas, 496
- Hemiballismus, 461
 brain lesions and, 464
- Hemicholinium, 243
- Hemidesmosome, 438
 autoantibody to, 207
- Hemihypertrophy, 551
- Hemiparesis, in multiple sclerosis, 492
- Hemispatial neglect syndrome, 464
- Hemochromatosis, **371**
 calcium pyrophosphate deposition disease and, 431
 cardiomyopathy caused by, 291
 chromosome associated with, 75
 free radical injury and, 221
 hepatocellular carcinoma and, 368
 HLA-A3 and, 193

- Hemochromatosis (*continued*)
 key associations, 643
 liver cancer and, 645
 restrictive/infiltrative
 cardiomyopathy caused
 by, 291
- Hemoglobin, **611**
 carbon dioxide transport and, 615
 development of, 381
 high altitude and, 615
 kinetics of, 236
 modifications of, **612**
- Hemoglobin electrophoresis, **383**
- Hemoglobinuria
 acute tubular necrosis caused
 by, 554
 G6PD deficiency as cause, 392
 intravascular hemolysis as
 cause, 391
- Hemolysis
 alpha toxin as cause, 117
Clostridium perfringens as
 cause, 122
 in HELLP syndrome, 590
 sulfonamides as cause, 177
- Hemolysis in G6PD deficiency
 as drug reaction, 252
- Hemolytic anemia, **388, 391**
 babesiosis as cause, 141
 cold agglutinin disease as
 cause, 632
 folate deficiency caused by, 390
 penicillin as cause, 170
 pyruvate kinase deficiency as
 cause, 392
 ribavirin as cause, 187
 spherocytes in, 387
 sulfa drug allergies as cause, 254
 vitamin E deficiency as cause, 81
 Wilson disease as cause, 371
- Hemolytic reactions, and blood
 types, 382
- Hemolytic-uremic syndrome (HUS)
Escherichia coli as cause, 128
 schistocytes in, 387
Shigella spp. and, 116
- Hemophilia, **396**
 deficiencies causing, 383
 as X-linked recessive disorder, 72
- Hemoptysis
 bronchiectasis as cause, 618
 choriocarcinomas and, 587
 HIV and, 160
 lung cancer as cause, 626
 tuberculosis as cause, 124
 Wegener granulomatosis as
 cause, 296
- Hemorrhage
 acute pancreatitis as cause, 373
 acute tubular necrosis caused
 by, 554
 baroreceptors and, 279
 bevacizumab as cause, 412
 delirium caused by, 512
 intracranial, **469**
 shock caused by, 292
 subarachnoid, 468
 ulcers as cause, 357
 Weil disease as cause, 130
- Hemorrhagic cystitis
 adenoviridae as cause, 148
 cyclophosphamide as cause, 410
 as drug reaction, 253
 treatments for, 639
- Hemorrhagic fever
 as bunyavirus, 151
 as filovirus, 151
- Hemorrhagic infarcts, 219
- Hemorrhagic stroke, 468
- Hemorrhoids, 345
- Hemosiderinuria, 391
- Hemostasis, 378
- Henderson-Hasselbalch
 equation, 543, 647
- Henoch-Schönlein purpura, **297**
 in IgA nephropathy, 546
 presentation of, 633
- Hepadnaviruses
 characteristics of, 148
 as DNA viruses, 147
 genome of, 147
- Heparin, **405**
 for acute coronary syndromes, 290
 for anticoagulation, 383, 640
 for anticoagulation during
 pregnancy, 639
 in basophils, 379
 in coagulation cascade, 384
 for deep venous thrombosis, 616
 mast cells and, 379
 osteoporosis caused by, 253
 reversal, treatments for, 639
 thrombocytopenia caused by, 252
 toxicity treatment for, 251
 vs. warfarin, **406**
 warfarin and, 406
- Heparin-induced thrombocytopenia
 (HIT), 405
- Hepatic adenomas, 368
- Hepatic arteries, 343, 346
- Hepatic ascites, 558
- Hepatic cirrhosis, 623
- Hepatic ducts, 347
- Hepatic encephalopathy, **367**
 cirrhosis as cause, 365
 lactulose for, 375
- Hepatic necrosis, 446
- Hepatic steatosis, 367
- Hepatic TG lipase, 104
- Hepatitis
 alcoholic, 367
 alcoholism as cause, 523
 aplastic anemia and, 391
 cirrhosis caused by, 365
 as drug reaction, 252
 heroin addiction and, 523
 hyperbilirubinemia caused by, 369
 Wilson disease as cause, 371
- Hepatitis A (HAV), 151
 characteristics of, 156
 killed vaccine for, 146
 as picornavirus, 152
 serologic markers for, 157
 vaccine for, 203
- Hepatitis B (HBV)
 characteristics of, 156
 hepatocellular carcinomas and, 368
 IFN- α for, 187
 medical importance of, 148
 membranous nephropathy and, 548
 MPGN and, 547
 as nosocomial infection, 168
 as oncogenic microbe, 231
 passive antibodies for, 203
 polyarteritis nodosa and, 296
 recombinant cytokines for, 213
 serologic markers for, 157
 as STI, 167
 treatments for, 639
- Hepatitis C (HCV), 151
 as antigenic variation, 202
 blood transfusions and, 643
 characteristics of, 156
 drug therapy for, **187**
 hepatocellular carcinoma and, 368
 lichen planus and, 444
 membranous nephropathy and, 548
 MPGN and, 547
 as oncogenic microbe, 231
 recombinant cytokines for, 213
 treatments for, 639
- Hepatitis D (HDV), 156
- Hepatitis E (HEV), 151, 156
- Hepatitis viruses, **156**
 aplastic anemia caused by, 391
 diagnostic tests for, 157
 serologic markers for, 157
- Hepatocellular carcinomas, **368, 645**
Aspergillus fumigatus as cause, 137
 Budd-Chiari syndrome and, 368
 carcinogens causing, 231
 cirrhosis and, 365
 hemochromatosis as cause, 371
 key associations, 643, 645
 non-alcoholic fatty liver disease
 and, 367
 oncogenic microbes and, 231
 polycythemia and, 229
- Hepatocytes, 98
- Hepatoduodenal ligament, 340
- Hepatomas, **368**
- Hepatomegaly, 292
 amyloidosis and, 225
 Budd-Chiari syndrome as
 cause, 368, 630
 Cori disease as cause, 632
 galactosemia as cause, 91
 hepatocellular carcinoma as
 cause, 368
 pulmonary hypertension as
 cause, 613
 Reye syndrome as cause, 366
 Von Gierke disease as cause, 99
- Hepatosplenomegaly
 β -thalassemia and, 389
 biliary tract disease as cause, 371
 Gaucher disease as cause, 100, 631
 graft-versus-host disease as
 cause, 211
 Hurler syndrome as cause, 100
- hyperchylomicronemia as
 cause, 105
- leishmaniasis as cause, 142
 mononucleosis as cause, 149
 mycosis fungoides as cause, 631
 Niemann-Pick disease as cause, 100
 ToRCHeS infections as cause, 165
- Hepatotoxicity
 amiodarone as cause, 303
 bosentan as cause, 627
 carbamazepine as cause, 500
 danazol as cause, 602
 glitazone/thiazolidinediones as
 cause, 334
 HMG-CoA reductase inhibitors as
 cause, 300
 inhaled anesthetics as cause, 502
 isoniazid as cause, 180
 leflunomide as cause, 447
 methotrexate as cause, 409
 pyrazinamide as cause, 180
 rifamycins as cause, 179
 terbinafine as cause, 182
 thionamides as cause, 335
 valproic acid as cause, 500
 zileuton as cause, 628
- Hepcidin
 as acute-phase reactant, 198
 in anemia of chronic disease, 391
- Hepeviruses
 characteristics of, 151
 genomes of, 147
 as naked viruses, 147
- “Herald patch” in pityriasis rosea, 444
- Hereditary angioedema, 602
- Hereditary bleeding disorders, 643
- Hereditary hemorrhagic
 telangiectasia, 71
 presentation of, 634
- Hereditary hyperbilirubinemias, **370**
- Hereditary nephritis, 632
- Hereditary spherocytosis, 392
 in anemia taxonomy, 388
 autosomal dominance of, 71
 spherocytes in, 387
- Heritable amyloidosis, 225
- Hermaphrodites, 586
- Hernias, **349**
 site of, 348
- Herniation syndromes, **498**
- Heroin
 addiction to, **523**
 focal segmental glomerulosclerosis
 and, 548
 intoxication and withdrawal, 522
 opioids for withdrawal from, 499
- Herpes encephalitis, 64
- Herpes genitalis, 149
- Herpes labialis, 149
- Herpes simplex virus 1 (HSV-1), 149,
 442
 as STI, 167
 viral encephalitis and, 646
- Herpes simplex virus 2 (HSV-2), 149,
 442
 as STI, 167
 as ToRCHeS infection, 165

- Herpes simplex virus (HSV)
 cidofovir for, 185
 erythema multiforme and, 443
 facial nerve palsy caused by, 480
 foscarnet for, 185
 guanosine analogs for, 184
 identification of, 150
 meningitis caused by, 163
 retinitis and, 486
- Herpesviruses, 149–150, 442
 characteristics of, 148
 as DNA viruses, 147
- Herpes zoster
 facial nerve palsy caused by, 480
 famciclovir for, 184
 retinitis and, 486
- Hesselbach triangle, 349
- Heterochromatin, 48
- Heterodimer, 60
- Heterodisomy, 69
- Heterogeneous nuclear RNA (hnRNA), 54
- Heterophile antibodies, 636
- Heteroplasmy, 69
- Heterozygosity, loss of, 68
- Hexokinase
 vs. glucokinase, 86
 in metabolic pathways, 85
- Hexosaminidase A, 100
- HFE gene
 hemochromatosis and, 371, 643
- HGPRT, 409
- HGPRT (hypoxanthine guanine phosphoribosyltransferase), 50
- Hiatal hernias, 349
- Hiccups, 461
- High altitude, respiratory response to, 615
- High-frequency recombination (Hfr) cells, 114
- Highly active antiretroviral therapy (HAART), 186
- Hilar adenopathy, 630
- Hilar lymphadenopathy, 636
- Hilar lymph nodes, 190
 silicosis and, 620
- Hilar nodes, 124
- Hindbrain, 450
- Hindgut
 blood supply/innervation of, 342
 development of, 338
- Hip dislocation, nerve injury caused by, 422
- Hippocampus, 458
 lesions in, 464
 pyramidal cells, 218
- Hippurate test, for *Streptococcus agalactiae*, 121
- Hirschsprung disease, 361
 Down syndrome as cause, 74
- Hirsutism
 cyclosporine as cause, 212
 danazol as cause, 602
 epilepsy drugs causing, 500
 menopause as cause, 582
 PCOS as cause, 591
 SHBG and, 316
- Hirudin, 405
- Histaminase, 379
- Histamine receptors, 242
- Histamines
 in basophils, 379
 cortisol effect on, 313
 derivatives of, 94
 ingested seafood and, 250
 location of, 351
 mast cells and, 379
 signaling pathways for, 316
 vitamin B₆ and, 78
- Histidine, 92
 derivatives of, 94
- Histone acetylation, 48
- Histone methylation, 48
- Histones, 207
- Histoplasma* spp.
 amphotericin B for, 182
 itraconazole for, 182
- Histoplasma capsulatum*
 HIV and, 160
 necrosis and, 217
- Histoplasmosis, 135
 erythema nodosum and, 444
 as granulomatous disease, 223
- Histrionic personality disorder, 519
- HIV (human immunodeficiency virus), 151, 158
 as antigenic variation, 202
 aplastic anemia caused by, 391
 cervical cancer and, 591
 dementia caused by, 491
 diagnosis of, 158
 diseases associated with, 160
 drug therapy for, 184, 186
 ex vacuo ventriculomegaly caused by, 471
 flow cytometry diagnosis, 66
 focal segmental glomerulosclerosis and, 548
 hairy leukoplakia and, 442
 heroin addiction and, 523
 Kaposi sarcoma and, 149, 441
 lymphopenia caused by, 394
 meningitis caused by, 163
 microglia in, 453
 non-Hodgkin lymphoma and, 399
 PCR diagnosis of, 64
Pneumocystis jirovecii and, 138
 primary central nervous system lymphoma (PCL) and, 400
 prophylaxis for, 181
 pulmonary arterial hypertension caused by, 622
 receptors for, 150
 rifamycins in, 179
 as STI, 167
 T cells and, 380
 time course of untreated, 159
 as ToRCHeS infection, 165
 Western blot diagnosis of, 65
- HIZ shrinkage in muscle contraction, 424
- HLA genes
 celiac disease and, 358
 diabetes mellitus type 1 and, 331
 diseases associated with, 193, 322
 key associations, 643
 MHC I and II and, 192
 seronegative spondyloarthritis and, 433
 uveitis and, 484
- HMG-CoA reductase, 84
 in cholesterol synthesis, 103
 in metabolic pathways, 85
- HMG-CoA reductase inhibitors, 300
 naming convention for, 255
- HMG-CoA synthase, 84
- HMP shunt, 90
 diagram of, 85
 rate-determining enzyme for, 84
- Hoarseness
 gastroesophageal reflux disease as cause, 354
 heart enlargement as cause, 265
 lung cancer and, 626
 Pancoast tumor as cause, 625
 stroke as cause, 467
- “Hobnail” liver in alcoholic cirrhosis, 367
- Hodgkin lymphoma, 644
 bleomycin for, 410
 key associations, 645
 vs. non-Hodgkin lymphoma, 399
 oncogenic microbes and, 231
 paraneoplastic cerebellar degeneration and, 229
 vinca alkaloids for, 411
- Holoprosencephaly, 451
 fetal alcohol syndrome as cause, 565
 Patau syndrome as cause, 74, 632
 Sonic hedgehog gene and, 562
- Holosystolic murmurs, 643
- Homan sign, 616
- Homatropine, 245
- Homeobox genes, 562
- Homer-Wright rosettes, 635
 in medulloblastomas, 497
- Homicidal patients, 41
- Homicide, as common cause of death, 45
- Homocysteine
 in B₁₂ deficiency, 390
 in folate deficiency, 390
 in vitamin B₉ deficiency, 79
 in vitamin B₁₂ deficiency, 80
- Homocysteine methyltransferase deficiency in, 96
 diagram of, 80
 vitamin B₁₂ and, 80
- Homocystinuria, 96
- Homovanillic acid (HVA)
 in neuroblastomas, 319
 in tyrosine catabolism, 95
- Homunculus, 465
- “Honeycomb lung,” 636
- Hookworms, 143
- Horizontal fissure, 609
- Hormone replacement therapy, 601
 endometrial hyperplasia and, 594
 estrogens for, 601
 for hypopituitarism, 329
 thrombotic complications caused by, 252
- Hormone-sensitive lipase, 104
- Hormones, reproductive, 600
- Horn cysts, 440
- Horner syndrome, 487
 cluster headaches and, 494
 lung cancer and, 626
 Pancoast tumor as cause, 625
 presentation of, 633
 stroke as cause, 467
- Horner-Wright rosettes, 319
- Horse flies, as disease vectors, 143
- Horseshoe kidney, 531
 Turner syndrome as cause, 634
- Hospital readmissions, causes of, 45
- Hot flashes
 as drug reaction, 252
 menopause as cause, 582
- “Hourglass stomach,” 349
- “Housemaid’s knee,” 417
- Howell-Jolly bodies, 387, 635
 postsplenectomy, 191
 sickle cell anemia as cause, 392
- Hu antigens, 229
- Human chorionic gonadotropin (hCG), 580
 choriocarcinomas and, 587, 598
 in ectopic pregnancy, 589
 embryonal carcinomas and, 598
 in hydatidiform moles, 636
 hydatidiform moles and, 587
 in pregnancy, 580
 secretion, timing of, 562
 signaling pathways of, 316
- Human factors design, 45
- Human growth hormone. *See* Growth hormone (GH)
- Human herpesvirus 6 (HHV-6), 149, 166
- Human herpesvirus 7 (HHV-7), 149
- Human herpesvirus 8 (HHV-8), 149
 HIV and, 160
 Kaposi sarcoma and, 441
 as oncogenic microbe, 231
- Humanized monoclonal A_b, 255
- Humanized monoclonal antibodies, 203
- Human papillomavirus 6 (HPV-6), 167
- Human papillomavirus 11 (HPV-11), 167
- Human papillomavirus 16 (HPV-16), 616
- Human papillomavirus (HPV)
 cervical cancer and, 591
 HIV and, 160
 as oncogenic microbe, 231
 penile cancer and, 597
 verrucae caused by, 440
 warts caused by, 148
- Humerus injury
 axillary nerve and, 419
 median nerve injury caused by, 419
 radial nerve and, 419
- Humor, as ego defense, 509
- Hunger, and hypothalamus, 456
- Hunter syndrome, 100
 as X-linked recessive disorder, 72

- Huntington disease, **462**, 513
 antipsychotic drugs for, 525
 autosomal dominance of, 71
 basal ganglia lesions in, 464
 drug therapy for, **505**
 neurotransmitter changes in, 511
 neurotransmitters for, 455
 presentation of, 630
 as trinucleotide repeat expansion disease, 73
- Hurler syndrome, 100
- Hürthle cells, 322
- Hutchinson teeth, 131
- Hyaline arteriosclerosis, 285
- Hyaline casts, 544
- Hyaline membrane disease, 619
- Hydatid cysts, 144, 145
- Hydatidiform moles, **587**
 hCG in, 580
 lab findings in, 636
 theca-lutein cysts and, 592
- Hydralazine, **298**
 for gestational hypertension, 298, 590
 for heart failure, 292
 lupus-like syndrome caused by, 253
- Hydrocephalus, **471**
 congenital toxoplasmosis as cause, 630
 dementia caused by, 491, 513
 headaches caused by, 494
 medulloblastoma as cause, 497
Toxoplasma gondii as cause, 165
 in toxoplasmosis, 140
- Hydrochlorothiazide (HCTZ), 558
 for diabetes insipidus, 328, 639
 hyperglycemia caused by, 252
 pancreatitis caused by, 252
- Hydrocortisone, 336. *See also* Glucocorticoids
 arachidonic acid pathway and, 446
- Hydrogen peroxide, as infection control technique, 187
- Hydronephrosis, **550**
 BPH as cause, 599
 horseshoe kidney and, 531
 kidney stones as cause, 549
- Hydrophobia, 155
- Hydrops fetalis
 α -thalassemia as cause, 388
 parvovirus as cause, 148
 parvovirus B19 as cause, 165, 166
 syphilis as cause, 165
- Hydrosalpinx, 167
- Hydrothorax, 592
- Hydroxocobalamin, 251
- Hydroxychloroquine
 for lupus, 434
 myopathy caused by, 253
 for rheumatoid arthritis, 430
- Hydroxylases, 84
- Hydroxylation, 57
- Hydroxyurea, **411**
 in cell cycle, 408
 purine synthesis, effect on, 49
 for sickle cell anemia, 392
 for sickle cell disease, 641
 targets of, 408
- Hyoid artery, 568
- Hyoscyamine, 245
- Hyperactivity, 321
- Hyperacute transplant rejection, 211
- Hyperaldosteronism, **318**
 hypertension caused by, 284
 key associations, 645
 metabolic alkalosis caused by, 543
 potassium-sparing diuretics for, 558
 treatments for, 639
- Hyperammonemia, **93**
- Hyperbilirubinemia
 cirrhosis as cause, 365
 hereditary, **370**
 jaundice and, 369
- Hypercalcemia, 542
 acute pancreatitis caused by, 373
 adult T-cell lymphoma as cause, 400
 bisphosphonates for, 447
 calcium carbonate as cause, 375
 diabetes insipidus caused by, 328
 granulomatous diseases and, 223
 hyperparathyroidism as cause, 326
 loop diuretics for, 557
 lung cancer as cause, 626
 as paraneoplastic syndrome, 229
 PTH-independent, 325
 sarcoidosis and, 435
 succinylcholine as cause, 503
 teriparatide as cause, 447
 thiazides as cause, 558
 vitamin D toxicity as cause, 81
 Williams syndrome as cause, 75
- Hypercalciuria
 hyperparathyroidism as cause, 326
 thiazides for, 558
 vitamin D toxicity as cause, 81
- Hypercapnia
 bronchitis as cause, 618
 chronic bronchitis as cause, 632
 contractility in, 267
- Hypercholesterolemia, 105, 321
 nephrotic syndrome as cause, 633
 presentation of, 630
 treatments for, 640
- Hyperchylomicronemia, 105
- Hypercoagulability
 key associations, 643
 in pregnancy, 580
 Trousseau syndrome as cause, 636
- Hyperdocility, in Klüver-Bucy syndrome, 632
- Hyperemesis gravidarum, 587
- Hyperemia
 in MI, 288
 pseudoephedrine/phenylephrine for, 627
- Hyperestrogenism, 592
- Hyperglycemia. *See also* Diabetes mellitus
 Cushing syndrome as cause, 317
 in diabetic ketoacidosis, 331
 diabetic retinopathy caused by, 485
 as drug reaction, 252
 glucagon and, 309
 glucagonomas as cause, 332
 glucocorticoids as cause, 212
 hyperkalemia caused by, 542
 niacin as cause, 300
 prednisone as cause, 412
 protease inhibitors as cause, 186
 somatostatinomas as cause, 332
 thiazides as cause, 558
 vitamin B₃ toxicity as cause, 78
- Hypergranulosis, 439
- Hyper-IgE syndrome, 633
- Hyper-IgM syndrome, 209
- Hyperinsulinemia, 591
- Hyperkalemia, 542
 aliskiren as cause, 559
 angiotensin II receptor blockers as cause, 559
 cardiac glycosides as cause, 301
 causes of, 542
 in diabetic ketoacidosis, 331
 potassium-sparing diuretics as cause, 558
 primary adrenal insufficiency as cause, 318
 renal failure as cause, 553
 SGLT-2 inhibitors as cause, 335
 succinylcholine as cause, 503
- Hyperkalemic renal tubular acidosis, 544
- Hyperkeratosis, 439
 verrucae as cause, 440
- Hyperlipidemia, **285**
 atherosclerosis and, 286
 atypical antipsychotics as cause, 525
 cyclosporine as cause, 212
 glomerular filtration barrier and, 533
 nephrotic syndrome as cause, 548
 sirolimus as cause, 212
 thiazides as cause, 558
- Hypermagnesemia, 542
- Hypernatremia, 542
- Hyperopia, 483
- Hyperorality
 Klüver-Bucy syndrome as cause, 464, 632
- Hyperosmolar coma, in type 2 diabetes, 330
- Hyperosmolar hyperglycemia nonketotic syndrome, **332**
- Hyperosmolarity, 542
- Hyperparathyroidism, **326**
 calcium pyrophosphate deposition disease and, 431
 cinacalcet for, 336
 key associations, 645
 lab findings in, 635
 lab values in, 428
 osteoporosis and, 426
 renal osteodystrophy and, 553
- Hyperphagia
 depression with, 515
 hypothalamus and, 456
 Klüver-Bucy syndrome as cause, 464, 632
 Prader-Willi syndrome as cause, 69
- Hyperphosphatemia, 542
 hyperparathyroidism as cause, 326
 hypoparathyroidism as cause, 325
 renal osteodystrophy and, 553
- Hyperphosphorylated tau,
 in frontotemporal dementia, 491
- Hyperpigmentation
 adrenocortical insufficiency as cause, 633
 bleomycin as cause, 410
 busulfan as cause, 410
 fludrocortisone as cause, 336
 hemochromatosis as cause, 371
 melasma as, 439
 Peutz-Jeghers syndrome as cause, 363, 631
 primary adrenal insufficiency as cause, 318
- Hyperplasia, 226, 227
 in primary hyperparathyroidism, 325
- Hyperplastic arteriosclerosis, 285
- Hyperplastic colonic polyps, 363
- Hyperprolactinemia
 anovulation caused by, 591
 antipsychotics as cause, 525
 calcium channel blockers as cause, 298
 dopamine antagonists and, 309
 GnRH and, 309
 risperidone as cause, 525
- Hyperpyrexia
 neuroleptic malignant syndrome as cause, 525
 tricyclic antidepressants as cause, 527
- Hyperreflexia
 serotonin syndrome as cause, 527
 UMN damage as cause, 632
- Hyperresonance, with pneumothorax, 623
- Hypersegmented neutrophils, 636
- Hypersensitivity pneumonitis, 223, **619**
 as restrictive lung disease, 619
- Hypersensitivity reactions, **204–205**
 antipseudomonal penicillins as cause, 171
 to blood transfusions, 206
 C3 deficiency and, 199
 cephalosporins as cause, 172
 to helminths, 142
 IgE antibodies and, 197
 insulin as cause, 334
 mast cells and, 379
 to organ transplants, 211
 penicillin as cause, 170
 penicillinase-resistant penicillins as cause, 171
 penicillinase-sensitive penicillins as cause, 171
 rheumatic fever as, 294
 sulfonamides as cause, 177
- Hypersexuality
 Klüver-Bucy syndrome as cause, 464, 632

- Hypersomnia, 515
- Hypertension, **284**
- ACE inhibitors for, 559
 - acute poststreptococcal glomerulonephritis as cause, 546
 - alcohol withdrawal as cause, 523
 - aliskiren for, 559
 - alpha*-blockers for, 248
 - angiotensin II receptor blockers for, 559
 - aortic dissection and, 287, 641
 - atherosclerosis and, 286
 - atrial fibrillation and, 278
 - autosomal recessive polycystic kidney disease and, 555
 - β -blockers for, 249
 - calcium channel blockers for, 298
 - Charcot-Bouchard microaneurysms and, 468
 - Cushing syndrome as cause, 317
 - cyclosporine as cause, 212
 - in diabetes mellitus, 298
 - endometrial cancer and, 594
 - glucocorticoids as cause, 212
 - Guillain-Barré syndrome as cause, 493
 - in heart failure, 298
 - hydralazine for, 298
 - hyperaldosteronism as cause, 318
 - immunosuppressants as cause, 212
 - intraparenchymal hemorrhage caused by, 469
 - key associations, 643
 - leflunomide as cause, 447
 - local anesthetics as cause, 503
 - loop diuretics for, 557
 - MDMA as cause, 523
 - microangiopathic anemia caused by, 393
 - minoxidil for, 603
 - nephritic syndrome and, 546
 - PCP as cause, 523
 - pheochromocytomas as cause, 320
 - placental abruption and, 588
 - polyarteritis nodosa as cause, 296
 - prednisone as cause, 412
 - preeclampsia and, 590
 - in pregnancy, 247, 298, **590**
 - primary hyperaldosteronism as cause, 636
 - pseudoephedrine/phenylephrine as cause, 627
 - renal cyst disorders as cause, 555
 - renal failure as cause, 553
 - saccular aneurysms and, 468
 - sleep apnea as cause, 621
 - syndrome of apparent mineralocorticoid excess as cause, 538
 - thiazides for, 558
 - thoracic aortic aneurysms and, 286
 - treatment for, **298**
 - tyramine and, 243
- Hypertensive crisis
- MAO inhibitors as cause, 528
 - phenoxybenzamine for, 248
- Hypertensive emergency, 284, **298**
- cleveldipine for, 298
- Hypertensive nephropathy, 284
- Hypertensive urgency, 284
- cleveldipine for, 298
- Hyperthermia
- atropine as cause, 245
 - MDMA as cause, 523
 - serotonin syndrome as cause, 527
- Hyperthyroidism, **323**
- amiodarone as cause, 303
 - choriocarcinomas as cause, 598
 - hydatidiform moles and, 587
 - vs. hypothyroidism, **321**
 - osteoporosis and, 426
 - pulse pressure in, 266
 - thionamides for, 335
- Hypertonia
- serotonin syndrome as cause, 527
 - UMN damage as cause, 632
- Hypertriglyceridemia, 105
- acute pancreatitis caused by, 373
 - treatments for, 640
- Hypertrophic cardiomyopathy, 291
- Pompe disease as cause, 99
 - systolic murmur in, 272
- Hypertrophic osteoarthropathy, 626
- Hypertrophic pyloric stenosis, **339**
- Hypertrophic scars, 222
- Hypertrophy, 226
- Hypertropic cardiomyopathy, 475
- Hyperuricemia
- as drug reaction, 253
 - gout and, 431
 - kidney stones and, 549
 - Lesch-Nyhan syndrome as cause, 50
 - niacin as cause, 300
 - pyrazinamide as cause, 180
 - thiazides as cause, 558
 - vitamin B₃ toxicity as cause, 78
- Hyperventilation
- emphysema as cause, 633
 - Kussmaul respirations as, 631
 - metabolic acidosis as cause, 543
 - in pregnancy, 580
- Hypervitaminosis D, 428
- Hypnagogic hallucinations, 513
- in narcolepsy, 521
- Hypnopompic hallucinations, 513
- in narcolepsy, 521
- Hypoalbuminemia
- alcoholic cirrhosis as cause, 367
 - nephrotic syndrome as cause, 545, 548, 633
- Hypocalcemia, 313, 542
- 22q11 deletion syndromes as cause, 76
 - acute pancreatitis as cause, 373
 - cinacalcet as cause, 336
 - DiGeorge syndrome as cause, 570
 - hypermagnesemia as cause, 542
 - hyperparathyroidism as cause, 326
 - hypoparathyroidism as cause, 325
 - pseudohypoparathyroidism as cause, 325
 - renal osteodystrophy and, 553
 - thymic aplasia as cause, 208
 - thyroidectomy as cause, 324
- Hypocalcemic tetany, 81
- Hypocholesterolemia
- hyperthyroidism as cause, 321
- Hypocretin, 521
- Hypodermis, 437
- Hypofibrinogenemia, 224
- Hypogammaglobulinemia, 229
- Hypoglossal canal, 478
- Hypoglossal nerve (12th cranial nerve), **479**
- lesion in, 480
 - location in brain stem, 477
 - pathway for, 478
 - in tongue, 452
- Hypoglycemia
- amylin analogs as cause, 335
 - carnitine deficiency as cause, 101
 - Cori disease as cause, 632
 - fructose intolerance as cause, 91
 - GH secretion in, 311
 - glucagon production in response to, 309
 - gluconeogenesis and, 89
 - insulin as cause, 334
 - insulinomas as cause, 332
 - loss of orientation caused by, 512
 - low birth weight and, 581
 - meglitinides as cause, 335
 - Reye syndrome as cause, 366
 - somatostatinomas as cause, 332
 - sulfonylureas as cause, 334
 - Von Gierke disease as cause, 99
- Hypoglycemic drugs, 334–335, 639
- Hypogonadism
- estrogens for, 601
 - gynecomastia caused by, 595
 - hemochromatosis as cause, 371
 - pituitary prolactinomas as cause, 309
 - Prader-Willi syndrome as cause, 69
 - testosterone/methyltestosterone for, 603
 - zinc deficiency as cause, 82
- Hypogonadotropic hypogonadism, 586
- Hypokalemia, 542
- antacids as cause, 375
 - Bartter syndrome as cause, 538
 - causes of, 542
 - cystic fibrosis as cause, 72
 - diabetes insipidus caused by, 328
 - on EKG, 276
 - Gitelman syndrome as cause, 538
 - loop diuretics as cause, 557
 - primary hyperaldosteronism as cause, 636
 - syndrome of apparent mineralocorticoid excess as cause, 538
 - VIPomas as cause, 350
- Hypomagnesemia, 542
- Hypomania, 515
- Hypomaniac episodes, **515**
- Hyponatremia, 542
- cirrhosis as cause, 365
- Cushing syndrome and, 229
- MDMA as cause, 523
- osmotic demyelination syndrome and, 492
- as paraneoplastic syndrome, 229
- thiazides as cause, 558
- Hypoparathyroidism, **325**
- key associations, 643
- Hypophosphatemia, 542
- aluminum hydroxide as cause, 375
 - hyperparathyroidism as cause, 326
- Hypophosphatemic rickets, 70
- Hypopituitarism, **329**
- key associations, 643
 - pituitary adenomas as cause, 326
- Hypoplasia, 563
- Hypoproteinemia, 533
- Hyporeflexia
- LMN damage as cause, 632
 - LMN lesion as cause, 475
 - magnesium hydroxide as cause, 375
- Hypospadias, 573
- Hyposplenias, 387
- Hypotension
- acute tubular necrosis caused by, 554
 - adrenal insufficiency as cause, 318
 - adrenocortical insufficiency as cause, 633
 - aliskiren as cause, 559
 - amphotericin B as cause, 182
 - angiotensin II receptor blockers as cause, 559
 - antipsychotic drugs as cause, 525
 - in Beck triad of cardiac tamponade, 632
 - cardiac tamponade as cause, 294
 - cilostazol/dipyridamole as cause, 407
 - ephedrine for, 246
 - Guillain-Barré syndrome as cause, 493
 - hypermagnesemia as cause, 542
 - key associations, 642
 - local anesthetics as cause, 503
 - magnesium hydroxide as cause, 375
 - metronidazole as cause, 178
 - midodrine for, 246
 - norepinephrine for, 246
 - phenylephrine for, 246
 - primary adrenal insufficiency as cause, 318
 - scombroid poisoning as cause, 250
 - sympatholytic drugs as cause, 247
 - Waterhouse-Friderichsen syndrome as cause, 630
- Hypothalamic drugs, **336**
- Hypothalamic-pituitary hormones, **309**
- Hypothalamus, **456**
- antidiuretic hormone secretion by, 311
 - sleep physiology and, 457
 - thyroid hormones and, 315
- Hypothenar muscles, 421
- Clumpke palsy and, 420

- Hypothyroidism, **322**
 amiodarone as cause, 303
 anemia caused by, 390
 in anemia taxonomy, 388
 carpal tunnel syndrome and, 418
 cold intolerance caused by, 631
 cretinism and, 642
 dementia caused by, 491, 513
 as drug reaction, 252
 vs. hyperthyroidism, **321**
 lithium as cause, 526
 thyroid hormones for, 335
- Hypotonia
 carnitine deficiency as cause, 101
 LMN damage as cause, 632
 Menkes disease as cause, 63
 Prader-Willi syndrome as cause, 69
- Hypoventilation, 543
- Hypovolemia, 330
- Hypovolemic shock, 292
- Hypoxanthine, 448
- Hypoxanthine guanine
 phosphoribosyltransferase
 (HGPRT), 50
- Hypoxemia, 614
 alveolar gas equation and, 614
 asthma as cause, 618
 chronic bronchitis as cause, 632
 fat emboli as cause, 617
 pulmonary embolism and, 617
 respiratory alkalosis caused
 by, 543
- Hypoxia, 614
 apoptosis caused by, 216
 contractility in, 267
 erythropoietin and, 541
 hemoglobin modifications
 and, 612
 regions susceptible to, 218
 vasoconstriction/vasodilation
 and, 280
- Hypoxia inducible factor 1a, 230
- Hypoxic stroke, 470
- Hysterectomy, for adenomyosis, 594
- Hysteresis, 611
- Hysteria, respiratory alkalosis caused
 by
 respiratory alkalosis caused by, 543
- I**
- Ibandronate, 447
- Ibuprofen, 447
 arachidonic acid pathway
 and, 446
 hemolysis in G6PD deficiency
 caused by, 252
- Ibutilide, 303
- ICAM-1 protein
 in leukocyte extravasation, 221
 as receptor, 150
- I-cell disease, **59**
- I cells, 350
- Icosahedral viruses, 147
- Idealization, as ego defense, 508
- Identification, as ego defense, 508
- Idiopathic intracranial
 hypertension, **471**
- Idiopathic thrombocytopenic purpura
 lab findings in, 635
 rituximab for, 412
 as type II hypersensitivity
 reactions, 204
- Idiopathic thrombocytopenic purpura
 (ITP)
 rituximab for, 214
- IDL (intermediate-density
 lipoprotein), 105
- IFN- α (Interferon- α), **201**
 clinical uses, 213
 natural killer cells, effect on, 193
- IFN- α (interferon- α), 184
 clinical use for, 187
 for hepatitis, 639
- IFN- β (Interferon- β), **201**
 clinical use for, 187
 clinical uses, 213
 natural killer cells, effect on, 193
- IFN- γ (Interferon- γ), 200, 208
 cachexia and, 232
 clinical use for, 187
 clinical uses, 213
 granulomatous diseases and, 223
 Graves disease and, 323
 helper T cells and, 194
- Ifosfamide, 410
 Fanconi syndrome caused by, 538
 hemorrhagic cystitis caused by, 253
- IgA antibodies, 197
 ataxia-telangiectasia and, 209
 in breast milk, 581
 in celiac disease, 358
 deficiency in, 208, 630
 in hyper-IgM syndrome, 209
 multiple myeloma production
 of, 401
 as passive immunity, 203
 Peyer patches and, 352
 in Wiskott-Aldrich syndrome, 209
- IgA nephropathy, 546, 643
 Henoch-Schönlein purpura
 and, 297
- IgA protease, 113
- IgD antibodies, 197
- IgE antibodies, 197
 in ataxia-telangiectasia, 209
 in eczema, 440
 in hyper-IgM syndrome, 209
 mast cells and, 379
 type I hypersensitivity reactions
 and, 204
 in Wiskott-Aldrich syndrome, 209
- IGF-1. *See* Insulin-like growth factor
 1 (IGF-1)
- IgG antibodies, 197
 anemia and, 393
 in ataxia-telangiectasia, 209
 in bullous pemphigoid, 443
 complement activation and, 199
 to hepatitis A (HAV), 157
 in hyper-IgM syndrome, 209
 multiple myeloma production
 of, 401
 in multiple sclerosis, 492
 as passive immunity, 203
- in pemphigus vulgaris, 443
 in pregnancy, 382
 in type III hypersensitivity
 reactions, 205
 in Wiskott-Aldrich syndrome, 209
- IgM antibodies, 197
 anemia and, 393
 in biliary cirrhosis, 371
 complement activation and, 199
 to hepatitis A (HAV), 157
 in hyper-IgM syndrome, 209
 in pregnancy, 382
 in sclerosing cholangitis, 371
 splenic dysfunction and, 191
 in Wiskott-Aldrich syndrome, 209
- IL-1 (Interleukin 1), 200
 cachexia and, 232
 endotoxins and, 117
- IL-2 (Interleukin 2), 200
 cyclosporine and, 212
 natural killer cells, effect on, 193
 sirolimus and, 212
 tacrolimus and, 212
- IL-2R (Interleukin 2 receptor), 212
- IL-3 (Interleukin 3), 200
- IL-4 (Interleukin 4), 200
 helper T cells and, 194
- IL-5 (Interleukin 5), 200
 helper T cells and, 194
- IL-6 (Interleukin 6), 200
 acute-phase reactants and, 198
 cachexia and, 232
 endotoxins and, 117
- IL-8 (Interleukin 8), 200
 neutrophils and, 378
- IL-10 (Interleukin 10), 200
 helper T cells and, 194
- IL-12 (Interleukin 12), 200
 natural killer cells, effect on, 193
- IL-12 (Interleukin 12) receptor
 deficiency, 208
- IL-13 (Interleukin 13), 194
- Ileum, 341
- Ileus, 362
- Illness anxiety disorder, 518
- Iloperidone, 525
- Iloprost, 627
- Imatinib, **412**
 for chronic myelogenous
 leukemia, 639
- IMG registration timeframe, 7
- Imipenem, 170, 173
 seizures caused by, 253
- Imipramine, 527
- Immature teratomas, 593
- Immune responses, 198–211
 passive vs. active, 203
- Immunocompromised patients
 acyclovir/famciclovir/valacyclovir
 for, 184
Candida albicans in, 137
 common organisms affecting, 162
Cryptococcus neoformans in, 137
Cryptosporidium in, 139
 ecthyma gangrenosum in, 127
 esophagitis in, 354
 fungal infections and, 169
- infections in, **210**
Listeria monocytogenes and, 123
Pneumocystis jirovecii in, 138
 squamous cell carcinomas
 and, 445
- Immunodeficiency syndromes, **208–209**
 flow cytometry diagnosis, 66
- Immunoglobulins
 adaptive immunity and, 192
 in breast milk, 581
 for Guillain-Barré syndrome, 493
 for Kawasaki disease, 296
 isotypes of, **197**
- Immunology, 190–214
 immune responses, 198–211
 immunosuppressants, 212–214
 lymphocytes, 192–197
 lymphoid structures, 190–191
- Immunomodulator signaling
 pathways, 316
- Immunophenotypes, assessing, 66
- Immunosuppressants, **212**
 for aplastic anemia, 391
 for lupus, 434
 for polymyositis/
 dermatomyositis, 436
 targets of, **213**
- Immunosuppression
 vitamin A deficiency as cause, 77
 vitamin C deficiency as cause, 80
- Impaired glucose tolerance.
See Insulin resistance
- Impetigo, 442
 skin crust in, 438
Streptococcus pyogenes as
 cause, 120
 sunburn and, 444
- Imprinting, in genetics, **69**
- Inactivated vaccines, 203
- Incidence vs. prevalence, **33**
- Incomplete penetrance, **68**
- Incorrect results, in statistical
 hypothesis testing, 38
- Incus bone, 481
 as branchial arch derivative, 569
- India ink stain, 110
- Indicator media, 110
- Indinavir, 184
 for HIV, 186
- Indirect inguinal hernias, 349
- Indomethacin, 447
 arachidonic acid pathway and, 446
 for diabetes insipidus, 328, 639
 for gout, 431, 448
 for patent ductus arteriosus
 (PDA), 640
 for PDA closure, 264
- Infarcts
 atherosclerosis as cause, 286
 calcification and, 220
 red vs. pale, **219**
 regions susceptible to, 218
 vascular dementia caused by, 491
- Infection control techniques, **187**
- Inferior colliculi, 477
- Inferior gluteal nerve, 422

- Inferior lobe, 609
- Inferior mesenteric artery, 342
in horseshoe kidney, 531
- Inferior mesenteric lymph nodes, 190
- Inferior mesenteric vein, 344
- Inferior oblique muscle, 488
- Inferior phrenic arteries, 342
- Inferior rectal artery, 345
- Inferior rectal vein, 344
- Inferior rectus muscle, 488
- Inferior sagittal sinus, 470
- Inferior vena cava, 339
in diaphragm, 609
gonadal drainage and, 573
- Infertility
clomiphene for, 601
cystic fibrosis as cause, 72
ectopic pregnancy and, 589
endometriosis as cause, 594
impaired sperm mobility as cause, 583
Kallmann syndrome as cause, 586
Kartagener syndrome as cause, 60, 633
Klinefelter syndrome as cause, 585
leuprolide for, 601
mumps as cause, 155
ovarian neoplasms and, 592
PCOS as cause, 591
salpingitis and, 167
septate uterus as cause, 572
treatments for, 640
varicoceles as cause, 597
- Infiltrative cardiomyopathy, 291
- Infiltrative lymphohistiocytosis, 209
- Inflammation, **219**
acute-phase reactants, 198
ESR in, 224
IL-1 as cause, 200
pathology of, 216–225
- Inflammatory bowel disease (IBD), **359**
AA amyloidosis and, 225
azathioprine for, 409
erythema nodosum and, 444
infliximab/adalimumab for, 448
methotrexate for, 409
sclerosing cholangitis and, 371
spondyloarthritis and, 433
therapeutic antibodies for, 214
- Inflammatory breast cancer, 596
- Inflammatory diseases,
Staphylococcus aureus as cause, 119
- Infliximab, 214, 448
for Crohn disease, 359, 639
for ulcerative colitis, 359, 641
- Influenza, **153**
as antigenic variation, 202
killed vaccine for, 146
live attenuated vaccine for, 146
as orthomyxovirus, 151
pneumonia caused by, 624
Reye syndrome and, 366
treatment/prevention of, 184
treatments for, 640
vaccine for, 203
- Informed consent, **40**
- Infraspinatus muscle, 417
in Erb palsy, 420
- Infundibulopelvic ligament, 574
anatomy of, 574
- Infundibulum, 477
- Ingested seafood toxins, **250**
- Inguinal canal, **348**
- Inguinal hernia, 349, 573
- Inguinal ligament, 347, 348
- Inguinal triangle, 349
- Inhalational general anesthetic, 255
- Inhalational injury, **222**
- Inhaled anesthetics, **502**
- Inheritance modes, **70**
- Inhibin
in cryptorchidism, 597
in Klinefelter syndrome, 585
Sertoli cell secretion of, 576
in spermatogenesis, 576
- Inhibin A
in Down syndrome, 74
in Edwards syndrome, 74
- Inhibitors of complement activation, 199
- Inhibitory pathway, 460
- Initiation of protein synthesis, 57
- Innate immunity, **192**
- Inositol trisphosphate (IP₃), 316
- Inotropes, 292
- Inotropy, 269
- Insomnia
AChE inhibitors as cause, 505
barbiturates for, 501
benzodiazepines for, 501
hyperthyroidism as cause, 321
marijuana withdrawal as cause, 523
nonbenzodiazepine hypnotics for, 501
stimulants as cause, 522
- Inspiration, effect on auscultation, 272
- Inspiratory capacity (IC), 610
- Inspiratory reserve volume (IRV), 610
- Insulin, **308**
anabolic effects of, 308
deficiency in, 330
for diabetes mellitus type 2, 639
for diabetes treatment, 334
for diabetic ketoacidosis, 331, 639
fructose biphosphatase-2 and, 87
GIP effect on, 350
glucagon and, 309
glycogen regulation and, **97**
for hyperosmolar hyperglycemia nonketotic syndrome, 332
hypokalemia caused by, 542
in pregnancy, 308
production of, 307
secretion of, 308
signaling pathways for, 316
somatostatin and, 350
somatostatinomas and, 332
sulfonylurea effect on, 334
- Insulin-like growth factor I (IGF-I)
in acromegaly, 327
in Laron syndrome, 327
signaling pathways for, 316
- Insulinomas, 308, **332**
MEN 1 syndrome as cause, 333
- Insulin resistance
acanthosis nigricans and, 444
acromegaly as cause, 327
cortisol as cause, 313
Cushing syndrome as cause, 317
in diabetes mellitus type 2, 331
GH as cause, 308, 311
glitazone/thiazolidinedione effect on, 334
metformin effect on, 334
in PCOS, 591
- Insurance
disregarding in treatment, 42
Medicare/Medicaid as, 44
- Integrase inhibitors, 186
- Integrins
in epithelial cells, 438
as receptor, 150
- Intellectual disabilities
in WAGR complex, 551
- Intellectual disability
autism and, 511
fetal alcohol syndrome as cause, 565
hydrocephalus as cause, 471
key associations, 643
Lesch-Nyhan syndrome as cause, 631
in Rett syndrome, 511
- Intellectualization, as ego defense, 509
- Intention tremor, 461
cerebellar hemisphere lesions and, 464
multiple sclerosis as cause, 492
- Intention tremors
multiple sclerosis as cause, 632
- Interactions, drug, **237**
- Intercostobrachial nerve, 419
- Interferon- α
myopathy caused by, 253
- Interferon- γ release assay (IGRA), 124
- Interferons, **187**, 201
focal segmental glomerulosclerosis and, 548
- Interlobar artery, 532
- Interlobular artery, 532
- Intermediate filaments
as cytoskeletal element, 60
immunohistochemical stains for, 60
- Internal auditory meatus, 478
- Internal capsule
intraparenchymal hemorrhage in, 469
stroke effects, 467
- Internal carotid artery
in cavernous sinus, 481
in circle of Willis, 466
- Internal hemorrhoids, 345
- Internal iliac arteries, 342
- Internal iliac artery, 264
- Internal iliac lymph nodes, 190
- Internal inguinal ring, 349
- Internal jugular vein, 470
- Internal oblique muscle, 348
- Internal spermatic fascia, 348
- International Foundations of Medicine (IFOM), 11
- Internuclear ophthalmoplegia, **490**, 631
multiple sclerosis as cause, 632
- Interosseal muscles, in Klumpke palsy, 420
- Intersex, 586
- Interstitial fluid, 281
- Interstitial lung disease, 430
- Interstitial nephritis
as drug reaction, 253
NSAID toxicity as cause, 447
penicillinase-resistant penicillins as cause, 171
- Interstitial pneumonia, 624
- Interstitial pulmonary fibrosis, 636
- Interstitiality, in leukocyte extravasation, 221
- Interventricular foramen, 263
- Intestinal obstruction
hernias as cause, 349
superior mesenteric artery syndrome as cause, 342
- Intestinal stomach cancer, 356
- Intestinal villi, 341
- Intracellular fluid (ICF), 533
- Intracellular organisms, **112**
- Intracellular receptors
as endocrine hormone messengers, 316
- Intracranial hemorrhage, **469**
eclampsia as cause, 590
- Intracranial pressure, 465
in hydrocephalus, 471
papilledema caused by, 486
superior vena cava syndrome and, 625
- Intraductal papillomas, 595
- Intraocular pressure in glaucoma, 484
- Intraparenchymal hemorrhage, 469
- Intrauterine device (IUD)
copper, 602
endometritis and, 594
- Intrauterine growth restriction (IUGR)
low birth weight caused by, 581
smoking as cause, 564
- Intravascular hemolysis, 391
- Intravenous anesthetics, **502**
- Intraventricular hemorrhage
low birth weight and, 581
neonatal respiratory distress syndrome as cause, 607
- Intrinsic factor, 351
location of, 351
- Intrinsic hemolytic anemia, **392**
- Intrinsic pathway, **216**
for coagulation, 383
coagulation defects of, 396
heparin and, 406
- Intrinsic renal failure, 553
- Introns, vs. exons, **55**

- Intrusive thoughts, 517
- Intussusception, **362**
Meckel diverticulum as cause, 361
presentation of, 633
- Inulin
extracellular volume and, 533
glomerular filtration rate and, 534
in proximal convoluted tubules, 539
- Invariant chain, 192
- Invasive carcinomas, 227
ductal, 596, 642
lobular, 596
- In vivo biofilm-producing bacteria, **113**
- Iodine
cretinism and, 642
deficiency in, 321, 322
as infection control technique, 187
teratogenic effects of, 564
thionamide effect on, 335
- Iodophors, as infection control techniques, 187
- Iodoquinol, 139
- Ipratropium, 245, 628
- Ipsilateral nucleus cuneatus, 473
- Irinotecan, **411**
in cell cycle, 408
targets of, 408
- Iris, 482
- Iritis, 484
- Iron
absorption of, 352
in anemia, 394
in anemia of chronic disease, 391
in hemochromatosis, 371
lab values in anemia, 394
metabolic acidosis caused by, 543
in sideroblastic anemia, 389
toxicity treatment for, 251
- Iron deficiency anemia, **388, 644**
in anemia taxonomy, 388
colorectal cancer as cause, 364
fibroid tumors as cause, 594
lab findings in, 636
Plummer-Vinson syndrome as cause, 354, 631
- Iron poisoning, **396**
- Irritable bowel syndrome (IBS), **360**
antispasmodic drugs for, 245
- Ischemia, **218, 614**
atherosclerosis as cause, 286
Fanconi syndrome caused by, 538
necrosis and, 217
vascular dementia caused by, 491
- Ischemic brain disease, **470**
- Ischemic heart disease, **287**
- Ischemic priapism, 597
- Ischemic stroke, **470**
- Ishikawa diagram, 46
- Islets of Langerhans, 307
- Isocarboxazid, 528
- Isocitrate dehydrogenase, 84
in metabolic pathways, 85
- Isodisomy, 69
- Isoflurane, 502
- Isolation of affect, as ego defense, 509
- Isoleucine, 92
maple syrup urine disease and, 95
- Isoniazid, **180**
cytochrome P-450 and, 254
hemolysis in G6PD deficiency caused by, 252
hepatitis caused by, 252
lupus-like syndrome caused by, 253
for *Mycobacterium tuberculosis*, 179, 640
as *Mycobacterium tuberculosis* prophylaxis, 179
seizures caused by, 253
sideroblastic anemia caused by, 389
- Isoproterenol, 246
vs. norepinephrine, **247**
- Isosorbide dinitrate, 299
- Isosorbide mononitrate, 299
- Isotretinoin
for cystic acne, 77
as teratogen, 564
- Isovolumetric contraction, 270
- Isovolumetric relaxation, 270
- Itraconazole, 181, 182
for *Sporothrix schenckii*, 138, 641
for systemic mycoses, 135
- IV drug use
common organisms, 162
osteomyelitis and, 163
- Ivermectin, 183
- IV phlebitis, caused by amphotericin B, 182
- Ixodes* ticks, 130
as disease vectors, 132, 141
- J**
- JAK2 gene, 230
in myeloproliferative disorders, 404
- Janeway lesions, 633
bacterial endocarditis as cause, 293
- Jarisch-Herxheimer reaction, **131, 631**
- Jaundice, **369**
ABO hemolytic disease of the newborn as cause, 382
alcoholic cirrhosis as cause, 367
biliary tract disease as cause, 371
cholangitis as cause, 372
cirrhosis as cause, 365
Courvoisier sign and, 632
Crigler-Najjar syndrome as cause, 633
as drug reaction, 252
fructose intolerance as cause, 91
galactosemia as cause, 91
graft-versus-host disease as cause, 211
hepatitis B as cause, 167
hepatocellular carcinoma as cause, 368
hereditary hyperbilirubinemias as cause, 370
key associations, 643
leptospirosis as cause, 130
pancreatic cancer as cause, 373, 633
- ToRCHeS infections as cause, 165
yellow fever as cause, 152
- Jaw jerk reflex, 479
- JC virus (John Cunningham virus)
HIV and, 160
polyomaviruses as cause, 148
progressive multifocal leukoencephalopathy and, 493
- JC virus (John Cunningham Virus)
in immunocompromised patients, 210
- Jejunum, 341
- Jervell and Lange-Nielsen syndrome, 277
- Jimson weed, 245
- Jod-Basedow phenomenon, 323. *See also* Wolff-Chaikoff effect
- JONES criteria for acute rheumatic fever, 120
- J point, in ECG, 276
- Jugular foramen, 470, 478
- Jugular venous distention (JVD), 292, 613
superior vena cava syndrome as cause, 625
- Jugular venous pulse, 270
- Justice, as ethical principle, 39
- Juvenile idiopathic arthritis, 484
- Juvenile polyposis, 363
- Juxtaglomerular apparatus, **540**
- Juxtaglomerular cells, 532
in filtration, 535
in juxtaglomerular apparatus, 540
renin secreted by, 540
tumors in, 318
- K**
- Kallikrein
C1 esterase inhibitor deficiency and, 199
neutrophils and, 378
- Kallmann syndrome, **586, 644**
- Kaposi sarcoma, 441
AIDS and, 167
vs. bacillary angiomatosis, 441
HHV-8 as cause, 149
HIV and, 160
IFN- α for, 187
oncogenic microbes and, 231
presentation of, 631
recombinant cytokines for, 213
- Kartagener syndrome, 60, 262
bronchiectasis and, 618
infertility caused by, 583
presentation of, 633
- Karyolysis, 218
- Karyorhexis, 218
- Karyotyping, **67**
- Kawasaki disease, **296**
presentation of, 630, 634
treatments for, 640
- Kayser-Fleischer rings, 631
Wilson disease as cause, 371
- K cells, 350
- Kegel exercises, 551
- Keloid scars, 222
- Keratinocytes
in sunburn, 444
in wound healing, 223
- Keratin pearls, 636
in lung cancer, 626
- Keratoacanthomas, 445
- Keratoconjunctivitis, 149
- Keratoconjunctivitis sicca, 432
- Keratomalacia, 77
- Kernicterus, 177, 187
- Kernohan notch, 498
- Ketamine, 502
- Ketoconazole, 181, 182, 603
cytochrome P-450 and, 254
gynecomastia caused by, 595
for PCOS, 591
reproductive hormones and, 600
- Ketogenesis
in diabetic ketoacidosis, 331
diagram of, 85
in insulin deficiency, 330
location of in cell, 83
rate-determining enzyme for, 84
- Ketone bodies, **102**
- Ketonemia, 330
- Ketones, 309
- Ketorolac, 330
- Ketorolac, 447
arachidonic acid pathway and, 446
- Kidney disease
anemia of chronic disease and, 391
hypertension as cause, 284
- Kidney endocrine functions, **541**
- Kidneys
autoregulation of, 280
embryologic derivatives of, 563
embryology of, **530**
in gastrointestinal anatomy, 339
hormones acting on, **541**
ischemia in, 218
sclerosis of, 437
solitary functioning, 531
- Kidney stones, **549**
Crohn disease as cause, 359
hematuria caused by, 544
horseshoe kidney and, 531
hydronephrosis caused by, 550
hypercalcemia as cause, 542
hyperparathyroidism as cause, 326
hyperphosphatemia as cause, 542
key associations, 644
postrenal azotemia caused by, 553
UTIs and, 164
- Kiesselbach plexus, 616
- Killed vaccines, 146
- Killian triangle, 361
- Kimmelstiel-Wilson nodules, 637
diabetes mellitus as cause, 330
in diabetic glomerulonephropathy, 548
- Kinases, 84
- Kinesin, 60
- Kingella* spp., 293
- Kinin cascade, 383
- Kinin pathways, **383**
- Kissing bug, as disease vector, 142

- Klebsiella* spp., **128**
 alcoholism and, 162
 currant jelly sputum caused by, 169
 in Gram-negative algorithm, 125
 kidney stones caused by, 549
 lactose fermentation by, 126
 morphology of, 109
 as nosocomial infection, 168
 pneumonia caused by, 624
 as urease-positive organism, 112
 urinary tract infections caused by, 552
- Klebsiella pneumoniae*
 cephalosporins for, 172
 as encapsulated bacteria, 112
 in immunodeficient patients, 210
 presentation of, 633
 splenic dysfunction and, 191
 UTIs caused by, 164
- Klinefelter syndrome, 585
 chromosome associated with, 75
 gynecomastia caused by, 595
 testicular tumors and, 598
- Klumpke palsy, 420
- Klüver-Bucy syndrome, 464, 632
- Knee pain, from “unhappy triad,” 417
- Knees
 common conditions of, **417**
 examination of, **416**
- Knock out genes/Knock in genes, 68
- Koilocytes, 635
 condylomata acuminata as cause, 167
- Koilocytosis, 440
- Koplik spots, 154, 166, 634
- Korsakoff psychosis, 523
- Korsakoff syndrome, 512
- Krabbe disease, 100, 493
- KRAS gene, 230
 adenomatous colonic polyps and, 363
 colorectal cancer and, 364
 lung cancer and, 626
- Krukenberg tumors, 356, 593, 642
- K_m , 236
- Kulchitsky cells, 319, 626
- Kupffer cells, 346
- Kuru, 161
- Kussmaul respirations
 diabetic ketoacidosis as cause, 331
 presentation of, 631
- Kussmaul sign, **295**
- Kwashiorkor, **82**
- Kyphoscoliosis, 475
- Kyphosis, 96
- L**
- Labetalol, 249
 for gestational hypertension, 298, 590
 for hypertensive emergency, 298
- Labia, 574
 male homolog of, 572
- Labile cells, 58
- Laboratory techniques, 64–68
- Lachman test, 416
- Lac operons, **52**
- Lacrimation reflex, 479
- Lactase deficiency, **92**
- Lactation, **581**. *See also* Breast milk
 dopamine and, 310
 oxytocin for, 336
 progesterone and, 577
 prolactin and, 310
 Sheehan syndrome and, 329, 632
- Lactational mastitis, 595
- Lactic acid dehydrogenase, 88
- Lactic acidosis
 ethanol metabolism and, 83
 exercise and, 615
 in MELAS syndrome, 70
 metabolic acidosis caused by, 543
 metformin as cause, 334
 pyruvate dehydrogenase complex deficiency as cause, 88
- Lactiferous sinus, diseases of, 595
- Lactobacillus* spp.
 morphology of, 109
 as normal flora, 161
- Lactoferrin
 in neutrophils, 378
 in respiratory burst, 201
- Lactose-fermenting enteric organisms, **126**
 culture requirements for, 111
- Lactose intolerance, 358
- Lactose metabolism, 52
- Lactotroph hyperplasia, 496
- Lactulose, 375
 for hepatic encephalopathy, 367
 for hyperammonemia, 93
- Lambert-Eaton myasthenic syndrome, **436**
 autoantibody associated with, 207
 as paraneoplastic syndrome, 229
 small cell lung cancer as cause, 626
- Lamina propria, 341
 Peyer patches in, 352
 in Whipple disease, 358
- Lamins, 60
- Lamivudine, 184
 for HIV, 186
- Lamotrigine
 for epilepsy, 500
 rash caused by, 253
- Landmark dermatomes, **476**
- Langerhans cell histiocytosis, **403**
- Langerhans cells, 380
 Birbeck granules in, 638
- Language development, 43
- Lanosterol synthesis, 181
- Lansoprazole, 374
- Lanugo, in anorexia nervosa, 520
- Laplace law, 267, 607
- Large cell carcinomas of lungs, 626
- Laron syndrome, **327**
- Larva migrans, 143
- Larynx, 608
- Larynx muscles, 569
- Lassa fever encephalitis, 151
- Latanoprost, 498
- Latent errors, 46
- Lateral collateral ligament (LCL)
 injury, 416
- Lateral corticospinal tract, 472, 473
 stroke effects, 467
- Lateral epicondylitis, 417
- Lateral femoral circumflex artery, 427
- Lateral fold closure defects, 338
- Lateral geniculate nucleus (LGN), 458
- Lateral lesions of cerebellum, 459
- Lateral medullary syndrome, 467
- Lateral pterygoid muscle, 569
- Lateral rectus muscle, 488
- Lateral thoracic artery, 423
- Lateral ventricles, in herniation syndromes, 498
- Laxatives, 375
- LDH, exudate vs. transudate, 224
- LDL (low-density lipoprotein), 105
- Lead paralysis, 515
- “Lead pipe” appearance of colon, 636
- Lead poisoning, 389, **395**
 acute tubular necrosis caused by, 554
 in anemia taxonomy, 388
 basophilic stippling in, 386
 Fanconi syndrome caused by, 538
 lab findings in, 635, 636
 presentation of, 630
 sideroblastic anemia caused by, 389
 treatment for, 251
- Lead-time bias, in studies, 36
- Lecithins, in pulmonary surfactant, 607
- Lectin pathway of complement activation, 199
- Ledipasvir, 187
- Leflunomide, **447**
 pyrimidine synthesis and, 49
 for rheumatoid arthritis, 430
- Left anterior descending artery, 265
 myocardial infarction and, 288
- Left anterior division, 276
- Left bundle branch, 276
- Left bundle branch block, 271
- Left circumflex coronary artery, 265
- Left common iliac artery, 342
- Left gastroepiploic artery, 343
- Left hemianopia with macular sparing, 489
- Left heart disease, 622
- Left horn of sinus venosus, 262
- Left lower quadrant hemiopia, 489
- Left main coronary artery, 265
- Left marginal artery, 265
- Left posterior division, 276
- Left recurrent laryngeal nerve, 568
- Left shift, **394**
- Left-to-right shunts, 283
- Legg-Calvé-Perthes disease, 427
- Legionella* spp.
 as atypical organism, 162
 culture requirements for, 111
 as intracellular organism, 112
 macrolides for, 176
 morphology of, 109
 as nosocomial infection, 168
 pneumonia caused by, 624
 silver stain for, 110
- Legionella pneumophila*, **127**, 640
- Legionnaires’ disease, 127
- Leiomyomas, 594, 645
 nomenclature for, 228
 polycythemia and, 229
- Leiomyosarcomas, 228
- Leishmania donovani*, **142**
- Leishmaniasis, 142
 sodium stibogluconate for, 183
- Lens, 482
 collagen in, 61
 subluxation of, 96
- Lenticulostriate artery, 467
- Lentiform, 460
- Leonine facies, in Hansen disease, 125
- Lepromatous Hansen disease, 125
- Leptin, 311
 hypothalamus and, 456
- Leptospira* spp.
 animal transmission of, 132
 as spirochete, 130
- Leptospira interrogans*, **130**
- Leptospirosis, 130
 animal transmission of, 132
- Lesch-Nyhan syndrome, **50**
 gout and, 431
 lab findings in, 636
 presentation of, 631
 as X-linked recessive disorder, 72
- Leser-Trélat sign, 229, 440
 stomach cancer as cause, 356
- Lesser sac, 340
- Lethal median dose, 240
- Letrozole, 601
- Leucine, 92
 maple syrup urine disease and, 95
- Leucovorin, 409
- Leukemias, **402**
 allopurinol for, 448
 aplastic anemia and, 391
 carcinogens causing, 231
 cyclophosphamide for, 410
 cytarabine for, 409
 doxorubicin for, 410
 etoposide/teniposide for, 411
 vs. lymphomas, **399**
 mucormycosis and, 137
 nomenclature for, 228
 vinca alkaloids for, 411
- Leukocyte adhesion deficiency, 209, 221
- Leukocyte alkaline phosphatase (LAP), 378
- Leukocyte esterase, 164, 552
- Leukocyte extravasation, **221**
- Leukocytes, **378**
 extravasation of, 221
 in leukemias, 402
 in myeloproliferative disorders, 404
 in urine, 164, 544, 552
- Leukocytosis
Clostridium difficile as cause, 168, 630
 in diabetic ketoacidosis, 331
- Leukodystrophies, 493
- oligodendroglia in, 454

- Leukopenia, **394**
 azathioprine as cause, 212
 cytarabine as cause, 409
 ganciclovir as cause, 185
 sirolimus as cause, 212
 trimethoprim as cause, 177
- Leukoplakia, **442**
- Leukotriene receptor antagonists, **446**
- Leukotrienes
 arachidonic acid pathway and, **446**
 basophils and, 379
 cortisol effect on, 313
 synthesis of, **446**
- Leuprolide, **601, 640**
- Levator veli palatini muscle, **569**
- Levetiracetam
 for epilepsy, 500
 for tonic-clonic seizures, 641
- Levodopa, **504, 505**
- Levofloxacin, 170, 178
 for *Pseudomonas aeruginosa*, 127
- Levomilnacipran, 527
- Levonorgestrel, 602
- Levothyroxine, **335**. *See also* Thyroid hormones
- Lewy bodies, **636**
 in Parkinson disease, 461
- Lewy body dementia, 491, 513
- Leydig cells, 571, 576
- Leydig cell tumors, 598
- LFA-I antigens, 221
- LH. *See* Luteinizing hormone (LH)
- Libido
 in geriatric patients, 44
 testosterone and, 582
- Libman-Sacks endocarditis, 434
- Lice, **145**
 as disease vectors, 132, 133
 treatment for, **183**
- Lichen planus, 444
 hypergranulosis and, 439
 presentation of, 633
- Liddle syndrome, **538**
 markers in, 542
- Lidocaine, 302, 503
 for arrhythmia, 638
- Li-Fraumeni syndrome
 autosomal dominance of, 71
 osteosarcomas and, 429
 tumor suppressor genes and, 230
- Ligaments, gastrointestinal, **340**
- Ligamentum arteriosum, 264
- Ligamentum teres hepatis, 264, 340
- Ligamentum venosum, 264
- Ligand receptors, 216
- Limbic system, **458**
- Limit dextrin, 98
- Limited scleroderma, 437
- Linagliptin, 335
- Lindane, 183
- Linea alba, 348
- Linear ulcers, in esophagitis, 354
- Linear viruses, 147
- Lines of Zahn, 617, 638
- Lineweaver-Burk plot, 236
- Linezolid, 170, 174, 176
 for MRSA, 181
 for *Staphylococcus aureus*, 641
 for VRE, 181
- Linkage disequilibrium, 68
- Lipase
 as pancreatic secretions, 352
 in pancreatitis, 373
- Lipid-lowering agents, **300**
- Lipids
 metabolism of, 85
 transport of, **104**
 in viruses, 146
- Lipodystrophy
 insulin as cause, 334
 protease inhibitors as cause, 186
 tesamorelin for, 309
- Lipofuscin, **225**
- Lipoic acid, 87
- Lipoid nephrosis, 548
- Lipolysis
 cortisol and, 313
 glucagon and, 309
 insulin and, 308
 in insulin deficiency, 330
 niacin and, 300
 sympathetic receptors and, 242
 thyroid hormones and, 315
- Lipomas, 228
- Lipoprotein lipase, 104
- Lipoproteins, **105**
- Liposarcomas, 228
- Lipoteichoic acid, 108
- Liquefactive necrosis, 217
 calcification and, 220
- Liraglutide, 335
- Lisch nodules
 causes of, 630
 neurofibromatosis type 1 as
 cause, 71, 495
- Lisinopril, 559
- Lispro insulin, 334. *See also* Insulin
- Listeria* spp.
 as catalase-positive organism, 112
 chronic granulomatous disease
 and, 209
 in Gram-positive algorithm, 118
 as intracellular organism, 112
 meningitis caused by, 163
 morphology of, 109
- Listeria monocytogenes*, **123**
 β -hemolytic nature of, 119
 granulomatous diseases caused
 by, 223
 in neonates, 165
 penicillinase-sensitive penicillins
 for, 171
- Lithium, **526**
 for bipolar disorder, 515, 524, 638
 cardiac defects associated with in
 utero exposure, 284
 diabetes insipidus caused by, 253,
 328
 Ebstein anomaly caused by, 282
 hypothyroidism caused by, 252, 322
 as teratogen, 564
 therapeutic index value of, 240
- Live attenuated vaccines, 146, 203
- Livedo reticularis, 504
- Liver
 blood supply and innervation
 of, 342
 in gastrointestinal anatomy, 340
 ischemia in, 218
 lipid transport and, 104
 as metastasis site, 233
 tissue architecture, **346**
- Liver disease
 acanthocytes in, 386
 alcoholic, 367
 anemia caused by, 390
 in anemia taxonomy, 388
 cystic fibrosis as cause, 72
 echinocytes in, 386
 key associations, 644
 loading and maintenance dose
 in, 237
 target cells in, 387
- Liver failure
 Budd-Chiari syndrome and, 368
 myoclonus in, 461
 Wilson disease as cause, 371
- Liver fluke
 hyperbilirubinemia caused by, 369
 as oncogenic microbe, 231
- Liver pathology serum markers, **366**
- Liver tumors, **368**
- Living wills, 41
- LMN facial nerve palsy, 634
- Loading dose, 237, 646
- Loa loa*, 143
 infection routes, 142
- Lobar pneumonia, 622, 624
- Lobular carcinomas, 595
- Local anesthetics, **503**
 naming convention for, 255
- Locked-in syndrome
 basilar artery lesions as cause, 467
 osmotic demyelination syndrome
 as cause, 492
- Lockjaw
Clostridium tetani as cause, 122
 tetanospasmin as cause, 116
- Locus heterogeneity, **69**
- Löffler medium, 111
- Löffler syndrome, 291
- Lomustine, 410
 in cell cycle, 408
- Lone Star tick, as disease vector, 132
- Long QT syndrome
 ranolazine as cause, 299
 sudden cardiac death caused
 by, 287
- Loop diuretics, **557**
 for heart failure, 292
 lab findings in, 636
 metabolic alkalosis caused by, 543
 site of action, 556
 toxicity caused by, 254
- Loop of Henle, 556
- Loperamide, **376, 499**
- Lopinavir, 184
 for HIV, 186
- Loratadine, 627
- Lorazepam, 501
 for alcohol withdrawal, 524
- Losartan, 559
- Lovastatin, 300
- Low birth weight, **581**
- Löwenstein-Jensen agar, 111
- Lower esophageal sphincter
 achalasia and, 354
 in Barrett esophagus, 355
- Lower extremity nerves, **422**
- Lower left quadrant (LLQ) pain, 360
- Lower motor neuron (LMN)
 lesions, 480, 632
 in Brown-Séquard syndrome, 475
 poliomyelitis and, 475
- LPS, and endotoxins, 117
- LSD (lysergic acid diethylamide), 523
- LTB₄ (Leukotriene B₄), 378, 446
- Lumbar puncture
 location of, 472
 for pseudotumor cerebri, 471
- Lumbosacral radiculopathy, **423**
- Lumbrical muscles, 421
 Klumpke palsy and, 420
- Lumefantrine, 183
- “Lumpy bumpy” glomeruli, 637
- Lunate bone, 418
- Lung abscesses, **624**
- Lung and chest wall, **611**
- Lung cancer, **626**
 asbestosis and, 620
 bone metastases in, 644
 brain metastases in, 644
 carcinogens causing, 231
 cisplatin/carboplatin for, 411
 Cushing syndrome and, 229
 eriotinib for, 412
 hypercalcemia and, 229
 incidence/mortality of, 228
 metastases of, 233
 neuromuscular paraneoplastic
 syndromes and, 229
 oncogenes and, 230
 topotecan for, 411
- Lung diseases
 obstructive, **618**
 restrictive, **619**
- Lungs
 autoregulation of, 280
 congenital malformations of, **606**
 development of, **606**
 physical findings, **622**
 relations between, **609**
 sclerosis of, 437
- Lung volumes, **610**
- Lupus, **434**
 acute interstitial nephritis caused
 by, 554
 anemia of chronic disease and, 391
 antiphospholipid syndrome
 and, 434
 autoantibody associated with, 207
 autoimmune hemolytic anemia
 and, 393
 azathioprine for, 409
 bacterial endocarditis caused
 by, 293
 death caused by, 642
 DPGN caused by, 546

- HLA-DR2 and, 193
 HLA-DR3 and, 193, 643
 isoniazid as cause, 180
 key associations, 642
 lab findings in, 634, 635
 lymphopenia caused by, 394
 membranous nephropathy and, 548
 microangiopathic anemia caused by, 393
 neutropenia caused by, 394
 presentation of, 630
 Raynaud phenomenon and, 437
- Lupus-like syndrome
alpha-methyl dopa for, 247
 as drug reaction, 253
 hydralazine as cause, 298
 procainamide as cause, 302
- Lupus nephritis, 434
 Lupus nephropathy, 642
 Lupus pernio, 435
 Lurasidone, 525
 Luteal phase of menstrual cycle, 579
 Luteinizing hormone (LH)
 in androgen insensitivity syndrome, 586
 clomiphene effect on, 601
 in cryptorchidism, 597
 in Kallmann syndrome, 586
 in Klinefelter syndrome, 585
 in menopause, 582
 in ovulation, 310, 578
 in PCOS, 591
 pharmacologic control of, 600
 in premature ovarian failure, 591
 progesterone and, 577
 secretion of, 307
 signaling pathways of, 316
 in spermatogenesis, 310, 576
 in Turner syndrome, 585
- Lyme disease, **130**
 animal transmission of, 132
 AV block caused by, 278
 ceftriaxone for, 172
 facial nerve palsy caused by, 480
 presentation of, 632
- Lymphadenopathy
 follicular lymphoma as cause, 400
 Ghon complex and, 636
 mononucleosis as cause, 149
 mycosis fungoides as cause, 631
 rubella as cause, 153, 165
 serum sickness as cause, 205
 syphilis as cause, 131, 167
 tinea capitis and, 136
- Lymphatic ducts, 190
 Lymphatic gonadal drainage, 573
 Lymphatic pleural effusion, 623
 Lymph drainage, **190**
 Lymphedema, 585, 634
 Lymph nodes, **190**
 absent, in X-linked agammaglobulinemia, 208
 T cell differentiation in, 194
 Lymphocyte casts in urine, 638
 Lymphocytes, 192–197, 378, **380**
 in breast milk, 581
 corticosteroid effect on, 394
 in lymph node, 190
 in spleen, 191
 in thymus, 191
- Lymphocytic choriomeningitis virus (LCMV), 151
 Lymphocytosis, 191
 Lymphogranuloma venereum, 134
 as STI, 167
 Lymphohistiocytosis, 209
 Lymphoid hyperplasia, 360
 Lymphoid structures, 190–191
 Lymphomas
 allopurinol for, 448
 carcinogens causing, 231
 celiac disease and, 358
 cyclophosphamide for, 410
 cytarabine for, 409
 doxorubicin for, 410
 EBV and, 149
 etoposide/teniposide for, 411
 hypercalcemia and, 229
 vs. leukemias, **399**
 methotrexate for, 409
 minimal change disease and, 548
 nomenclature for, 228
 non-Hodgkin, 400
 oncogenic microbes and, 231
 presentation of, 631
 of stomach, 356
 of thyroid, 324
- Lymphopenias, 394
 ataxia-telangiectasia as cause, 209
 corticosteroid effect on, 394
- Lynch syndrome, 363
 endometrial cancer and, 594
 mismatch repair and, 53
 ovarian neoplasms and, 592
- Lysine, 92
 in cystinuria, 96
 kidney stones and, 549
 for pyruvate dehydrogenase complex deficiency, 88
- Lysosomal α -1,4-glucosidase, 99
 Lysosomal storage diseases, 59, **100**, 644
 Lysosome rupture, 218
 Lysozyme
 innate immunity and, 192
 in neutrophils, 378
- LYST* gene, 209
 Lysyl oxidase, 63
 Lytic bone lesions
 adult T-cell lymphoma as cause, 400
 Langerhans cell histiocytosis as cause, 403
 multiple myeloma and, 401, 637
- M**
 MacConkey agar, 110, 111
 lactose-fermenting enteric bacteria on, 126
 Macroangiopathic anemia, 388, 393
 Macrocytic anemia, 388, **390**
 Macroglossia, 551
 Macrolides, 170, **176**
 cytochrome P-450 and, 254
 hypertrophic pyloric stenosis and, 339
 for *Legionella pneumophila*, 127, 640
 for *Mycoplasma pneumoniae*, 134
 naming convention for, 255
 as protein synthesis inhibitors, 174
 torsades de pointes caused by, 251
- Macroorchidism, 73
 Macro-ovalocytes, 386
 Macrophages, **379**
 in alveoli, 608
 apoptosis and, 216
 bilirubin and, 353
 binding of, 196
 in breast milk, 581
 cell surface proteins, 202
 in chronic inflammation, 219
 cytokines secreted by, 200
 endotoxins/lipopolysaccharide, effect on, 202
 innate immunity and, 192
 in lymph node, 190
 in MI, 288
 necrosis and, 217
 in silicosis, 620
 in spleen, 191
 in wound healing, 223
- Macrosomia, caused by maternal diabetes, 564
 Macula, cherry-red spot on, 100, 486, 630, 632
 Macula densa, 532
 in filtration, 535
 in juxtaglomerular apparatus, 540
 Macular degeneration, **485**
 Macules, 438
 Maculopapular rash
 graft-versus-host disease as cause, 211
 syphilis as cause, 131
- Magnesium
 amphotericin B and, 182
 as antiarrhythmic drug, 304
 for cardiac glycoside toxicity, 301
 decrease, causes of, 314
 proton pump inhibitor effect on, 374
 PTH and, 314
 in renal disorders, 542
 torsades de pointes and, 277
- Magnesium citrate, 375
 Magnesium hydroxide, 375
 Magnesium sulfate
 for eclampsia, 590
 for preeclampsia, 590
 for torsades de pointes, 277
- Maintenance dose, 237, 646
 Maintenance stage of overcoming addiction, 521
 Major basic protein (MBP), 379
 Major depressive disorder, 514, **515**
 tricyclic antidepressants for, 527
 Major ducts (breast), 595
 Malabsorption syndromes, **358**, 359
 fat-soluble vitamin deficiencies caused by, 76
 osteoporosis and, 426
- Malaria
 anemia caused by, 393
 artesunate for, 183
Plasmodium as cause, 141
 quinidine/quinine for, 183
 treatments for, 640
- Malassezia* spp., 136
 Malathion, 183
 Male genital embryology, 571
 Male reproductive anatomy, **575**
 Male sexual response, 575
 Maleylacetoacetic acid, 95
 Malformation, in organogenesis, 563
 Malignancy, 644
 Malignant hypertension
 microangiopathic anemia caused by, 393
 RBC casts in, 544
 Malignant hyperthermia, 502
 dantrolene for, 503
 succinylcholine as cause, 503
 treatments for, 640
- Malignant melanomas
 IFN- α for, 187
 recombinant cytokines for, 213
- Malignant mesotheliomas, 232
 Malignant tumors, 228
 Malingering, **518**
 Malleus bone, 481, 569
 Mallory bodies, 636
 in alcoholic hepatitis, 367
 Mallory-Weiss syndrome, 354, 523, 634
- Malnutrition, **82**
 superior mesenteric artery syndrome and, 342
 wet beriberi as cause, 631
- Malrotation, **361**
 Maltese cross appearance of babesiosis, 141
 “Maltese cross” sign, 544
 MALT lymphomas
Helicobacter pylori as cause, 130, 356
 oncogenic microbes and, 231
 Sjögren syndrome as cause, 432
- Mammary gland cysts, 637
 Mammary glands, 563
 Mammillary bodies, 458, 477
 in Korsakoff syndrome, 512
 lesions in, 464
 in Wernicke-Korsakoff syndrome, 523
- Mammillary body atrophy, 641
 Mandibular process, 569
 Mango flies, as disease vectors, 143
 Manic episodes, **514**
 Mannitol, **557**
 extracellular volume and, 533
 site of action, 556
- Mantle cell lymphomas, 400
 chromosomal translocations and, 403
- Mantle zone
 in lymph node, 190
 in spleen, 191
- MAO inhibitors, **528**
 for atypical depression, 515
 mechanism of, 526
 in Parkinson disease, 504

- MAO inhibitors (*continued*)
 for phobias, 517
 selegiline/rasagiline as, 505
 serotonin syndrome caused by, 527
 tyramine and, 243
- Maple syrup urine disease, **95**
- Marantic endocarditis, 642
- Marasmus, **82**
- Maraviroc, 184, 186
- Marburg hemorrhagic fever, 151
- Marcus Gunn pupils, **487**
 multiple sclerosis as cause, 492
- Marfanoid habitus
 homocystinuria as cause, 96
 MEN 2B syndrome and, 333
- Marfan syndrome
 aortic aneurysms and, 641
 aortic dissection and, 287
 autosomal dominance of, 71
 cardiac defects associated with, 284
 cataracts and, 483
 chromosome associated with, 75
 elastin and, 64
 heart murmur caused by, 273
 presentation of, 630
 thoracic aortic aneurysms and, 286
- Marijuana
 intoxication and withdrawal, 523
 schizophrenia and, 514
- Masseter muscle, 569
- Massive hepatic necrosis, 252
- Mast cells, **379**
 IgE antibody and, 197
- Mastectomy, as cause of winged scapula, 420
- Mastication muscles, **480**
- Mastitis, 595
- Mastoid air cells, 570
- Mastoiditis
 brain abscesses caused by, 163
 Wegener granulomatosis as cause, 296
- Maternal-fetal blood barrier of placenta, 455
- Maternal PKU, 95
- Mature cystic teratomas, 592
- Maturity-onset diabetes of the young (MODY), 86
- Maxillary artery, 568
- Maxillary process, 569
- Mayer-Rokitansky-Küster-Hauser syndrome, 571
- McArdle disease, 99, 631
- McBurney point, 360
- McBurney sign, 633
- McCune-Albright syndrome, 69, 630
- McMurray test, 416
- MDMA (ecstasy) intoxication and withdrawal, 523
- Mean arterial pressure, 266, 465, 647
- Mean, in statistical distribution, 37
- Measles, **154, 166**
 as paramyxovirus, 151
 paramyxoviruses as cause, 153
 presentation of, 631
 in unvaccinated children, 169
 vaccine for, 203
 vitamin A for, 77
- Measurement bias in studies, 36
- Mebendazole, 183
- microtubules and, 60
- “Mechanic’s hands” in dermatomyositis, 436
- Meckel diverticulum, **361, 567**
- Meconium ileus, 362
 cystic fibrosis as cause, 72
- Medial antebrachial cutaneous nerve, 419
- Medial brachial cutaneous nerve, 419
- Medial calcific sclerosis, 285
- Medial collateral ligament (MCL) injury
 abnormal passive abduction in, 416
 in “unhappy triad,” 417
- Medial epicondylitis, 417
- Medial femoral circumflex artery, 427
- Medial geniculate nucleus (MGN), 458
- Medial hypertrophy, in pulmonary hypertension, 622
- Medial lemniscus, 467
- Medial lesions of cerebellum, 459
- Medial longitudinal fasciculus, 490
- Medial medullary syndrome, 467
- Medial meniscal tear, 417
- Medial pterygoid muscle, 569
- Medial rectus muscle, 488
- Medial umbilical ligament, 264, 348
- Median, 37
- Median claw, 421
- Median nerve, 419
 in carpal tunnel syndrome, 418
 injury to, 421
- Median umbilical ligament, 348, 532
- Mediastinal lymph nodes, 190
- Mediastinitis, 121
- Medical abortion
 as ethical situation, 42
 methotrexate for, 409
 treatments for, 640
- Medical errors, **46**
- Medical power of attorney, 41
- Medicare/Medicaid, **44**
- Medium-chain acyl-CoA dehydrogenase deficiency, **101**
- Medroxyprogesterone, 602
- Medulla
 brain, 450
 lymph node, 190
 thymus, 194
- Medullary carcinomas, 596
- Medullary cords, lymph node, 190
- Medullary cystic disease, 555
- Medullary pyramids, 477, 532
- Medullary thyroid carcinomas, 324
 MEN 2A as cause, 333
 MEN 2B syndrome as cause, 333
 oncogenes and, 230
- Medulloblastomas, 497, 642, 644
- Mefloquine, 141, 640
- Megacolon
 Chagas disease as cause, 142
 in Hirschsprung disease, 361
- Megakaryocytes, in essential thrombocytemia, 404
- Megaloblastic anemia, 388, 390
 cytarabine as cause, 409
Diphyllobothrium latum as cause, 144
 as drug reaction, 252
 epilepsy drugs causing, 500
 lab findings in, 636
 macro-ovalocytes in, 386
 orotic aciduria as cause, 390
 trimethoprim as cause, 177
 tropical sprue as cause, 358
 vitamin B₁₂ deficiency as cause, 80
 vitamin B₉ deficiency as cause, 79
- Megestrol, 602
- Meglitinides, 335
- Meigs syndrome, 592
- Meissner corpuscles, 454
- Melanocytes
 embryologic derivatives of, 563
 tumor nomenclature in, 228
 in vitiligo, 439
- Melanocyte-stimulating hormone (MSH)
 secretion of, 307
 signaling pathways of, 316
- Melanocytic nevus, 440
- Melanomas
 brain metastases in, 644
 hydroxyurea for, 411
 nomenclature for, 228
 oncogenes and, 230
 of skin, 445
 sunburn and, 444
 tumor suppressor genes and, 230
- Melarsoprol, 183
 for *Trypanosoma brucei*, 140
- Melasma, 439
- MELAS syndrome, 70
- Melatonin
 circadian rhythm and, 457
 as derivative, 94
 for *Trypanosoma brucei*, 140
- Melena
 Meckel diverticulum as cause, 361, 567
 polyarteritis nodosa as cause, 296
- Meloxicam, 447
- Memantine, 505
- Membrane attack complex (MAC), 196
 complement and, 199
 in type II hypersensitivity reactions, 204
- Membranoproliferative glomerulonephritis (MPGN), 547
 DPGN caused by, 546
 lab findings in, 638
- Membranous glomerular disorders, 544
- Membranous interventricular septum, 263
- Membranous nephropathy, 548, 638
- Membranous ossification, 425
- Membranous ventricular septum, 263
- Memory loss, in Wernicke-Korsakoff syndrome, 77, 464, 523
- MEN1 gene, 230
 multiple endocrine neoplasias and, 71
- Ménétrier disease, **356**
- Ménière disease
 presentation of, 631
 vertigo caused by, 495
- Menin, 230
- Meningiomas, 496, 642
 lab findings in, 637
 neurofibromatosis type 2 as cause, 71
- Psammoma bodies in, 232
- Meningitis
 ceftriaxone for, 172
 cerebrospinal fluid (CSF) findings in, 163
 chloramphenicol for, 175
 coccidioidomycosis as cause, 135
 common causes of, 163
Cryptococcus neoformans as cause, 137
 fluconazole for, 182
 flucytosine for, 182
Haemophilus influenzae as cause, 126
 headaches caused by, 494
 HIV and, 160
Listeria monocytogenes as cause, 123
 meningococci as cause, 126
 mumps as cause, 155
 in neonates, 165
 rifamycins as prophylaxis for, 179
Streptococcus pneumoniae as cause, 120
Streptococcus agalactiae as cause, 121
 tuberculosis and, 124
 in unvaccinated children, 169
- Meningocele, 451
- Meningococcal prophylaxis, 181
- Meningococcal vaccine, 112
- Meningococemia
 endotoxins as cause, 115
 meningococci as cause, 126
- Meningococci, 126
- Meningoencephalitis, 140
- Meningomyelocele, 451
- Meniscal tear, 416, 417
- Menkes disease, **63**
 collagen and, 62
- Menometrorrhagia, 579
- Menopause, **582**
 fibroid tumors in, 594
 hormone replacement therapy for, 601
- Menorrhagia, 579
 adenomyosis as cause, 594
 anemia caused by, 388
- Menstrual cycle, **579**
 estrogens for, 601
- Meperidine, 499
- Mepivacaine, 503

- Mercury poisoning, 251
Merkel discs, 454
Merlin protein, 230
Meropenem, 170, 173
MERS (Middle East respiratory syndrome), 151
Mesalamine, 359, 641
Mesangial cells, 532
in filtration, 535
in juxtaglomerular apparatus, 540
Mesencephalon, 450
Mesenchymal tumors
nomenclature of, 228
vimentin stain for, 60
Mesenteric arteries, 531
Mesenteric ischemia, 362, 633
Mesenteric veins, 344
Mesna, 639
Mesocortical pathway, 458
Mesoderm, 450
branchial arches derived from, 568
derivatives of, 563
Mesolimbic pathway, 458
Mesonephric duct, 571
Mesonephros, 530
Mesosalpinx, 574
Mesotheliomas, **624**
asbestosis and, 620
carcinogens causing, 231
lab findings in, 637
Psammoma bodies in, 232
Mesovarium, 574
Mestranol, 601
Metabolic acidosis, 543
Fanconi syndrome as cause, 538
neonatal respiratory distress syndrome and, 607
primary adrenal insufficiency as cause, 318
renal failure as cause, 553
symptoms of, 543
Metabolic alkalosis, 543
acetazolamide for, 557
Bartter syndrome as cause, 538
causes of, 543
Gitelman syndrome as cause, 538
hyperaldosteronism as cause, 318
hypertrophic pyloric stenosis as cause, 339
loop diuretics as cause, 557
primary hyperaldosteronism as cause, 636
syndrome of apparent mineralocorticoid excess as cause, 538
thiazides as cause, 558
Metabolic fuel use, **103**
Metabolic syndrome
atypical antipsychotics as cause, 525
non-alcoholic fatty liver disease and, 367
Metabolism, 83–105
amino acid derivatives, 94
amino acids, 92
apolipoproteins, 104
catecholamine synthesis/tyrosine catabolism, 95
disorders of, 91, 92, 94, 95–96, 99, 100–101, 105
of drugs, **238**
of ethanol, **83**
fatty acid, 101
fuel use, 103
gluconeogenesis, 89
glycogen and, 98
lipoprotein functions, 105
pathway summary, 85
pyruvate, 88
rate-determining enzymes, 84
sites of, 83
TCA cycle, 88
urea cycle, 93
Metabolites, 526
Metacarpophalangeal (MCP) joints, 421
Metachromatic leukodystrophy, 100, 493
Metalloproteinases, 223
Metal storage diseases, 221
Metanephric mesenchyme, 530
Metanephries
pheochromocytoma effect on, 320
in tyrosine catabolism, 95
Metanephros, 530
Metaphase, 58
Metaphysis, tumors in, 429
Metaplasia, 226
Metastases, **233**, 626
key associations, 644
of liver cancer, 368
in neoplastic progression, 227
Metastatic calcification, 220
Metastatic melanomas
recombinant cytokines for, 213
vemurafenib for, 413
Metencephalon, 450
Metformin, 334
diarrhea caused by, 252
Methacholine, 244, **628**
Methadone, 499
for heroin addiction, 523
intoxication and withdrawal, 522
for opioid withdrawal, 522
Methamphetamine, 524
Methanol toxicity, 251, 639
Methemoglobin, 612
toxicity treatment for, 251
Methemoglobinemia, 612
local anesthetics as cause, 503
Methicillin, 253
Methimazole, 335. *See also* Thionamides
agranulocytosis caused by, 252
aplastic anemia caused by, 252
as inhibitor, 315
as teratogen, 564
Methionine, 92, 177
start codons, 53
in tRNA charging, 56
Methotrexate, 409
in cell cycle, 408
folate deficiency caused by, 390
for hydatidiform moles, 587
megaloblastic anemia caused by, 252
for polymyositis/dermatomyositis, 436
pulmonary fibrosis caused by, 254
pyrimidine synthesis and, 49
for rheumatoid arthritis, 430
targets of, 408
as teratogen, 564
toxicities of, 413, 619
vitamin B₉ deficiency caused by, 79
as weak acid, 238
Methoxyflurane, 502
Methylation, 57
Methyl dopa
Coombs-positive hemolytic anemia caused by, 252
for hypertension in pregnancy, 298
Methylene blue, 251, 612
Methylmalonic acid
in vitamin B₉ deficiency, 79
in vitamin B₁₂ deficiency, 80
Methylmalonyl-CoA mutase
diagram of, 80
vitamin B₁₂ and, 80
Methylmercury teratogenicity, 564
Methylphenidate
for ADHD, 511, 524, 638
as CNS stimulant, 524
Methylprednisolone, 336, 446. *See also* Glucocorticoids
Methyltestosterone, **603**
Methylxanthines, **628**
Metoclopramide, **376**
Parkinson-like syndrome caused by, 253
tardive dyskinesia caused by, 253
Metolazone, 558
Metoprolol, 249, 303
Metronidazole, 170, **178**
for bacterial vaginosis, 132
vs. clindamycin, 175
for *Clostridium difficile*, 122, 639
for *Trichomonas vaginalis*, 641
for vaginal infections, 164
for vaginitis, 142
for *Entamoeba histolytica*, 139
for *Giardia lamblia*, 139
for *Helicobacter pylori*, 130
for *Trichomonas vaginalis*, 641
for vaginal infections, 164
for vaginitis, 142
Metrorrhagia, 579
Metyrapone, 318
Metyrosine, 243
Mevalonate synthesis, 300
Mexiletine, 302
for arrhythmia, 638
Meyer loop, 489
MHC I and II, **192**
dendritic cells and, 380
locations of, 202
Micafungin, 181, 183
Michaelis-Menten kinetics, 236
Miconazole, 181, 182
Microalbuminuria, 330
Microangiopathic anemia, 393
in anemia taxonomy, 388
Microangiopathic hemolytic anemia
hypertensive emergency and, 284
intravascular hemolysis caused by, 391
Microarrays, **66**
targets of, 408
Microbiology
antimicrobials, 170–187
bacteriology, 108–118
bacteriology, clinical, 118–134
mycology, 135–138
parasitology, 139–145
systems, 161–169
virology, 146–161
Microcephaly
cri-du-chat syndrome as cause, 75
Edwards syndrome as cause, 632
fetal alcohol syndrome as cause, 565
maternal phenylketonuria as cause, 95
maternal X-rays as cause, 564
Patau syndrome as cause, 74, 632
Microcytic anemia, **388**
Ancylostoma and, 145
key associations, 644
Microcytosis, 224
Microfilaments, in cytoskeleton, 60
Microglia, 450, **453**
Micrognathia
Edwards syndrome as cause, 74
Pierre Robin sequence as cause, 569
Microhematuria, 392
Micomelia, 564
Microphthalmia, 74
MicroRNAs, **55**
Microscopic polyangiitis, **296**
lab findings in, 634
RPGN and, 546
Microrosporum, 136
Microtubule inhibitors, **411**
in cell cycle, 408
Microtubules, 60
Midazolam, 501, 502
Midbrain, 450
development of, 450
lesions in, 464
stroke effect on, 467
Middle cerebellar peduncle, 477
Middle cerebral artery, 466
in circle of Willis, 466
saccular aneurysm effect on, 468
stroke, effect on, 467
Middle meningeal artery
epidural hematoma and, 469
rupture of, 643
Middle rectal vein, 344
Midgut
blood supply/innervation of, 342
development of, 338
Midodrine, 246
Midshaft of humerus, 423
Mifepristone, 602, 640
Miglitol, 335

- Migraine headaches, 494
 butorphanol for, 499
 hormonal contraception
 contraindication, 602
 treatments for, 640
 tricyclic antidepressants as
 prophylaxis, 527
 triptans for, 505
- Migrating motor complexes
 (MMC), 350
- Migratory polyarthritis, 294
- Milestones, developmental, 43
- Miliary tuberculosis, 124
- Milnacipran, 527
- Mineralocorticoids
 in adrenal insufficiency, 318
 adrenal steroids and, 312
- Mineral oil, 76
- Minimal alveolar concentration, 502
- Minimal change disease, 548
 lab findings in, 637
 nephrotic syndrome and, 644
- Minocycline, 170, 175
- Minors, consent for, 40
- Minoxidil, 603
- Minute ventilation, 610
- Miosis, 487
 cholinesterase inhibitor poisoning
 as cause, 244
 Horner syndrome as cause, 487,
 633
 opioids as cause, 499
 Pancoast tumor as cause, 625
 sympatholytic drugs as cause, 247
- Mirtazapine, 248, 528
 for anorexia nervosa, 638
 for major depressive disorder, 515
 mechanism of, 526
- Mismatch repair, 53
- Misoprostol, 375
 diarrhea caused by, 252
- Missense mutations, 52
- Mistakes, informing patients of, 42
- Mites, treatment for, 183
- Mitiglinide, 335
- Mitochondria
 autoantibody to, 207
 high altitude and, 615
 metabolism in, 83
 swelling, in cell injury, 218
 in type I muscle fibers, 424
- Mitochondrial encephalopathy, 70
- Mitochondrial inheritance, 70, 644
- Mitochondrial myopathies, 70
- Mitosis, 58
 griseofulvin and, 183
- Mitral regurgitation
 heart murmurs caused by, 273
 holosystolic murmur and, 643
 in MI, 288
 S3 heart sound and, 645
 systolic murmur in, 272
 tuberous sclerosis as cause, 495
- Mitral stenosis
 diastolic murmur in, 272
 heart murmurs caused by, 273
 left heart disease and, 622
 opening snap in, 644
- Mitral valve
 in cardiac cycle, 270
 regurgitation in, 294
- Mitral valve prolapse, 273, 643
 fragile X syndrome as cause, 73
 renal cyst disorders and, 555
- Mitral valve stenosis, 644
- Mittelschmerz, 578
- Mivacurium, 503
- Mixed connective tissue disease, 434
 anti-UI RNP antibodies and, 55
 autoantibody associated with, 207
 Raynaud phenomenon and, 437
- Mixed motor neuron disease, 644
- Mixed transcortical aphasia, 463
- MMR vaccine, 146, 155
- Mobitz AV blocks, 278
- Modafinil, 521
- Mode, 37
- Molecular biochemistry, 48–57
- Molecular motor proteins, 60
- Molluscum contagiosum, 148, 442
- Mönckeberg arteriosclerosis, 220
- Mönckeberg sclerosis, 285
- “Monday disease,” 299
- Monoamine oxidase (MAO), 243
- Monobactams, 170, 173
 for *Pseudomonas aeruginosa*, 127
- Monoclonal antibodies, 637
- Monoclonal gammopathy of
 undetermined significance
 (MGUS), 401, 637
- Monocytes, 378, 379
 innate immunity and, 192
 morulae in, 133
- Mononucleosis
 anemia and, 393
 EBV as cause, 149
- Monospot test, 149
- Montelukast, 628
 arachidonic acid pathway
 and, 446
- Mood disorders, 514
 readmissions caused by, 45
- Moon facies, in Cushing
 syndrome, 317
- Moraxella* spp., 125
- Moraxella catarrhalis*
 morphology of, 109
 rhinosinusitis caused by, 616
- Moro reflex, 43, 476
- Morphine, 499
 for acute coronary syndromes, 290
 buprenorphine and, 240
 intoxication and withdrawal, 522
- Morphogenesis of heart, 262–263
- Morulae, in monocytes, 133
- Mosaicism, 69
- Mosquitoes, as disease vectors, 141
- Motilin, 350
- Motion sickness, 245
- Motor cortex, 467
- Motor neuron signs, 473
- Movement disorders, 461
- Moxifloxacin, 178
- M phase, 58
- MPO-ANCA, 207
- M protein
 in multiple myeloma, 401
 rheumatic fever and, 120
 as virulence factor, 113
- mRNA, 54
 pre-mRNA splicing, 55
 stop codons, 53
 synthesis of, 170, 179
- MRSA (methicillin-resistant
Staphylococcus aureus), 119
 antimicrobials for, 181
 cephalosporins for, 172
 oxazolidinones for, 176
 treatments for, 641
 vancomycin for, 173
- MSH. See Melanocyte-stimulating
 hormone (MSH)
- mTOR, 212
- Mucicarmine stain, 110
- Mucinous cystadenocarcinomas, 593
- Mucinous cystadenomas, 592
- Mucociliary escalator, 608
- Mucoepidermoid carcinomas, 353
- Mucoid polysaccharide capsule, 127
- Mucopolysaccharides, 110
- Mucopolysaccharidoses, 100
- Mucor* spp., 137
 amphotericin B for, 182
 presentation of, 630
- Mucormycosis, 137
 diabetic ketoacidosis as cause, 331
- Mucosa, 341
- Mucosal bleeding
 Glanzmann thrombasthenia as
 cause, 632
 scurvy as cause, 634
- Mucositis
 bleomycin as cause, 410
 methotrexate as cause, 409
- Mucus, 242
- Mulberry molars, 131
- Müllerian agenesis, 571
- Müllerian duct, 571
 anomalies of, 572
- Müllerian inhibitory factor
 (MIF), 571
 Sertoli cell production of, 576
- Multicystic dysplastic kidney, 531
- Multifactorial pulmonary
 hypertension, 622
- Multiorgan drug reactions, 254
- Multiple endocrine neoplasia
 (MEN), 71
- Multiple endocrine neoplasias (MEN
 syndromes), 333
 MEN 1, 332, 333
 MEN 2A, 333
 MEN 2B, 333
- Multiple myeloma, 401
 bone tumors caused by, 645
 ESR in, 224
 Fanconi syndrome caused by, 538
 lab findings in, 637
 osteoporosis and, 426
 as plasma cell cancer, 381
- Multiple sclerosis, 492
 findings associated with, 643
- heart murmur caused by, 273
 HLA-DR2 and, 193
 IFN- β for, 187
 internuclear ophthalmoplegia
 and, 490
 natalizumab for, 214
 oligodendroglia in, 454
 presentation of, 632
 recombinant cytokines for, 213
 treatments for, 640
 as type IV hypersensitivity
 reaction, 205
- Mumps, 155
 acute pancreatitis caused by, 373
 as paramyxovirus, 151
 paramyxoviruses as cause, 153
 vaccine for, 203
- Munchausen syndrome, 518
- Munchausen syndrome by
 proxy, 518
- Muscarinic acetylcholine (ACh)
 receptors, 241
- Muscarinic antagonists, 245, 628
- Muscle fibers, 424
- Muscle relaxants, 503
- Muscles
 conduction to contraction, 424
 metabolism in, 98
 ragged red fibers in, 70
- Muscle spasms
 baclofen for, 503
 cyclobenzaprine for, 503
- Muscle tumors, stain for, 60
- Muscular dystrophies, 73
 frameshift mutation as cause, 52, 73
 presentation of, 630
 as X-linked recessive disorder, 72
- Muscularis externa, 341
- Muscularis mucosa, 341
- Muscular ventricular septum, 263
 Marfan syndrome as cause, 284
- Musculocutaneous nerve, 419
- Musculoskeletal drug reactions, 253
- Musculoskeletal system
 anatomy, 416–424
 pathology, 426–434
 pharmacology, 446–448
- Mutases, 84
- Mutations in DNA, 52
- Mutism, 518
- Myalgias
 fluoroquinolones as cause, 178
 Lyme disease as cause, 130
Trichinella spiralis and, 145
 trichinosis as cause, 143
- Myasthenia gravis, 436
 autoantibody associated with, 207
 diagnosis of, 244
 neostigmine for, 244
 as paraneoplastic syndrome, 229
 pyridostigmine for, 244
 as restrictive lung disease, 619
 thymus in, 191
 as type II hypersensitivity
 reactions, 204
- MYCL1 gene, 230
- MYCN gene, 230

- Mycobacterial cells, 179
Mycobacterium spp., **124**
 granulomatous diseases caused by, 223
 as intracellular organism, 112
 morphology of, 109
 Ziehl-Neelsen stain for, 110
Mycobacterium avium-intracellulare, 124
 antimicrobial prophylaxis for, 181
 antimycobacterials for, 179
 HIV and, 160
Mycobacterium leprae, 125
 animal transmission of, 132
 antimycobacterials for, 179
Mycobacterium marinum, 124
Mycobacterium pneumoniae, 111
Mycobacterium scrofulaceum, 124
Mycobacterium tuberculosis, 124
 as aerobic organism, 111
 antimycobacterials for, 179
 culture requirements for, 111
 ethambutol for, 180
 isoniazid for, 180
 osteomyelitis caused by, 163
 pyrazinamide for, 180
 rifamycins for, 179
 streptomycin for, 180
 treatments for, 640
 Mycolic acid
 isoniazid and, 180
 synthesis of, 179
 Mycology, 135–138
 Mycophenolate mofetil, 49, 212, 213
Mycoplasma spp.
 as atypical organism, 162
 macrolides for, 176
 morphology of, 109
 pneumonia caused by, 162, 624
Mycoplasma pneumoniae, **134**
 anemia and, 393
 erythema multiforme and, 443
 tetracyclines for, 175
 Mycoses
 cutaneous, **136**
 granulomatous diseases caused by, 223
 systemic, **135**
 Mycosis fungoides, 400
 presentation of, 631
 Mydriasis, 487
 α -agonists as cause, 498
 muscarinic antagonists for, 245
 saccular aneurysm as cause, 468
 Myelencephalon, 450
 Myelin, **453**
 Myelodysplastic syndromes, **401**
 sideroblastic anemia as cause, 389
 Myelofibrosis, 404
 dacrocytes in, 386
 Myeloperoxidase, 201
 in neutrophils, 378
 Myeloproliferative disorders, **404**
 Myelosuppression
 alkylating agents as cause, 410
 antimetabolites as cause, 409
 drugs causing, 413
 hydroxyurea as cause, 411
 irinotecan/topotecan as cause, 411
 Myenteric nerve plexus, 341
 Mylohyoid muscle, 569
 Myocardial action potential, **274**
 Myocardial depression, 502
 Myocardial infarction (MI), 287
 β -blockers for, 249
 Class IB antiarrhythmics after, 302
 complications of, **290**
 diabetes mellitus as cause, 330
 diagnosis of, **289**
 on EKG, 276
 evolution of, **288**
 heart failure caused by, 292
 heparin for, 405
 homocystinuria as cause, 96
 hypertensive emergency and, 284
 shock caused by, 292
 thrombolytics for, 407
 Myocardial oxygen demand, 267
 Myocarditis
 diphtheria as cause, 123
 key associations, 644
 Myoclonic seizures, 494
 Myoclonus, 461
 Creutzfeldt-Jakob disease as cause, 491
 Myofibroblasts, 223
 Myoglobin
 oxygen-hemoglobin dissociation curve, 612
 in type 1 muscle fibers, 424
 Myoglobinuria
 acute tubular necrosis caused by, 554
 McArdle disease as cause, 99
 neuroleptic malignant syndrome as cause, 525
 Myometrium, 574
 Myopathy
 daptomycin as cause, 178
 as drug reaction, 253
 HMG-CoA reductase inhibitors as cause, 300
 interferons as cause, 187
 Pompe disease as cause, 632
 Myophosphorylase, 99
 Myopia, 483
 retinal detachment and, 485
 Myosin
 in muscle contraction, 424
 in smooth muscle contraction, 425
 Myosin-light-chain kinase (MLCK), 425
 Myositis ossificans, **436**
 Myotonic dystrophy, 73
 cataracts and, 483
 as trinucleotide repeat expansion disease, 73
 Myotonic type 1 muscular dystrophy, **73**
 Myxedema
 hypothyroidism as cause, 321
 thyroid hormones for, 335
 Myxomas, 295, 642
 Myxomatous degeneration, 273
N
 N-acetylcysteine, 627
 for acetaminophen toxicity, 251
 for cystic fibrosis, 72
 N-acetylglucosaminyl-1-phosphotransferase, 59
 N-acetylglutamate synthase deficiency, **94**
 NADH (nicotinamide adenine dinucleotide)
 in electron transport chain, 89
 in fructose metabolism, 91
 in TCA cycle, 88
 Nadolol, 249
 NADPH (nicotinamide adenine dinucleotide phosphate)
 in ethanol metabolism, 83
 HMP shunt and, 90
 respiratory burst and, 201
 as universal electron acceptors, 86
Naegleria fowleri, **140**
 Nafcillin, 170
 characteristics of, 171
 for *Staphylococcus aureus*, 641
 Nails, splinter hemorrhages under, 293
 Naive T cell activation, 195
 Naked viral genome infectivity, **147**
 Nalidixic acid, 170
 Naloxone
 for dextromethorphan overdose, 627
 for heroin addiction, 523
 for opioid toxicity, 251, 499, 522
 Naltrexone
 for alcoholism, 523, 638
 for heroin addiction, 523
 for opioid toxicity, 499, 522
 Naproxen, 447
 arachidonic acid pathway and, 446
 for gout, 448
 Narcissistic personality disorder, 519
 Narcolepsy, **521**
 amphetamines for, 246
 CNS stimulants for, 524
 hypnagogic hallucinations and, 513
 Nasal cavity, in cleft palate, 570
 Nasal congestion, 627
 Nasal decongestion
 ephedrine for, 246
 Nasal polyps, in cystic fibrosis, 72
 Nasal septum perforation, 296
 Nasopharyngeal carcinomas
 EBV and, 149
 oncogenic microbes and, 231
 Natalizumab, 214
 for multiple sclerosis, 492, 640
 progressive multifocal leukoencephalopathy and, 493
 Nateglinide, 335
 National Board of Medical Examiners (NBME), 2, 10
 Natriuresis, 540
 Natural killer (NK) cells, **193**
 cell surface proteins, 202
 function of, 380
 innate immunity and, 192
 Nausea
 inhaled anesthetics as cause, 502
 iron poisoning as cause, 396
 loperamide as cause, 376
 MI as cause, 288
 octreotide as cause, 375
 ranolazine as cause, 299
 vitamin C toxicity as cause, 80
 NE. See Norepinephrine (NE)
 Nebivolol, 249
Necator spp.
 diseases associated with, 145
 infection routes, 142
Necator americanus, 143
 Neck and head cancer, **616**
 cetuximab for, 412
 Necrosis, **217**
 acute pancreatitis as cause, 373
 Arthus reaction as cause, 205
 calcification and, 220
 retinitis and, 486
 Stevens-Johnson syndrome as cause, 443
 warfarin as cause, 406
 Necrotizing enterocolitis, 362
 low birth weight and, 581
 neonatal respiratory distress syndrome and, 607
 Necrotizing fasciitis, 120, 442
 Necrotizing glomerulonephritis, 296, 637
 Necrotizing vasculitis, 637
 Negative predictive value (NPV), 33, 646
 Negative reinforcement, 508
 Negative skew distribution, 37
 Negative-stranded viruses, 152
 Neglect, child, **510**
 Negri bodies of rabies, 155, 636
Neisseria spp., **126**
 C5-C9 deficiencies and, 199
 cephalosporins for, 172
 fluoroquinolones for, 178
 IgA protease and, 113
 as intracellular organism, 112
 morphology of, 109
 transformation in, 114
Neisseria gonorrhoeae, 126
 as antigenic variation, 202
 culture requirements for, 111
 in Gram-negative algorithm, 125
 osteomyelitis caused by, 163
 pelvic inflammatory disease caused by, 167, 644
 septic arthritis caused by, 432
 as STI, 167
 treatments for, 640
 UTIs caused by, 552
Neisseria meningitidis
 bacterial meningitis caused by, 642
 chloramphenicol for, 175
 culture requirements for, 111
 as encapsulated bacteria, 112
 in Gram-negative algorithm, 125
 in immunodeficient patients, 210

- Neisseria meningitidis* (continued)
 meningitis caused by, 163
 penicillin G/V for, 170
 splenic dysfunction and, 191
 treatments for, 640
 Waterhouse-Friderichsen syndrome
 caused by, 318
- Nelson syndrome, **326**
- Nematodes, **143**
 infection routes, 142
- Neomycin, 170, 174
 for bowel surgery, 174
 for hepatic encephalopathy, 367
- Neonatal respiratory distress
 syndrome, **607**
 as restrictive lung disease, 619
- Neonates
 ABO hemolytic disease of, **382**
 Apgar score, 581
Candida albicans in, 137
Chlamydia trachomatis in, 134
 conjunctivitis in, 126, 134
 C-section delivery, flora and, 161
 deprivation effects, **510**
 esophageal atresia in, 338
 galactosemia in, 91
 gastroenteritis in, 152
 gray baby syndrome in, 175
 hemolytic anemia in, 392
 herpes in, 149
 HIV in, 158
 hyperthermia in, 245
 hypertrophic pyloric stenosis
 in, 339
 indirect inguinal hernia in, 349
 jaundice in, **369**
Listeria monocytogenes in, 123
 low birth weight, 581
 meningitis in, 123, 165
N-acetylglutamate synthase
 deficiency in, 94
 pneumonia in, 134
 primitive reflexes in, 476
 Rh hemolytic disease of, **382**
 sickle cell anemia in, 392
Streptococcus agalactiae in, 121
 Vitamin D for, when breastfed, 81
 Vitamin K for, 81
- Neoplasia, 226
 pathology of, 226–233
 progression of, **227**
- Neostigmine, 244, 503
- Nephritic-nephrotic syndrome, 545
- Nephritic syndrome, 545, **546–547**,
 548
- Nephritis, 557
- Nephrogenic diabetes insipidus, 328
- Nephrolithiasis, 551
- Nephron physiology, **537**
- Nephropathy
 diabetes mellitus as cause, 330
 hypertension as cause, 284
 in lupus, 642
 protease inhibitors as cause, 186
 transplant rejection as cause, 211
- Nephrotic syndrome, 545, **548**
 amyloidosis and, 225
 charge barrier in, 533
 ESR in, 224
 fatty casts in, 544
 key associations, 644
 lab findings in, 637, 638
 loop diuretics for, 557
 pleural effusion caused by, 623
 presentation of, 633
- Nephrotoxicity
 aminoglycosides as cause, 174
 amphotericin B as cause, 182
 cidofovir for, 185
 cisplatin/carboplatin as cause, 411
 cladribine as cause, 409
 cyclosporine as cause, 212
 as drug reaction, 254
 drugs causing, 413
 inhaled anesthetics as cause, 502
 streptomycin as cause, 180
 sulfonamides as cause, 177
 tacrolimus as cause, 212
 vancomycin as cause, 173
- Nerve blockade in local
 anesthetics, 503
- Nerve fibers, 454
- Nerves
 lower extremity, **422**
 upper extremity, 419
- Nerve trunk, 454
- Net filtration pressure, 535
- Neural crest, 450
 derivatives of, 563
 Schwann cells derived from, 453
- Neural crest cells, 450
 neuroblastomas in, 319
- Neural development, **450**
- Neural fold, 450
- Neural plate, 450
- Neural tube, 450
 in fetal development, 562
- Neural tube defects, **451**
 maternal diabetes as cause, 564
 prevention of, 79, 640
 as teratogenic effect, 564
 valproic acid as cause, 500
- Neuraminidase, 153
- Neuraminidase inhibitors, 255
- Neuroblastomas, **319**, 645
 neurofilament stain for, 60
 oncogenes and, 230
 opsoclonus-myoclonus ataxia
 syndrome and, 229
- Neurocutaneous disorders, **495**
- Neurocysticercosis, 144
- Neuroectoderm, 450
 astrocytes derived from, 453
 derivatives of, 563
 pituitary gland and, 307
 in teratomas, 593
- Neuroendocrine tumors, **319**
- Neurofibrillary tangles in Alzheimer
 disease, 491
- Neurofibromatosis type 1, 495
 autosomal dominance of, 71
 chromosome associated with, 75
 presentation of, 630
 tumor suppressor genes and, 230
- Neurofibromatosis type 2
 autosomal dominance of, 71
 cataracts and, 483
 chromosome associated with, 75
 presentation of, 630
 tumor suppressor genes and, 230
- Neurofilaments, 60
- Neurogenic ileus, 244
- Neurohumoral transmission, 241
- Neurohypophysis, 307
 hypothalamus and, 456
- Neuroleptic drugs, 520
- Neuroleptic malignant
 syndrome, 503, 525
- Neurologic drug reactions, **253**
- Neurology, 450–504
 anatomy/physiology, 453–475
 embryology, 450–452
 ophthalmology, 482–489
 pathology, 491–498
 pharmacology, 498–505
- Neuromuscular blocking drugs, **503**
- Neuromuscular junction
 diseases, **436**
- Neuromuscular paraneoplastic
 syndromes, 229
- Neuronal tumors, 60
- Neuron migration failure, 644
- Neurons, **453**
 Huntington disease effect on, 462
- Neuropathy
 amyloidosis and, 225
 diabetes mellitus as cause, 330
- Neurosyphilis
 dementia caused by, 513
 syphilis as cause, 131
- Neurotoxicity
 cladribine as cause, 409
 cyclosporine as cause, 212
 fetal methylmercury exposure as
 cause, 564
 methylxanthines as cause, 628
 vincristine as cause, 411
- Neurotransmitters, **455**
 disease changes to, **511**
 tyramine and, 243
- Neurovascular pairing, **423**
- Neutralization, antibody, 196
- Neutropenia
 ganciclovir as cause, 185
 interferons as cause, 187
 rheumatoid arthritis as cause, 430
- Neutropenias, 394
 ticlopidine as cause, 407
- Neutrophil chemotaxis
 complement and, 199
 endotoxins and, 117
- Neutrophils, **378**
 corticosteroid effect on, 394
 IL-8 and, 200
 inflammation and, 219
 innate immunity and, 192
 in leukocyte adhesion
 deficiency, 209
 in megaloblastic anemia, 390
 in MI, 288
 necrosis and, 217
 in pseudo-Pelger-Huet
 anomaly, 401
 in wound healing, 223
- Nevi, 228
- Nevirapine, 184
 cytochrome P-450 and, 254
 for HIV, 186
- Nevus flammeus
 presentation of, 634
 Sturge-Weber syndrome as
 cause, 495
- NF1* gene
 neurofibromatosis type 1 and, 71,
 495
 pheochromocytomas and, 320
- NF1/NF2* genes, 230
- NF- κ B, 212
- N-formylmethionine (fMet), 53
- Niacin
 cutaneous flushing caused by, 251
 gout caused by, 253
 hyperglycemia caused by, 252
 myopathy caused by, 253
- Nicardipine, 298
- Nicotinamides, 86
- Nicotine intoxication and
 withdrawal, 522
- Nicotinic acetylcholine
 receptors, 150, 241
- Niemann-Pick disease, 100, 630, 632
- Nifedipine, 298, 590
- Nifurtimox, 183
 for Chagas disease, 142
- Night sweats, 631
- Night terrors, 457, 501
- Nigrostriatal pathway, 458
- Nikolsky sign, 442
 in pemphigus vulgaris, 443
- Nimodipine, 298
 for subarachnoid hemorrhage, 469
- Nipple
 discharge, with intraductal
 papilloma, 595
 eczematous patches on, 596
 rash on, 633
- Nissl bodies, 58
- Nissl substance
 in chromatolysis, 220
 neurons and, 453
- Nitazoxanide, 139
- Nitrates, 287, 299
- Nitric oxide, 350
 as derivative, 94
 free radical injury and, 221
- Nitric oxide synthase, 425
- Nitrites
 methemoglobin and, 612
 in urinary tract infections, 164
- Nitroblue tetrazolium dye reduction
 test, 209
- Nitrofurantoin
 hemolysis in G6PD deficiency
 caused by, 252
 pulmonary fibrosis caused by, 254
- Nitroglycerin, 299
 for acute coronary syndromes, 290
 for angina, 287
 for stable angina, 641

- Nitroprusside, 298
 Nitrosamines
 as carcinogens, 231
 stomach cancer and, 356
 Nitrosoureas, 410
 Nitrous oxide, 502
 Nizatidine, 374
 N-myc oncogene, 319
Nocardia spp.
 vs. *Actinomyces* spp., 123
 as aerobic organism, 111
 as catalase-positive organism, 112
 chronic granulomatous disease and, 209
 in Gram-positive algorithm, 118
 in immunodeficient patients, 210
 morphology of, 109
 necrosis and, 217
 sulfonamides for, 177
 as urease-positive organism, 112
 Ziehl-Neelsen stain for, 110
 Nocturia, 599
 Nocturnal enuresis, 311, 457
 Nodes of Ranvier, 453
 Nodular phlebitis, 296
 Nodular sclerosing Hodgkin lymphoma, 645
 Noise-induced hearing loss, 481
 Nonadherent patients, 42
 Non-alcoholic fatty liver disease, 367
 Nonbacterial thrombotic endocarditis, 229
 Nonbenzodiazepine hypnotics, 501
 Noncaseating granulomas
 as restrictive lung disease, 619
 in sarcoidosis, 435
 Noncommunicating hydrocephalus, 471
 Dandy-Walker syndrome and, 451
 Noncompetitive agonists, 240
 Noncompetitive inhibitors, 236
 Nondepolarizing paralytic drugs, 255
 Nondisjunction in meiosis, 74
 Nondominant parietal cortex lesions, 464
 Nonhemolytic anemia, 391
 Non-Hodgkin lymphoma, 400
 Hashimoto thyroiditis and, 322
 HIV and, 160
 vs. Hodgkin lymphoma, 399
 key associations, 646
 oncogenes and, 230
 prednisone for, 412
 rituximab for, 214, 412
 vinca alkaloids for, 411
 Nonhomologous end joining, 53
 Nonmaleficence, as ethical principle, 39
 Nonmegaloblastic macrocytic anemia, 390
 Nonnormal distributions, 37
 Nonreceptor tyrosine kinase, 316
 Non-response bias in studies, 36
 Nonsense mutations, 52
 Nonsteroidal anti-inflammatory drugs (NSAIDs), 447
 for acute gout attack, 638
 acute interstitial nephritis caused by, 554
 aplastic anemia caused by, 252
 for calcium pyrophosphate deposition disease, 431
 for endometriosis, 594
 gastric ulcers caused by, 357
 gastritis caused by, 356
 for gout, 431, 448
 interstitial nephritis caused by, 253
 loop diuretics and, 557
 for lupus, 434
 membranous nephropathy and, 548
 for migraine headaches, 494, 640
 for osteoarthritis, 430
 prostaglandin synthesis and, 541
 renal papillary necrosis and, 554
 for rheumatoid arthritis, 430
 for tension headaches, 494
 Non-ST-segment elevation MI (NSTEMI), 287, 289
 presentation of, 630
 treatment for, 290
 Noradrenergic drugs, 243
 Norepinephrine (NE), 246, 455. *See also* Catecholamines
 adrenal medulla secretion of, 306
 amphetamines and, 243
 in anxiety, 511
 bupropion effect on, 528
 circadian rhythm and, 457
 in depression, 511
 as derivative, 94
 vs. isoproterenol, 247
 in male sexual response, 575
 MAO inhibitor effect on, 528
 in nervous system, 241
 in noradrenergic drugs, 243
 opioid effect on, 499
 phenoxybenzamine and, 240
 pheochromocytoma secretion of, 320
 REM sleep, effect on, 457
 tramadol effect on, 499
 tricyclic antidepressant effect on, 527
 in tyrosine catabolism, 95
 vitamin B₆ and, 78
 Norethindrone, 602
 Norfloxacin, 178
 Normal distribution, 37
 Normal pressure hydrocephalus, 471
 Normal splitting, 271
 Normetanephrine, 95
 Normocytic anemia, 388, 391
 Norovirus, 151
 watery diarrhea caused by, 162
 Northern blot, 65
 Nortriptyline, 527
 Nosocomial infections, 46, 162, 168
 Ebola as, 156
 Klebsiella as cause, 128
 pneumonia as, 644
 Pseudomonas aeruginosa and, 127
 UTIs as, 164
 Notochord, 450
 postnatal derivative of, 264
 Novobiocin
 as Gram-positive antibiotic test, 118
 Staphylococcus epidermidis sensitivity to, 119
 Novobiocin response, 637
 NPH insulin, 334. *See also* Insulin
 NSE hormone, 319
 Nuclear envelope, 59
 Nucleic acids
 as pathogen-associated molecular pattern (PAMP), 192
 synthesis of, 181
 in viruses, 146
 Nucleosides, 49
 Nucleotide excision repair, 53
 Nucleotides, 49
 Nucleotide synthesis, 83
 Nucleotide triphosphate, 64
 Nucleus ambiguus, 479
 Nucleus pulposus
 collagen in, 61
 fetal precursor to, 264
 Nucleus solitarius, 479
 Null hypothesis, 37
 Nulliparity, and endometrial cancer, 594
 Number needed to harm (NNH), 34, 646
 Number needed to treat (NNT), 34, 646
 Nutmeg liver, 292, 368, 637
 Nutrition, in biochemistry, 76–83
 Nyctalopia, 77
 Nystagmus
 cerebellum and, 459
 Friedreich ataxia as cause, 475
 internuclear ophthalmoplegia as cause, 490
 multiple sclerosis as cause, 492, 632
 PCP as cause, 523
 stroke effect on, 467
 vertigo caused by, 495
 Wernicke-Korsakoff syndrome as cause, 464
 Nystatin, 181, 182
 for *Candida albicans*, 137, 639
- O**
 Obesity
 acanthosis nigricans and, 444
 amphetamines for, 246
 anovulation caused by, 591
 breast cancer and, 596
 breast milk as risk reduction for, 581
 cholelithiasis and, 372
 Cushing syndrome as cause, 317
 diabetes mellitus type 2 and, 331
 empty sella syndrome and, 329
 endometrial cancer and, 594
 esophageal cancer and, 355
 focal segmental glomerulosclerosis and, 548
 glucocorticoids as cause, 212
 hypertension and, 284
 leptin gene mutation as cause, 311
 olanzapine as cause, 525
 osteoarthritis and, 430
 PCOS and, 591
 Prader-Willi syndrome as cause, 69
 prednisone as cause, 412
 renal cell carcinoma and, 550
 sleep apnea and, 621
 stress incontinence and, 551
 Obesity hypoventilation syndrome, 621
 Obligate intracellular organisms, 112
 Oblique fissure, 609
 Oblique muscles, 488
 Observational studies, 32
 errors in, 36
 types of, 32
 Observer-expectancy bias in studies, 36
 Obsessive-compulsive disorder (OCD), 517
 antipsychotic drugs for, 525
 atypical antipsychotics for, 525
 drug therapy for, 524
 Selective serotonin reuptake inhibitors (SSRIs) for, 527
 Tourette syndrome and, 511
 tricyclic antidepressants for, 527
 venlafaxine for, 527
 Obsessive-compulsive personality disorder, 519
 Obstructive jaundice, 373
 Obstructive lung diseases, 618
 flow volume loops in, 619
 Obstructive shock, 292
 Obstructive sleep apnea, 621
 pulse pressure in, 266
 pulsus paradoxus in, 294
 Obturator artery, in osteonecrosis, 427
 Obturator nerve, 422
 Occipital cortex, 467
 Occipital lobe, 462
 Occipital sinus, 470
 Occult bleeding, 363
 Octreotide, 336, 350, 375
 for acromegaly, 327
 for carcinoid syndrome, 332, 639
 for GH excess, 311
 for glucagonomas, 332
 Ocular albinism, 72
 Ocular hyperemia, 498
 Ocular motility, 488
 Oculomotor nerve (3rd cranial nerve), 479
 in cavernous sinus, 481
 location in brain stem, 477
 ocular motility and, 488
 palsy of, 469, 489
 pathway for, 478
 in pupillary contraction, 487
 Odds ratio, 32, 34, 646
 Odontoblasts, 563
 Ofloxacin, 178
 Okazaki fragments, 51
 Olanzapine, 525
 Olfactory bulb, 477
 Olfactory hallucinations, 513
 Olfactory nerve (1st cranial nerve), 479
 location in brain stem, 477
 pathway for, 478

- Olfactory tract, 477
- Oligoclonal bands, 492
- Oligodendrocytes, 453
- in progressive multifocal leukoencephalopathy, 493
- Oligodendroglia, 450, **454**
- Oligodendrogliomas, 496
- Oligohydramnios, 589
- in Potter sequence, 530
- Oligomenorrhea, 579
- antipsychotics as cause, 525
- PCOS as cause, 591
- Oligomycin
- as ATP synthase inhibitor, 89
- in electron transport chain, 89
- Oligospermia, 375
- Oliguria, 546
- Omalizumab, 214, 628
- Omental foramen, 340
- Omeprazole, 374
- Omphalocele, 338
- Omphalomesenteric cysts, 361
- Onchocerca volvulus*, 143
- infection routes, 142
- Oncogenes, **230**
- Oncogenic microbes, **231**
- Ondansetron, **376**
- torsades de pointes caused by, 251
- 1,25-(OH)₂D₃, 541
- Onychomycosis
- terbinafine for, 182
- tinea unguium as cause, 136
- Oogenesis, **578**
- Oophorectomy, 574
- Open-angle glaucoma, 484
- carbachol for, 244
- epinephrine for, 246
- pilocarpine for, 244
- Opening snap, 644
- Operant conditioning, **508**
- Ophthalmology, 482–489
- Ophthalmoplegia
- Wernicke-Korsakoff syndrome as cause, 77, 464, 523
- Opioids, **499**
- intoxication and withdrawal, 522
- as intravenous anesthetics, 502
- pentazocine and, 499
- sleep apnea caused by, 621
- toxicity treatment for, 251
- Opponens digiti minimi muscle, 421
- Opponens pollicis muscle, 421
- Opportunistic fungal infections, 137–138
- Oppositional defiant disorder, 511
- Oprelvekin, 213
- Opsoclonus-myoclonus syndrome, 229, 319
- Oposonins, 199
- Oposonization, antibody, 196
- Optic atrophy, in Krabbe disease, 493
- Optic canal, 478
- Optic chiasm, 477
- in circle of Willis, 466
- in pupillary contraction, 487
- Optic disc, 482
- papilledema in, 486
- Optic gliomas
- neurofibromatosis type I as cause, 71, 630
- neurofibromatosis type I as cause, 495
- presentation of, 630
- Optic nerve (2nd cranial nerve), **479**
- embryologic derivatives of, 563
- in eye anatomy, 482
- location in brain stem, 477
- Marcus Gunn pupil and, 487
- pathway for, 478
- Optic neuritis, 492
- Optic neuropathy, 180
- Optic tract, 477
- Optochin
- as Gram-positive antibiotic test, 118
- organisms resistant to, 118, 637
- organisms sensitive to, 118, 637
- viridans streptococci and, 120
- Oral advance directives, 41
- Oral contraceptives (OCs)
- cytochrome P-450 and, 254
- for endometriosis, 594
- hepatic adenomas and, 368
- melasma and, 439
- ovarian neoplasms and, 592
- for PCOS, 591
- prolactin, effect on, 310
- reproductive hormones and, 600
- SHBG, effect on, 316
- thrombotic complications caused by, 252
- Oral glucose tolerance test, 330
- Oral hairy leukoplakia, 160
- Oral rehydration therapy, for *Vibrio cholerae*, 129
- Oral thrush, 160
- Orange body fluids, caused by rifamycins, 179
- Orchitis, 155
- Orexigenic effect, 311
- Orexin, 521
- Organ failure, in acute pancreatitis, 373
- Organogenesis
- errors in, **563**
- teratogens and, 564
- timing of, 562
- Organomegaly, 551
- Organophosphates
- poisoning by, 244
- toxicity treatment for, 251
- Organ transplants
- azathioprine for, 409
- cytomegalovirus and, 169
- hairy leukoplakia and, 442
- immunosuppressants and, 212
- of kidneys, 532
- rejection, **211**
- WBC casts in, 544
- Organum vasculosum of the lamina terminalis (OVLT), 456
- Orientation, **512**
- Origin of replication, 51
- Orlistat, **376**
- diarrhea caused by, 252
- Ornithine
- in cystinuria, 96
- kidney stones and, 549
- in urea cycle, 93
- Ornithine transcarbamylase, 85
- Ornithine transcarbamylase deficiency, **94**
- as X-linked recessive disorder, 72
- Orotic acid, 94
- Orotic aciduria, 390
- in anemia taxonomy, 388
- “Orphan Annie” eyes nuclei, 324, 636
- Orthomyxoviruses
- characteristics of, 151
- influenza viruses as, 153
- as negative-stranded, 152
- as segmented, 152
- Orthopnea, 292
- Orthostatic hypotension
- adrenal insufficiency as cause, 318
- alpha-blockers as cause, 248
- phenoxybenzamine as cause, 248
- Osetamivir, **184**
- for influenza, 640
- Osler nodes, 632
- bacterial endocarditis as cause, 293
- Osmotic demyelination syndrome, **492**
- SIADH and, 328
- Osmotic diarrhea, 358
- Osmotic diuresis, 330
- Osmotic laxatives, **375**
- Ossicles, 481
- cholesteatoma and, 482
- Osteitis fibrosa cystica, 326, 425, 428, 635
- Osteoarthritis, **430**
- anatomy of, 430
- celecoxib for, 447
- presentation of, 634
- Osteoblasts, 425
- bone formation and, 425
- cortisol effect on, 313
- in Paget disease of bone, 427
- teriparatide effect on, 447
- Osteochondromas, 429
- Osteoclasts, 425
- bisphosphonate effect on, 447
- bone formation and, 425
- in Paget disease of bone, 427
- Osteodystrophy, 375
- Osteogenesis imperfecta, **63**
- bisphosphonates for, 447
- collagen and, 62
- presentation of, 630
- Osteogenic sarcomas, 427
- Osteomalacia, **427**
- hypophosphatemia as cause, 542
- lab values in, 428
- treatments for, 640
- vitamin D deficiency as cause, 81, 313
- Osteomas
- Gardner syndrome as cause, 632
- nomenclature for, 228
- Osteomyelitis, **163**
- key associations, 644
- Pseudomonas aeruginosa* and, 127
- sickle cell anemia as cause, 392
- Staphylococcus aureus* as cause, 119
- Osteonecrosis, **427**
- bisphosphonates as cause, 447
- Osteopenia, 427
- Osteopetrosis, **426, 428**
- Osteophytes, 430
- Osteoporosis, **426**
- bisphosphonates for, 447
- Cushing syndrome as cause, 317
- denosumab for, 214
- as drug reaction, 253
- estrogen and, 425
- Gaucher disease as cause, 100, 631
- glucocorticoids as cause, 212
- heparin as cause, 405
- homocystinuria as cause, 96
- hormone replacement therapy for, 601
- lab values in, 428
- menopause as cause, 582
- pituitary prolactinomas as cause, 309
- prednisone as cause, 412
- raloxifene for, 413, 601
- teriparatide for, 447
- thiazides for, 558
- treatments for, 640
- vertebral compression fractures caused by, 646
- Osteosarcomas, 429
- nomenclature for, 228
- tumor suppressor genes and, 230
- Otitis externa, 127
- Otitis media
- bacteria causing, 113
- brain abscesses caused by, 163
- Haemophilus influenzae* as cause, 126
- Langerhans cell histiocytosis as cause, 403
- Streptococcus pneumoniae* as cause, 120
- Wegener granulomatosis as cause, 296
- Ototoxicity
- aminoglycosides as cause, 174, 187
- cisplatin/carboplatin as cause, 411
- as drug reaction, 254
- ethacrynic acid as cause, 557
- loop diuretics as cause, 557
- as teratogenic effect, 564
- vancomycin as cause, 173
- Ouabain, 61
- Outcome, as quality measurement, 46
- Outer membrane, 108
- Outflow tract formation, 263
- Ovarian artery, 574
- Ovarian cancer
- breastfeeding and, 581
- cisplatin/carboplatin for, 411
- epidemiology of, 590
- hypercalcemia and, 229
- irinotecan/topotecan for, 411

- key associations, 642, 644
lab findings in, 637
Lynch syndrome and, 363
oncogenes and, 230
paclitaxel for, 411
Psammoma bodies in, 232
tumor suppressor genes and, 230
- Ovarian cysts, **592**
Ovarian dysgenesis, 585
Ovarian ligament, 574
Ovarian teratomas, 229
Ovarian tumors, **592–593**
Ovaries
 anatomy of, 574
 descent of, **573**
 embryologic derivatives of, 563
 epithelial histology of, 574
 estrogen production by, 577
 lymphatic drainage of, 573
 premature failure of, 591
Overflow incontinence, 551
Oviducts, 571
Ovotesticular disorder of sex development, 585
Ovulation, **578**
 anovulation causes, 591
 mittelschmerz, 578
 progesterone and, 577
 prolactin effect on, 310
Owl eye inclusions, 636
Oxacillin, 170
 characteristics of, 171
 for *Staphylococcus aureus*, 641
Oxazepam, 501
Oxazolidinones, **176**
Oxidative phosphorylation, **89**
 location of in cell, 83
 poisons, 89
Oxybutynin, 245
Oxygen
 in blood, 613
 for carbon monoxide poisoning, 251
 for carboxyhemoglobin, 612
 for cluster headaches, 494
 deprivation of, **614**
 exercise and, 615
 hemoglobin and, 611
Oxygen-hemoglobin dissociation curve, **612**
Oxygen toxicity, 221
Oxytocin, 336
 hypothalamus production of, 456
 lactation and, 581
 pituitary gland and, 307
 signaling pathways for, 316
- P**
P-450, 180
Pacemaker action potential, **275**
Pacinian corpuscles, 454
Paclitaxel, 411
 in cell cycle, 408
 microtubules and, 60
 targets of, 408
Paget disease of bone, **427**
 bisphosphonates for, 447
 lab values in, 428
 osteosarcomas and, 429
 presentation of, 630
 woven bone in, 425
Paget disease of breast, 596
 location of, 595
 presentation of, 633
Pain receptors, 454
Palatine shelves, 570
Pale infarcts, vs. red, 219
Paliperidone, 525
Palivizumab, 214
 as pneumonia prophylaxis, 153
 for RSV, 187
Pallor, in aplastic anemia, 391
Palmar crease, in Down syndrome, 633
Palmar erythema, 365
Palmar interossei, muscle, 421
Palmar reflex, 476
Panacinar emphysema, 618
p-ANCA
 autoantibody to, 207
 sclerosing cholangitis and, 371
Pancoast tumor, **625**
 Horner syndrome and, 487
 lab findings in, 635
 lung cancer and, 626
 superior vena cava syndrome as cause, 625
 thoracic outlet syndrome caused by, 420
Pancreas
 biliary structures and, 347
 blood supply and innervation of, 342
 embryology, 339
 Pancreas divisum, 339
 Pancreatic buds, 339
 Pancreatic cancer, **373**
 5-fluorouracil for, 409
 adenocarcinomas, **373**
 biliary cirrhosis and, 371
 carcinogens causing, 231
 hyperbilirubinemia caused by, 369
 liver metastases in, 644
 MEN 1 and, 633
 metastases of, 233
 nonbacterial thrombotic endocarditis and, 229
 oncogenes and, 230
 presentation of, 633
 Trousseau's syndrome and, 229
 tumor suppressor genes and, 230
 Pancreatic cells, **307**. *See also* α cells; β cells; Δ cells
 Pancreatic ducts, 339, 347
 Pancreatic insufficiency, 358
 chronic pancreatitis as cause, 373
 Pancreatic lipase, 104
 Pancreatic secretions, **352**
 Pancreatitis, **373**
 acute respiratory distress syndrome as cause, 621
 alcoholism as cause, 523
 DIC and, 643
 as drug reaction, 252
 GLP-1s as cause, 335
 hyperchylomicronemia as cause, 105
 hyperparathyroidism as cause, 326
 hypertriglyceridemia as cause, 105
 key associations, 644
 mumps as cause, 155
 necrosis and, 217
 pancreas divisum as cause, 339
 pancreatic insufficiency caused by, 358
 valproic acid as cause, 500
Pancuronium, 503
Pancytopenia, 391
 Chédiak-Higashi syndrome as cause, 209
 cytarabine as cause, 409
 Gaucher disease as cause, 100, 631
 leishmaniasis as cause, 142
 osteopetrosis and, 426
 paroxysmal nocturnal hemoglobinuria as cause, 392
Pandemics, 153
Panic disorder, 516, **517**
 drug therapy for, 524
 Selective serotonin reuptake inhibitors (SSRIs) for, 527
 venlafaxine for, 527
Pansystolic murmur, 272
Pantoprazole, 374
Papillary carcinomas, 228
Papillary thyroid carcinomas, 324, 645
 carcinogens causing, 231
 lab findings in, 636, 637
 Psammoma bodies in, 232
Papilledema, **486**
 hypertensive emergency and, 284
 pseudotumor cerebri as cause, 471
Papillomas, 228
Papillomaviruses
 characteristics of, 148
 as DNA viruses, 147
 genome of, 147
 as naked viruses, 147
PAPP-A
 in Down syndrome, 74
 in Edwards syndrome, 74
 in Patau syndrome, 74
Pap smear, 591
Papules, 438
Para-aminohippuric acid (PAH), 534
Para-aortic lymph nodes, 190
Paracoccidioidomycosis, **135**
Paracortex, lymph node, 190
Paracrine, 541
Paradoxical splitting, 271
Paraesophageal hernias, 349
Parainfluenza
 croup and, 154
 paramyxovirus as cause, 151, 153
Parakeratosis, 439
Paralysis
 conversion disorder as cause, 518
 Guillain-Barré syndrome as cause, 493
 rabies as cause, 155
Paralytic ileus, 411
Paramedian pontine reticular formation lesions, 464
Paramesonephric duct, 571
Paramyxoviruses, **153**
 characteristics of, 151
 croup caused by, 154
 measles caused by, 154
 mumps as, 155
 as negative-stranded, 152
Paraneoplastic cerebellar degeneration, 229
Paraneoplastic encephalomyelitis, 229
Paraneoplastic syndromes, **229**
 lung cancer and, 626
 renal cell carcinoma and, 550
 renal tumors and, 645
Paranoia
 amphetamines as cause, 522
 LSD as cause, 523
Paranoid personality disorder, 519
Parasites
 eosinophilia caused by, 379
 hints for, 145
Parasitology, 139–145
Parasympathetic nervous system, 241
 male erection and, 575
Parasympathetic receptors, 242
Parathyroid adenomas
 hyperparathyroidism caused by, 326
 MEN 1 syndrome as cause, 333
 MEN 2A as cause, 333
Parathyroid hormone (PTH), **314**
 in bone disorders, 428
 in bone formation, 425
 calcitonin and, 315
 in hyperparathyroidism, 326
 kidney effects, 541
 in nephron physiology, 537
 in osteomalacia/rickets, 427
 in Paget disease of bone, 427
 pseudohypoparathyroidism and, 325
 signaling pathways of, 316
 in thymic aplasia, 208
 vitamin D and, 313, 314
Parathyroid tumors, 633
Paraumbilical vein, 344
Paresthesias
 panic disorder as cause, 517
 vitamin B₁₂ deficiency as cause, 80
Parietal cells, 207
Parietal lobe, 462
Parietal peritoneum, 348
Parinaud syndrome, 477
 pinealomas as cause, 497
Parkinson disease, **461**
 basal ganglia lesions in, 464
 benztropine for, 245
 dopaminergic pathways and, 458
 drug therapy for, **504**
 lab findings in, 635
 neurotransmitter changes in, 511
 neurotransmitters for, 455
 presentation of, 633
 proteasome and, 59
 resting tremor in, 461

- Parkinsonism
frontotemporal dementia as
cause, 491
Lewy body dementia as cause, 491
nigrostriatal pathway and, 458
Wilson disease as cause, 371
- Parkinson-like syndrome, 253
- Parotid gland
embryologic derivatives of, 563
enlargement of, 432
tumors in, 353
- Parotitis
bulimia nervosa as cause, 520
mumps as cause, 155
- Paroxetine, 527
- Paroxysmal nocturnal dyspnea, 292
- Paroxysmal nocturnal
hemoglobinuria, 392
in anemia taxonomy, 388
DAF deficiency and, 199
eculizumab for, 214
flow cytometry diagnosis, 66
intravascular hemolysis caused
by, 391
presentation of, 633
- Pars planitis, 484
- Partial agonists, 240
- Partial pressure, 613
- Partial seizures, 494
- Parvovirus
characteristics of, 148
as DNA viruses, 147
genome of, 147
as naked viruses, 147
- Parvovirus B19
aplastic anemia caused by, 391
hereditary spherocytosis and, 392
hydrops fetalis caused by, 165
presentation of, 630
rash caused by, 166
- Passive aggression, 509
- Passive immunity, 203
- Pasteurella* spp.
in Gram-negative algorithm, 125
morphology of, 109
- Pasteurella multocida*
animal transmission of, 132, 169
osteomyelitis caused by, 163
presentation of, 631
- Patau syndrome, 74
cataracts and, 483
chromosome associated with, 75
hCG in, 580
holoprosencephaly and, 451
horseshoe kidney and, 531
presentation of, 632
- Patches, 438
- Patellar reflex, 476
disc herniation and, 423
- Patent ductus arteriosus (PDA), 283
congenital rubella as cause, 284
cyanosis caused by, 642
fetal alcohol syndrome as
cause, 284
heart murmur caused by, 273, 631
indomethacin for, 447
misoprostol for, 375
- neonatal respiratory distress
syndrome and, 607
treatments for, 640
- Patent foramen ovale, 262
vs. atrial septal defect, 283
- Patent urachus, 567
- Pathogen-associated molecular
patterns (PAMPs), 192
- Pathogenic *Escherichia coli*
(EPEC), 128
- Pathologic grief, 516
- Pathology, 215–233
cardiovascular, 282–296
endocrinal, 317–333
gastrointestinal, 353–374
hematologic/oncologic, 386–406
inflammation, 216–225
musculoskeletal, 426–434
neoplasia, 226–233
neurological, 491–498
psychiatric, 510–524
renal, 544–555
reproductive, 585–599
respiratory, 616–626
USMLE Step 1 preparation
for, 259
- Pavlovian conditioning (classical
conditioning), 508
- PCO₂, 610
- PCP (phencyclidine) intoxication and
withdrawal, 523
- PDE-5 inhibitors, 603
for benign prostatic
hyperplasia, 638
for BPH, 599
naming convention for, 255
- PDGF. *See* Platelet-derived growth
factor (PDGF)
- PDSA cycle, 45
- Pearson correlation coefficient (*r*), 39
- Peau d'orange appearance of breast
cancer, 596
- Pectinate line, 345
- Pectus excavatum, 71
- Pediatric patients
aspirin use for, avoiding, 366
brain tumors in, 497
cystic fibrosis in, 72
dactinomycin for, 410
disorders of, 511
intussusception in, 362
juvenile polyposis syndrome in, 363
Munchausen syndrome by proxy
in, 518
nephrotic syndrome in, 548
neuroblastomas in, 319
precocious puberty in, 69, 312
rashes in, 166
rhabdomyomas in, 295
sleep terror disorder in, 520
staphylococcal scalded skin
syndrome in, 442
strawberry hemangiomas in, 441
tetracycline side effects in, 175
unvaccinated, organisms
affecting, 169
Wilms tumors in, 551
- Pegloticase, 448, 639
- Pegvisomant, 327
- Pellagra
presentation of, 631
vitamin B₃ deficiency as cause, 78
- Pelvic fracture, nerve injury caused
by, 422
- Pelvic inflammatory disease
(PID), 167
Actinomyces as cause, 123
chlamydia as cause, 134, 167
Chlamydia trachomatis as
cause, 134
copper IUD as cause, 602
ectopic pregnancy and, 589
gonococci as cause, 126
gonorrhea as cause, 167
key associations, 644
- Pelvic pain
endometriomas as cause, 592
endometriosis as cause, 594
- Pelvic surgery, 422
- Pemphigus vulgaris, 443
acantholysis and, 439
autoantibody associated with, 207
lab findings in, 634
as type II hypersensitivity
reactions, 204
- Penicillamine
for copper toxicity, 251
for gold poisoning, 251
for lead poisoning, 251
membranous nephropathy and, 548
myopathy caused by, 253
for Wilson disease, 371
- Penicillin, 170
for *Actinomyces* spp., 123
antipseudomonal, 171
Coombs-positive hemolytic anemia
caused by, 252
for *Neisseria meningitidis*, 640
penicillinase-resistant, 171
penicillinase-sensitive, 171
as prophylaxis, 181
for *Pseudomonas aeruginosa*, 640
rash caused by, 253
for rheumatic fever, 294
for *Streptococcus bovis*, 641
for *Streptococcus pneumoniae*, 641
for *Streptococcus pyogenes*, 641
for *Treponema pallidum*, 641
- Penicillinase-resistant penicillins, 171
- Penicillinase-sensitive penicillins, 171
- Penicillin G, 170
for meningococci, 126
as prophylaxis, 181
- Penicillin V, 170, 181
- Penile cancer, 231
- Penis
congenital abnormalities of, 573
female homolog of, 572
lymphatic drainage of, 573
pathology of, 597
Peyronie disease and, 631
- Pentamidine, 138
- Pentazocine, 499
- Pentobarbital, 501
- Pentostatin, 402
- PEP carboxykinase, 85
- Pepsin, 351
- Pepsinogen
location of, 351
somatostatin and, 350
- Peptic ulcer disease, 357
cholinomimetic agents and, 244
glucocorticoids as cause, 336
glycopyrrolate for, 245
H₂ blockers for, 374
Helicobacter pylori and, 356
Helicobacter pylori as cause, 130
key associations, 642
misoprostol for, 375
prednisone as cause, 412
proton pump inhibitors for, 374
- Peptidoglycan synthesis, 170
- Peptidoglycan synthesis
inhibitors, 255
- Peptostreptococcus* spp.
alcoholism and, 162
lung abscesses caused by, 624
- Perforation, caused by ulcers, 357
- Perforin
cytotoxic T cells and, 194
extrinsic pathway and, 216
natural killer cells and, 193
- Performance anxiety, in sexual
dysfunction, 520
- Perfusion, and ventilation, 614
- Perfusion-limited gas exchange, 613
- Periarterial lymphatic sheath
(PALS), 191
- Pericardial cavity, 265
- Pericardial effusion, 626
- Pericardial tamponade, 636
- Pericarditis
acute, 294
jugular venous pulse in, 270
Kussmaul sign in, 295
pulsus paradoxus in, 294
rheumatoid arthritis as cause, 430
- Pericardium, 265
- Perinephric abscesses, 552
- Perineurium, 454
- Periodic acid-Schiff stain, 110
glycogen storage diseases and, 99
- Periorbital edema
nephrotic syndrome as cause, 633
Trichinella spiralis and, 145
- Peripartum cardiomyopathy, 291
- Peripheral edema, 292
calcium channel blockers as
cause, 298
cirrhosis as cause, 365
nephrotic syndrome as cause, 633
- Peripheral nerves, 454
- Peripheral nervous system (PNS), 241
embryologic derivatives of, 563
origins of, 450
- Peripheral neuropathy
alcoholism as cause, 523
Chédiak-Higashi syndrome
and, 209
epilepsy drugs causing, 500
Fabry disease as cause, 100

- Krabbe disease as cause, 100, 493
 oxazolidinones as cause, 176
 sorbitol as cause, 92
 tricyclic antidepressants for, 527
 vincristine as cause, 413
 vitamin B₆ deficiency as cause, 78
- Peripheral resistance, 247
- Peripheral tissue, 615
- Peripheral vascular disease, 286
- Peripheral vertigo, 495
- Periplasm, 108
- Perirenal space, 339
- Peristalsis
 motilin receptor agonists and, 350
 parasympathetic receptors and, 242
- Peritoneum, 339
 hernias and, 349
- Peritonitis
 appendicitis as cause, 360
 diverticulitis as cause, 360
- Peritubular capillaries, 535
- Permanent cells, 58
- Permethrin, 145, 183
- Permissive drug interactions, 237
- Pernicious anemia
 autoantibody associated with, 207
 B₁₂ deficiency caused by, 390
 HLA-DR5 and, 193
 as type II hypersensitivity reactions, 204
 vitamin B₁₂ deficiency caused by, 80
- Peroxisome, 59
- Persistent cervical sinus, 568
- Persistent depressive disorder, 515
- Persistent fetal circulation, 581
- Persistent thyroglossal duct, 306
- Persistent truncus arteriosus, 263, 282
- Personality, 518
- Personality disorders, 518, 519–520
- Personality traits, 518
- Pertussis toxin, 116, 127
- Pes cavus
 Charcot-Marie-Tooth disease as cause, 493
 Friedreich ataxia as cause, 475
- Petechiae
 aplastic anemia as cause, 391
 cirrhosis as cause, 365
 fat emboli as cause, 617
 scurvy as cause, 634
- Peutz-Jeghers syndrome, 228, 363
 colonic polyps and, 363
 presentation of, 631
- Peyer patches, 341, 352
 bacterial GI infections and, 129
 IgA antibody production in, 197
 intussusception and, 362
- Peyronie disease, 597, 631
- PGI₂, 446
- P-glycoprotein, 232
- Phagocytes, 209
- Phagocytosis, 113
- Pharmacokinetics, 237
- Pharmacology, 236–255
 autonomic drugs, 241–250
 cardiovascular, 298–304
 endocrinal, 334–336
 gastrointestinal, 374–376
 hematologic/oncologic, 405–413
 musculoskeletal, 446–448
 neurology, 498–505
 pharmacodynamics, 238–240
 pharmacokinetics, 236–237
 psychiatric, 524–528
 renal, 556–559
 reproductive, 600–603
 respiratory, 627–628
 toxicities and side effects, 251–254
 USMLE Step 1 preparation for, 259
- Pharyngitis
 adenoviridae as cause, 148
 diphtheria as cause, 123
 mononucleosis as cause, 149
Streptococcus pyogenes as cause, 120
 in unvaccinated children, 169
- Pharynx
 blood supply and innervation of, 342
 in respiratory tree, 608
- Phenacetin, 551
- Phenelzine, 528
- Phenobarbital, 501
 cytochrome P-450 and, 254
 for epilepsy, 500
 as teratogen, 564
 as weak acid, 238
- Phenotypic mixing, 146
- Phenoxybenzamine, 248. *See also* α -antagonists
 norepinephrine and, 240
 for pheochromocytomas, 320, 640
- Phentolamine, 248
- Phenylalanine, 92
 derivatives of, 94
 in tyrosine catabolism, 95
- Phenylbutyrate, 93
- Phenylephrine, 246, 627
 α -blockade of, 248
- Phenylketones, 95
- Phenylketonuria, 95
- Phenytoin
 cytochrome P-450 and, 254
 for epilepsy, 500
 erythema multiforme caused by, 443
 folate deficiency caused by, 390
 gingival hyperplasia caused by, 253
 lupus-like syndrome caused by, 253
 megaloblastic anemia caused by, 252
 as teratogen, 564
 for tonic-clonic seizures, 641
 vitamin B₉ deficiency caused by, 79
 zero-order elimination of, 238
- Pheochromocytomas, 320, 645
 causes of, 630
 MEN 2A as cause, 333
 MEN 2B and, 634
 MEN 2B syndrome as cause, 333
 neurofibromatosis type 1 as cause, 71, 495
 phenoxybenzamine for, 248
 polycythemia and, 229
 presentation of, 630
 treatments for, 640
 von Hippel-Lindau disease as cause, 495, 633
- Philadelphia chromosome, 644, 645
 in myeloproliferative disorders, 404
 translocations of, 403
- Phlebotomy, 371
- Phobias, 516, 517
- Phocomelia, 564
- Phosphatases, 84
- Phosphate, in bone disorders, 428
- Phosphoenolpyruvate
 carboxykinase, 89
- Phosphofructokinase-1 (PFK-1)
 glycolysis and, 84
 in metabolic pathways, 85
- Phospholipase A₂
 autoantibody to, 207
 glucocorticoid effect on, 336
- Phospholipids, 352
- Phosphorus, in Paget disease of bone, 427
- Phosphorylases, 84
- Phosphorylation, 57
- Photophobia
 leptospirosis as cause, 130
 migraine headaches as cause, 494
 rabies as cause, 155
- Photosensitivity
 demeclocycline as cause, 336
 as drug reaction, 253
 lupus as cause, 434
 porphyria as cause, 395
 simeprevir as cause, 187
 sulfonamides as cause, 177
 tetracyclines as cause, 175
- Phototherapy for jaundice, 369
- Phrenic nerve, 609
- Phyllodes tumors, 595
- Physician-assisted suicide, 42
- Physiologic dead space, 610, 647
- Physiologic neonatal jaundice, 369
- Physiology
 cardiovascular, 266–280
 endocrinal, 308–316
 gastrointestinal, 350–354
 hematologic/oncologic, 381–385
 neurological, 453–475
 renal, 533–544
 reproductive, 577–584
 respiratory, 610–615
 USMLE Step 1 preparation for, 258
- Physostigmine, 244
 for glaucoma, 498
- Physostigmine salicylate, 251
- Pick bodies, 637
- Picornaviruses, 152
 characteristics of, 151
 genomes of, 147
 as naked viruses, 147
- Pierre Robin sequence, 569
- Pigmented skin disorders, 439
- Pigment-producing bacteria, 113
- Pigment stones, 372
- Pilocarpine, 244
 for glaucoma, 498
- Pilocytic astrocytomas, 497
- Pilus, 108
- Pimozide, 511, 524
- Pindolol, 249, 299
- Pineal gland, 477
- Pinealomas, 497
- Pinworms, 143
- Pioglitazone, 334
- Piperacillin, 170
 characteristics of, 171
 for *Pseudomonas aeruginosa*, 127
- Piroxicam, 447
- Pisiform bone, 418
- Pitting edema, in heart failure, 292
- Pituitary adenomas, 326, 496
 acromegaly caused by, 327
 Cushing syndrome and, 642
 GH and, 311
 goiter caused by, 321
 hypopituitarism caused by, 329, 643
- Pituitary apoplexy, 329
- Pituitary drugs, 336
- Pituitary gland, 307
- Pituitary hormones, 255
- Pituitary prolactinomas, 309
- Pituitary tumors
 diabetes insipidus caused by, 328
 key associations, 644
 MEN 1 and, 333, 633
- Pityriasis rosea, 444
- Pityrosporum* spp., 136
- PKD genes
 polycystic kidney disease and, 71
 renal cyst disorders and, 555
- Placebo, 36
- Placenta, 566
 estrogen production by, 577
 maternal-fetal blood barrier of, 455
 progesterone production in, 577
- Placenta accreta/increta/percreta, 588
- Placental abruption, 588
- Placental insufficiency
 oligohydramnios and, 589
 Potter sequence caused by, 530
- Placenta previa, 588
- Plague, 132
- Plantar reflex, 476
- Plaques, skin, 438
- Plasma cells, 381
- Plasma membrane composition, 61
- Plasma membrane damage, 218
- Plasma osmolality, 330
- Plasmapheresis, 493
- Plasma protein concentration, 535
- Plasminogen, 384
- Plasmodium* spp.
 chloroquine for, 183
 Giemsa stain for, 110

- Plasmodium falciparum*, **141**, 183
Plasmodium malariae, **141**
Plasmodium ovale, **141**
Plasmodium vivax, **141**
Platelet-activating factor, 378
Platelet-derived growth factor (PDGF)
in wound healing, 223
signaling pathways for, 316
Platelet plug formation, **385**
Platysma muscle, 569
Play therapy, for separation anxiety disorder, 511
Pleiotropy, **68**
Pleomorphic adenomas, 353
Pleomorphic bacteria, 109
Pleural effusion, 622, **623**
lung cancer and, 626
Pleuritis, 430
Plicae circulares, 341
Plummer-Vinson syndrome, 354, 388, 631
Pneumatosis intestinalis, 362
Pneumococcal vaccine, 112
Pneumoconiosis, 619, **620**
Pneumocystis spp., 209
Pneumocystis jirovecii, **138**
AIDS and, 644
dapsones for, 177
HIV and, 160
immunocompromised patients and, 162
silver stain for, 110
TMP-SMX for, 177
treatments for, 640
Pneumocystis pneumonia
antimicrobial prophylaxis for, 181
HIV and, 160
Pneumocytes, **607**, 608
Pneumonia, **624**
acute respiratory distress syndrome as cause, 621
adenoviridae as cause, 148
chlamydiae as cause, 134
coccioidomycosis as cause, 135
common causes of, 162
compliance in, 611
Haemophilus influenzae as cause, 126
as inhalational injury, 222
key associations, 644
Mycoplasma pneumoniae as cause, 134
Pneumocystis jirovecii as cause, 138
proton pump inhibitors and, 374
Pseudomonas aeruginosa and, 127
Q fever as cause, 133
readmissions caused by, 45
Staphylococcus aureus as cause, 119
Streptococcus pneumoniae as cause, 120
Streptococcus agalactiae as cause, 121
VZV as cause, 149
Pneumonitis
as granulomatous disease, 223
HIV and, 160
Pneumothorax, 622, **623**
Pneumovax, 112
Podagra
in gout, 431
presentation of, 634
Podocyte fusion, 637
Podocytes, 532
in filtration, 535
glomerular filtration barrier and, 533
in nephrotic syndrome, 548
Poikilocytosis, 378
Pleomorphic bacteria, 109
pol gene, 158
Poliomyelitis, **475**
as restrictive lung disease, 619
vaccine for, 203
Poliovirus, 151
in immunodeficient patients, 210
as picornavirus, 152
poliomyelitis caused by, 475
in unvaccinated children, 169
Polyadenylation signal, 54
Polyarteritis nodosa, **296**
necrosis and, 217
Polyarthralgias
gonococcal arthritis as cause, 432
rubella as cause, 165
Polyarthritis
rheumatic fever and, 120
rubella as cause, 165
Polycystic ovarian syndrome (PCOS), **591**
anovulation caused by, 591
antiandrogens for, 603
endometrial hyperplasia and, 594
ovarian neoplasms and, 592
Polycythemia, **404**
blood oxygen in, 613
bronchitis as cause, 618
chronic bronchitis as cause, 632
Eisenmenger syndrome as cause, 283
ESR in, 224
hepatocellular carcinoma as cause, 368
low birth weight and, 581
renal cell carcinoma as cause, 550
Polycythemia vera, 404
Budd-Chiari syndrome and, 368
Polydactyly, 74, 632
Polydipsia, 330
Polyenes, 181
Polyethylene glycol, 375
Polyhydramnios, 589
anencephaly and, 451
esophageal atresia as cause, 338
Polymenorrhea, 579
Polymerase chain reaction (PCR), **64**
Polymyalgia rheumatica, **435**, 645
ESR in, 224
giant cell arteritis and, 296
Polymyositis, **436**
autoantibody associated with, 207
Polymyxin B, 127
Polymyxins, 181
Polyneuritis, 77
Polyneuropathy, 395
Polyomaviruses
characteristics of, 148
as DNA viruses, 147
genome of, 147
as naked viruses, 147
Polyostotic fibrous dysplasia, 69, 630
Polyposis syndromes, **363**
Polyps, endometrial, 594
Polyuria
diabetes mellitus as cause, 330
Fanconi syndrome as cause, 633
hyperosmolar hyperglycemia nonketotic syndrome as cause, 332
lithium as cause, 526
Pompe disease, 99, 632
Pons, 477
development of, 450
stroke effect on, 467
Pontiac fever, 127
Pontine reticular formation, 467
“Pope’s blessing” (median nerve injury), 419, 421
Popliteal artery, 423
atherosclerosis in, 286, 645
Popliteal fossa, 423
Popliteal lymph nodes, 190
Porcelain gallbladder, **372**
Porphobilinogen deaminase, 395
Porphyria, **395**, 501
Porphyria cutanea tarda, 395
Porphyrin derivatives, 94
Portal hypertension, **365**
autosomal recessive polycystic kidney disease and, 555
pulmonary arterial hypertension caused by, 622
Schistosoma spp. as cause, 145
serum markers for, 366
varices and, 344
Portal triad, 340, 346
Portal vein, 340, 346
in fetal circulation, 264
Portal vein thrombosis, 365
Portosystemic anastomoses, **344**
Port-wine stain of face, 495, 634
Positive predictive value (PPV), 33, 646
Positive reinforcement, 508
Positive skew distribution, 37
Postcapillary venule, in lymph node, 190
Posterior cerebral artery, 466, 467
Posterior chamber of eye, 482
Posterior circumflex artery, 423
Posterior communicating artery
in circle of Willis, 466
saccular aneurysm effect on, 468
Posterior cruciate ligament (PCL)
injury, 416
Posterior descending artery, 265
Posterior drawer sign, 416
Posterior fossa
malformations of, **451**
pilocytic astrocytomas in, 497
Posterior horn, 471
Posterior hypothalamus, 456
Posterior inferior cerebellar artery
in circle of Willis, 466
stroke, effect on, 467
Posterior pituitary gland, 307
Posterior superior pancreaticoduodenal arteries, 343
Posterior tibial artery, 423
Posterior to medial malleolus, 423
Posterior uveitis, 484
Postoperative ileus, 244
Postpartum blues, 516
Postpartum depression, 516
Postpartum hemorrhage, 589
Postpartum mood disturbances, **516**
Postpartum psychosis, 516
Postrenal azotemia, 553
Posttranslational modifications, **57**
Post-traumatic stress disorder (PTSD), 516, **517**
dissociative identity disorder and, 512
drug therapy for, 524
prazosin for, 248
Selective serotonin reuptake inhibitors (SSRIs) for, 527
venlafaxine for, 527
Postural hypotension
midodrine for, 246
trazodone as cause, 528
Postviral infections, 162
Potassium
amphotericin B and, 182
in cardiac muscle, 274
for diabetic ketoacidosis, 331, 639
in diabetic ketoacidosis, 331
PTH and, 314
shifts in, **542**
torsades de pointes and, 277
vitamin D and, 313
Potassium channel blockers, **303**
Potassium channels
meglitinides and, 335
myocardial action potential and, 274
opioid effect on, 499
sulfonylurea effect on, 334
Potassium chloride, 252
Potassium iodide
for *Sporothrix schenckii*, 138
for thyroid storm, 323
Potassium-sparing diuretics, 556, **558**
Potency of drugs, vs. efficacy, 239
Pott disease, 163
Potter sequence, **530**
autosomal recessive polycystic kidney disease and, 555
oligohydramnios as cause, 589
Potter syndrome, 606
Poxviruses
characteristics of, 148
as DNA viruses, 147
molluscum contagiosum caused by, 442
PPAR- γ , 335
PPAR- γ activators, 255

- PPD test for tuberculosis, 124
 Practice tests for USMLE Step 1 exam, 18–19
 Prader-Willi syndrome, 69
 chromosome associated with, 75
 ghrelin in, 311, 350
 Pralidoxime, 244
 Pramlintide, 252, 335
 Prasugrel, 385, 407
 Pravastatin, 300
 Praziquantel, 183
 for tapeworms, 144
 for trematodes, 144
 Prazosin, 248
 Precision vs. accuracy, 35
 Precocious puberty
 adrenal steroids and, 312
 leuprolide for, 601
 McCune-Albright syndrome as cause, 69, 630
 pinealomas as cause, 497
 Precontemplation stage of
 overcoming addiction, 521
 Prednisolone, 412
 arachidonic acid pathway and, 446
 for thyroid storm, 323
 Prednisone, 336, 412. *See*
 also Glucocorticoids
 arachidonic acid pathway and, 446
 Preeclampsia, 590
 hydatidiform moles and, 587
 placental abruption and, 588
 Prefrontal cortex, 462
 Pregnancy, 580
 advanced maternal age, and Down
 syndrome risk, 74
 aminoaciduria in, 536
 amniotic fluid abnormalities, 589
 anemia caused by, 388
 antimicrobials to avoid in, 187
 carpal tunnel syndrome and, 418
 choriocarcinomas and, 587
 complications of, 588–589
 diabetes in. *See* Gestational
 diabetes mellitus
 ESR in, 224
 estrogen in, 577
 as ethical situation, 42
 fetal circulation, 264
 fetal hemoglobin, 611
 fetal respiration in, 606
 fibroid tumors in, 594
 folate deficiency caused by, 390
 folic acid supplementation in, 79
 glucosuria in, 536
 heparin in, 405
 hypertension in, 590
 hypertension treatment in, 247, 298
 hypothyroidism in, 322
 insulin in, 308
 Listeria monocytogenes in, 123
 lithium in, cardiac defects
 associated with, 284
 lithium in, Ebstein anomaly caused
 by, 282
 melasma in, 439
 ovarian neoplasms and, 592
 parental consent for minors and, 40
 phenylketonuria in, 95
 prolactin, effect on, 310
 propylthiouracil in, 335
 pyelonephritis and, 552
 pyogenic granulomas and, 441
 Rh factor in, 382
 SHBG, effect on, 316
 stillbirth, 165
 Streptococcus agalactiae in, 121
 syphilis in, 131
 termination of, 602
 ToRCHeS infections in, 165
 Turner syndrome and, 585
 twinning in, 565
 urinary tract infections in, 164
 vitamin B₉ deficiency in, 79
 Pregnancy-induced hypertension, 590
 Pregnenolone, 312
 Preload, in cardiac output, 267
 Premature ejaculation, 527
 Premature labor and delivery
 as common cause of death, 45
 cryptorchidism and, 597
 heart murmur caused by, 273
 low birth weight caused by, 581
 necrotizing enterocolitis and, 362
 neonatal respiratory distress
 syndrome and, 607
 smoking as cause, 564
 Premature ovarian failure, 591
 Premenstrual dysphoric disorder
 (PMDD), 527
 Premotor cortex, 462
 Preneoplastic and neoplastic cellular
 changes, 226
 Prepatellar bursitis, 417
 Preprocollagen, 62
 Preproinsulin, 308
 Prepuce, 575
 Prerenal azotemia, 553
 Presbycusis, 44
 Presbyopia, 483
 Presenilin proteins, 491
 Pressors, for shock, 292
 Pressure-volume loops, 270
 Pretectal nuclei, 487
 Pretest probability, 33
 Prevalence vs. incidence, 33
 Prevnar, 112
Prevotella spp., 162
 Priapism, 597
 sickle cell anemia as cause, 392
 trazodone as cause, 528
 Primaquine
 hemolysis in G6PD deficiency
 caused by, 252
 for malaria, 141, 640
 Primary adrenal insufficiency, 318
 Primary amyloidosis, 637
 Primary biliary cirrhosis, 371
 autoantibody associated with, 207
 as granulomatous disease, 223
 lab findings in, 634
 ursodiol for, 376
 Primary central nervous system
 lymphoma (PCL), 400
 Primary glomerular disease, 544
 Primary hemostasis, 385
 Primary hyperaldosteronism, 318
 hypertension caused by, 284
 lab findings in, 636
 markers in, 542
 Primary hyperparathyroidism, 325,
 326
 Primary hypertension, 298
 Primary hypogonadism, 586
 Primary hypoparathyroidism, 325
 Primary sclerosing cholangitis, 371
 autoantibody associated with, 207
 ulcerative colitis as cause, 359
 Primary spontaneous
 pneumothorax, 623
 Primase, 51
 Primidone, 461
 Primitive atrium, 262
 Primitive pulmonary vein, 262
 Primitive reflexes, 476
 Primitive ventricle, 262
 Pringle maneuver, 340
 PR interval, 278
 Prinzmetal angina, 287
 calcium channel blockers for, 298
 propranolol and, 303
 Prions, 161
 in Creutzfeldt-Jakob disease, 491
 Privacy, and confidentiality, 41
 Probenecid, 254
 cidofovir and, 185
 for gout, 448, 639
 Procainamide, 302
 lupus-like syndrome caused by, 253
 Procaine, 503
 Procarbazine, 254
 Procedure bias in studies, 36
 Process, as quality measurement, 46
 Processus vaginalis, 573
 Procoagulation, 384
 Progesterone, 577
 Granulosa cell tumors and, 593
 lactation and, 581
 in menstrual cycle, 579
 in ovulation, 578
 in pregnancy, 580
 signaling pathways for, 316
 Progestin, 602
 for contraception, 602
 for endometriosis, 594
 Progressive multifocal
 leukoencephalopathy
 (PML), 493
 HIV and, 160
 oligodendroglia in, 454
 polyomaviruses as cause, 148
 rituximab as cause, 412
 Proguanil
 for malaria, 640
 for *P. falciparum*, 183
 Projection, as ego defense, 509
 Prokaryotes
 DNA replication in, 51
 RNA polymerases in, 54
 Prolactin, 309, 310
 circadian rhythm and, 457
 lactation and, 581
 in pregnancy, 580
 secretion of, 307
 signaling pathways for, 316
 tuberoinfundibular pathway
 and, 458
 Prolactinomas, 644
 dopamine agonists for, 310
 pituitary adenomas as, 326, 496
 treatments for, 640
 Proliferative glomerular
 disorders, 544
 Proliferative phase of menstrual
 cycle, 579
 Prometaphase, 58
 Promoters, in gene expression, 54
 Promyelocytic leukemia, 77
 Pronephros, 530
 Proopiomelanocortin, 307
 Propafenone, 302
 Propranolol, 323
 Proper hepatic artery, 340
 Prophase, 58
Propionibacterium spp.
 morphology of, 109
Propionibacterium acnes, 440
 Propionyl-CoA carboxylase
 in metabolic pathways, 85
 vitamin B₇ and, 79
 Propofol, 502
 Propranolol, 249, 303
 for essential tremor, 461
 for migraines, 640
 Proprioception
 dorsal column and, 473
 in Friedreich ataxia, 475
 Propylthiouracil, 335. *See*
 also Thionamides
 agranulocytosis caused by, 252
 aplastic anemia caused by, 252
 as inhibitor, 315
 for thyroid storm, 323
 Prosencephalon, 450
 Prostacyclin, 446
 Prostaglandin analogs, 255
 Prostaglandins
 arachidonic acid pathway and, 446
 aspirin effect on, 447
 cortisol effect on, 313
 for glaucoma, 498
 kidney functions, 541
 PDA and, 264
 Prostate cancer, 644
 adenocarcinomas, 599
 bone metastases in, 644
 estrogens for, 601
 incidence/mortality of, 228
 leuprolide for, 601
 metastases of, 233
 treatments for, 640
 tumor suppressor genes and, 230
 Prostate gland, 575
 female homolog of, 572
 lymphatic drainage of, 573
 Prostatic acid phosphatase (PAP), 599
 Prostatitis, 599
 gonorrhea as cause, 167

- Prosthetic devices
osteomyelitis and, 163
Staphylococcus epidermidis
infection of, 119
- Prosthetic heart valves, 393
- Protamine sulfate, 251, 405, 639
- Protease inhibitors, 184
acute pancreatitis caused by, 373
fat redistribution caused by, 253
for HIV, 186
hyperglycemia caused by, 252
naming convention for, 255
- Proteases, 352
- Proteasome, 59
- Protein A, 113
- Proteinases, 378
- Protein kinase A
fructose biphosphatase-2 and, 87
in glycogen regulation, 97
- Protein metabolism, 85
- Protein phosphatase, 97
- Proteins
free radical effect on, 221
in HIV, 158
- Protein synthesis, 57, 170, 184
insulin and, 308
location of in cell, 83
- Protein synthesis inhibitors, 174, 255
- Proteinuria
ACE inhibitors for, 559
angiotensin II receptor blockers
for, 559
diabetes mellitus as cause, 330
nephritic syndrome and, 546
nephrotic syndrome as cause, 545,
548, 633
preeclampsia as cause, 590
serum sickness as cause, 205
- Proteolysis
cortisol and, 313
in insulin deficiency, 330
- Proteus* spp.
in Gram-negative algorithm, 125
morphology of, 109
as nosocomial infection, 168
as urease-positive organism, 112
- Proteus mirabilis*
cephalosporins for, 172
kidney stones caused by, 549
penicillinase-sensitive penicillins
for, 171
urinary tract infections caused
by, 552
UTIs caused by, 164
- Prothrombin
as liver marker, 366
warfarin effect on, 406
- Protofilament, 60
- Proton pump inhibitors, 374
acute interstitial nephritis caused
by, 554
gastrin and, 350
for *Helicobacter pylori*, 130
metronidazole and, 178
naming convention for, 255
- Protozoa
CNS infections, 140
GI infections, 139
hematologic infections, 141
miscellaneous, 142
watery diarrhea caused by, 162
Ziehl-Neelsen stain for, 110
- Proximal convoluted tubules
defects in, 538
diuretics and, 556
dopamine secretion by, 541
glucose clearance and, 536
ischemia susceptibility, 218
physiology of, 537
relative concentrations along, 539
renal cell carcinoma and, 550
renal tubular acidosis of, 544
- Proximal interphalangeal (PIP)
joints, 421
- Proximal vagina, 573
- PRPP (glutamine-phosphoribosyl-
pyrophosphate) amidotrans-
ferase, 84
- Pruritus
biliary tract disease as cause, 371
chloroquine as cause, 183
histamine receptors and, 242
- Prussian blue stain, 620
- Psammoma bodies, 232
calcification and, 220
causes of, 637
in meningiomas, 496
in mesotheliomas, 624
in papillary thyroid carcinoma, 324
in serous cystadenocarcinomas, 593
- PSA (prostate-specific antigen), 232
- Pseudoappendicitis, 129
- Pseudocyst, 518
- Pseudocyst, 373
- Pseudoephedrine, 627
- Pseudoglandular lung
development, 606
- Pseudogout, 431, 637
- Pseudohermaphrodites, 586
- Pseudohyperaldosteronism
Cushing syndrome and, 317
- Pseudohypoparathyroidism, 325
- Pseudomembranous colitis
bacteria causing, 114
clindamycin as cause, 175
Clostridium difficile as cause, 122
as drug reaction, 252
penicillinase-sensitive penicillins as
cause, 171
vancomycin for, 173
watery diarrhea caused by, 162
- Pseudomembranous pharyngitis
diphtheria as cause, 123
- Pseudomonas* spp.
antipseudomonal penicillins
for, 171
as catalase-positive organism, 112
ceftazidime for, 172
chronic granulomatous disease
and, 209
cystic fibrosis and, 72, 162, 635
fluoroquinolones for, 178
in Gram-negative algorithm, 125
morphology of, 109
as nosocomial infection, 162
osteomyelitis and, 644
osteomyelitis caused by, 163
pneumonia caused by, 644
tricuspid valve endocarditis
and, 293
type III secretion system of, 113
- Pseudomonas aeruginosa*, 127
as aerobic organism, 111
biofilm produced by, 113
as encapsulated bacteria, 112
exotoxin produced by, 116
in immunodeficient patients, 210
multidrug-resistant, 181
as nosocomial infection, 168
pigment produced by, 113, 127
pyocyanin of, 201
splenic dysfunction and, 191
treatments for, 640
UTIs caused by, 164
- Pseudo-Pelger-Huet anomaly, 401
- Pseudopseudohypoparathyroid-
ism, 325
- Pseudotumor cerebri, 471
acetazolamide for, 557
vitamin A toxicity as cause, 77
- Pseudovirion, phenotypic mixing
in, 146
- Psittacosis, 132
- Psoriasis, 440
arthritis and, 433
cyclosporine for, 212
etanercept for, 448
hyperkeratosis/parakeratosis in, 439
infliximab/adalimumab for, 448
methotrexate for, 409
as skin plaque, 438
skin scales in, 438
therapeutic antibodies for, 214
- Psoriatic arthritis, 433
HLA-B27 and, 193, 643
leflunomide for, 447
psoriasis and, 440
- Psychiatric genetics, 510
- Psychiatry, 508–530
pathology, 510–524
pharmacology, 524–528
psychology, 508–509
- Psychoactive drug intoxication and
withdrawal, 522–523
- Psychology, 508–509
- Psychosine, 493
- Psychosis, 513
antipsychotic drugs for, 525
diabetic ketoacidosis as cause, 331
glucocorticoids as cause, 212, 336
LSD as cause, 523
lupus as cause, 434
PCP as cause, 523
prednisone as cause, 412
- Psychotherapy
for anorexia/bulimia nervosa, 520
for anorexia nervosa, 638
for conduct disorder, 511
for oppositional defiant
disorder, 511
- Psychotic disorders
postpartum psychosis and, 516
readmissions caused by, 45
- PTEN* gene, 230
- Pterygoid muscles, 569
- PTH. See Parathyroid hormone
(PTH)
- PTH-independent
hypercalcemia, 325
- PTH-related peptide (PTHrP), 314
- PTHrP (parathyroid hormone-related
protein), 229
- Ptosis
Horner syndrome as cause, 487,
633
myasthenia gravis as cause, 436
Pancoast tumor as cause, 625
saccular aneurysm as cause, 468
- Puberty
GH secretion in, 311
GnRH and, 309
Kallmann syndrome and, 586
precocious, 69, 312
Tanner stages, 584
- Public health, 44–46
- Pudendal nerve, 422
- Pulmonary anthrax, 121
- Pulmonary arterial hypertension
(PAH), 622
bronchitis as cause, 618
high altitude and, 615
treatments for, 640
- Pulmonary artery, 568
in fetal circulation, 264
- Pulmonary artery stenosis, 284
- Pulmonary capillary wedge pressure
(PCWP), 280, 614
- Pulmonary circulation, 613
- Pulmonary edema, 292
acute respiratory distress syndrome
as cause, 621
compliance in, 611
consolidation in, 622
loop diuretics for, 557
mannitol as cause, 557
nitrates for, 299
opioids for, 499
renal failure as cause, 553
- Pulmonary embolism, 617
bacterial endocarditis as cause, 293
deep venous thrombosis and, 616
direct factor Xa inhibitors for, 407
heparin for, 405
lab findings in, 636
respiratory alkalosis caused by, 543
shock caused by, 292
tamoxifen/raloxifene and, 413
thrombolytics for, 407
- Pulmonary fibrosis
amiodarone as cause, 303
bleomycin as cause, 410
busulfan as cause, 410
compliance in, 611
diffusion in, 613
as drug reaction, 254
drugs causing, 413
lab findings in, 636
methotrexate as cause, 409
as restrictive lung disease, 619
- Pulmonary hemorrhage, 121

- Pulmonary hypertension, 613, **622**
 drug therapy for, **627**
 key associations, 645
 PDE-5 inhibitors for, 603
Schistosoma as cause, 144
 sleep apnea as cause, 621
- Pulmonary hypoplasia, 606
 in Potter sequence, 530
- Pulmonary Langerhans cell histiocytosis, 619
- Pulmonary surfactant
 compliance and, 611
 composition of, 607
 pneumocytes and, 607
- Pulmonary trunk, 262
- Pulmonary vascular resistance (PVR), **614**, 647
 chest wall and, 611
- Pulmonic regurgitation, 272
- Pulmonic stenosis
 carcinoid syndrome as cause, 332
 systolic ejection murmur in, 272
 wide splitting in, 271
- Pulmonic valves, 262
- "Pulseless disease," 296
- Pulse pressure, 266
- Pulsus paradoxus, 294
 asthma as cause, 618
 croup as cause, 154
- Punched-out ulcers, 354
- Punishment, 508
- Pupil, 482
- Pupillary control, **487**
- Pupillary light reflex, 479, 487
 in CN III palsy, 489
- Pure red cell aplasia, 229
- Purines, 49, 177
 de novo synthesis of, 49
 salvage deficiencies, **50**
- Purkinje cells
 of cerebellum, 218
 cerebellum and, 459
 in paraneoplastic cerebellar degeneration, 229
- Purkinje fibers, 276
- Purpura
 aplastic anemia as cause, 391
 cirrhosis as cause, 365
- Pustular psoriasis, 438
- Pustules, 438
- Putamen, 462
- Pyelonephritis, **552**
 kidney stones as cause, 549
 lab findings in, 638
 urinary tract infections as cause, 164
 WBC casts in, 544
- Pygmalion effect, 36
- Pyknosis, in cell injury, 218
- Pyloric sphincter, 351
- Pyloromyotomy, 339
- Pyoderma gangrenosum
 Crohn disease as cause, 359
 ulcerative colitis as cause, 359
- Pyogenic granulomas, 441
- Pyogenic osteomyelitis, 637
- Pyramidal cells, 218
- Pyramidal decussation, 477
- Pyramidalis muscle, 348
- Pyrantel pamoate, 183
- Pyrazinamide, **180**
 gout caused by, 253
 hepatitis caused by, 252
 for *Mycobacterium tuberculosis*, 179, 640
- Pyridostigmine, 244
- Pyridoxal phosphate, 78
- Pyrimethamine, 183
 pyrimidine synthesis and, 49
 for *Toxoplasma gondii*, 641
- Pyrimidine dimers, 53
- Pyrimidines, 49
- Pyrimidine synthesis, 447
- Pyruvate carboxylase, 88, 89
 in metabolic pathways, 85
 vitamin B₇ and, 79
- Pyruvate dehydrogenase, **87**
 deficiency in, **88**
 diagram of, 88
 in metabolic pathways, 85
 vitamin B₁ and, 77
- Pyruvate kinase, 85
- Pyruvate kinase deficiency, 392
 in anemia taxonomy, 388
 echinocytes in, 386
- Pyruvate metabolism, **88**
- Pyuria, 554
- Q**
- Q fever, **133**
 animal transmission of, 132
 bacteria causing, 114
- QRS complex, in EKG, 276
- QT interval
 atypical antipsychotic effect on, 525
 Class IA antiarrhythmic effect on, 302
 congenital long QT syndrome, 277
 on EKG, 276
 ondansetron effect on, 376
 in torsades de pointes, 277
- Quality measurements, **46**
- Quantifying risk, **34**
- Quetiapine, 525
- Quiescent cells, 58
- Quinidine, 302
 cinchonism caused by, 253
 cytochrome P-450 and, 254
 diarrhea caused by, 252
 for malaria, 141, 183
- Quinine
 cinchonism caused by, 253
 for malaria, 183
- Quinolone, 127, 170
- Quinupristin, 170, 181
- R**
- Rabies, **155**
 killed vaccine for, 146
 passive antibodies for, 203
 receptors for, 150
 as rhabdovirus, 151
 vaccine for, 203
- Radial nerve, 419
- Radiation exposure
 acute myelogenous leukemia and, 402
 aplastic anemia caused by, 391
 apoptosis caused by, 216
 as carcinogen, 231
 free radical injury caused by, 221
 hypopituitarism caused by, 329
 myelodysplastic syndromes caused by, 401
- Radiation therapy
 acute pericarditis caused by, 294
 angiosarcomas and, 441
 lymphopenia caused by, 394
 for Nelson syndrome, 326
 neutropenia caused by, 394
 osteosarcomas and, 429
 for pancreatic cancer, 373
 papillary thyroid carcinoma risk and, 324
 readmissions caused by, 45
 restrictive/infiltrative cardiomyopathy caused by, 291
- Radon
 as carcinogen, 231
 lung cancer and, 626
- Ragged red muscle fibers, 70
- Rales, in heart failure, 292
- Raloxifene, **413**, 601
- Raltegravir, 184, 186
- Ramipril, 559
- Ramsay Hunt syndrome, 480
- Ranibizumab, 214
 for macular degeneration, 485
- Ranitidine, 374
- RANK-L, 314
- Ranolazine, **299**
- Rapid-eye movement (REM), 457
- Rapidly progressive glomerulonephritis (RPGN), 546
- Rapid squatting, effect on auscultation, 272
- Rasagiline, **505**
- Rasburicase, **448**, 549
- RAS gene, 324
- Rashes
 bull's-eye, in Lyme disease, 632
 carbapenems as cause, 173
 of childhood, 166
 cytomegalovirus as cause, 165
 fluoroquinolones as cause, 178
 Kawasaki disease as cause, 296
 lupus as cause, 434
 macrolides as cause, 176
 measles as cause, 154, 631
 nematodes as cause, 143
 on palms/soles, 633
 penicillinase-sensitive penicillins as cause, 171
 in Rickettsial diseases, 133
 rubella as cause, 153, 165
 simeprevir as cause, 187
 syphilis as cause, 131, 167
 in unvaccinated children, 169
- Rathke pouch, 307
- Rationalization, as ego defense, 509
- Raynaud phenomenon, **437**
 Buerger disease as cause, 296
 calcium channel blockers for, 298
 in CREST syndrome, 437
 lupus as cause, 630
 presentation of, 632
- Rb, 58
- Rb gene, 230
- Reabsorption rate, **535**
- Reaction formation, as ego defense, 509
- Reactive arthritis, **433**
Campylobacter jejuni as cause, 128
 chlamydia as cause, 167
 chlamydiae as cause, 134
 HLA-B27 and, 193, 643
 presentation of, 634
- Reactive attachment disorder, 510
- Reactive cellular changes, **226**
- Readmissions, causes of, 45
- Reassortment, viral, 146
- Recall bias in studies, 36
- Receptor binding, **240**
- Receptors, viral, 150
- Receptor tyrosine kinase as endocrine hormone messenger, 316
 as oncogene product, 230
- Recessive inheritance, 70
- Recombinant cytokines, **213**
- Recombination, viral, 146
- Recruiting study participants, 36
- Rectal veins, 344
- Rectum
 anastomosis at, 344
 ischemia susceptibility, 218
- Rectus abdominis muscle, 348
- Rectus muscles, 488
- Recurrent branch of median nerve, 419
- Recurrent laryngeal nerves, 568
- Red cell casts, 296
- Red-green color blindness, 180
- Red infarcts, vs. pale, 219
- Red man syndrome, 173
- Redox reactions
 free radical injury and, 221
 vitamin B₂ and, 78
- Red pulp, in spleen, 191
- Red rashes of childhood, **166**
- Reduviid bug, as disease vector, 142
- Reed-Sternberg cells, **399**, 636
- Refeeding syndrome, 520
- Reflex bradycardia, 540
- Reflexes
 clinical, **476**
 cranial nerve, **479**
 as motor neuron sign, 473
 primitive, **476**
- Reflex tachycardia, 248
- Refractive errors (vision), **483**
- Refractory hypertension, 603
- Regadenoson, 287
- Regan-Lowe medium, 111
- Regional specification of developing brain, **450**

- Registering for USMLE Step 1 exam, 5–6, 7
- Regression, as ego defense, 509
- Regular insulin, 334. *See also* Insulin
- Regulation of gene expression, **54**
- Regulatory T cells, **194**
cell surface proteins, 202
- Regurgitation, in GERD, 354
- Reheated rice syndrome, 122
- Reichert cartilage, 569
- Reid index in chronic bronchitis, 618
- Reinke crystals, 598, 637
- Relapse stage of addiction, 521
- Relapsing fever
animal transmission of, 132
lice transmission of, 145
- Relative risk reduction (RRR), 34, 646
- Relative risk (RR), 32, 34, 646
- Reliability, 35
- Renal artery, 342, 532
in horseshoe kidney, 531
- Renal blood flow, 532, 647
dopamine, effect on, 541
prostaglandins, effect on, 541
- Renal cell carcinomas, **550, 645**
bevacizumab for, 214, 412
carcinogens causing, 231
chromosome associated with, 75
horseshoe kidney and, 531
hypercalcemia and, 229
IFN- α for, 187
key associations, 645
metastases of, 233
recombinant cytokines for, 213
tumor suppressor genes and, 230
von Hippel-Lindau disease as cause, 495, 633
- Renal clearance, **533, 647**
- Renal cortex, 532
in hydronephrosis, 550
- Renal cyst disorders, **555**
- Renal disease
ESR in, 224
lupus and, 434
maintenance and loading dose in, 237
waxy casts in, 544
Wilson disease as cause, 371
- Renal disorder markers, **542**
- Renal drug reactions, **253**
- Renal failure, **553**
consequences of, 553
diabetes mellitus as cause, 330
doxycycline in, 175
Fabry disease as cause, 100
lab findings in, 637
myoclonus in, 461
NSAIDs as cause, 541
preeclampsia as cause, 590
prolactin elimination in, 310
renal cyst disorders as cause, 555
vitamin D deficiency caused by, 313
waxy casts in, 544
- Renal hypoxia, 612
- Renal ischemia, 447
- Renal medulla, 532
in hydronephrosis, 550
- Renal oncocytomas, **550**
- Renal osteodystrophy, 326, 553
- Renal papillary necrosis, **554**
pyelonephritis and, 552
sickle cell anemia as cause, 392
- Renal pelvis, 532
- Renal plasma flow, 534
glomerular dynamics, effect on, 535
- Renal toxicity, medications causing, 185
- Renal tubular acidosis, **544**
Fanconi syndrome as cause, 633
metabolic acidosis caused by, 543
- Renal tubules
anatomy of, 532
defects in, **538**
in nephron physiology, 537
PTH and, 314
- Renal vascular smooth muscle, 242
- Renal vein, 532
- Renin, 540
ACE inhibitor effect on, 559
aliskiren effect on, 559
in hyperaldosteronism, 318
in renal disorders, 542
sympathetic receptors and, 242
- Renin-angiotensin, 306
- Renin-angiotensin-aldosterone system, **540**
- Renin secreting tumors, 542
- Renshaw cells, 116, 122
- Reoviruses
characteristics of, 151
genome of, 147
as naked viruses, 147
as segmented, 152
- Repaglinide, 335
- Reperfusion injury, 219, 288
- Reperfusion therapy, 290
- Replication fork, **51**
- Replication, viral, **147**
- Repression, as ego defense, 509
- Repressor proteins, 52
- Reproductive anatomy
female, 574
male, 575
- Reproductive hormones, **600**
- Reproductive system, 562–603
anatomy, 573–576
drug reactions in, **252**
embryology, 562–573
pathology, 585–599
pharmacology, 600–603
physiology, 577–584
- Reptiles, as disease vectors, 132
- Rescheduling USMLE Step 1 exam, 6
- Reserpine
for Huntington disease, 505
as noradrenergic drug, 243
Parkinson-like syndrome caused by, 253
- Residual volume (RV), 610, 619
- Resistance equation, 647
- Resistance, pressure, flow, **268**
- Respiratory acidosis, 543
- Respiratory alkalosis, 543
causes of, 543
high altitude and, 615
pulmonary embolism and, 617
- Respiratory burst, **201**
free radical injury and, 221
- Respiratory depression
barbiturates as cause, 501, 522
benzodiazepines as cause, 500, 522
epilepsy drugs causing, 500
inhaled anesthetics as cause, 502
opioids as cause, 499
tricyclic antidepressants as cause, 527
- Respiratory distress syndrome, 581
- Respiratory drug reactions, **254**
- Respiratory rate (RR), 610
- Respiratory syncytial virus (RSV)
as paramyxovirus, 151
paramyxoviruses as cause, 153
pneumonia caused by, 162, 624
prophylaxis for, 214
ribavirin for, 187
- Respiratory system, 606–629
anatomy, 608–609
embryology, 606–607
pathology, 616–626
pharmacology, 627–628
physiology, 610–615
- Respiratory tract infections, 199
- Respiratory tree, **608**
- Respiratory zone of respiratory tree, 608
- Resting tremor, 461, 633
- Restrictive cardiomyopathy, 291
amyloidosis and, 225
S4 heart sound and, 645
- Restrictive lung diseases, **619**
flow volume loops in, 619
sarcoidosis and, 435
- Reteplase, 383, 407
- Rete testis, 575
- RET gene, 230
Hirschsprung disease and, 361
medullary thyroid carcinoma and, 324
multiple endocrine neoplasias and, 71
papillary thyroid carcinoma and, 324
pheochromocytomas and, 320
- Reticular activating system
lesions, 464
- Reticular fibrous framework of spleen, 191
- Reticulate bodies in chlamydiae, 134
- Reticulin, collagen in, 61
- Reticulocytes, 378
in aplastic anemia, 391
in intravascular hemolysis, 391
- Retina, 482
embryologic derivatives of, 563
- Retinal artery, 482
- Retinal detachment, **485**
- Retinal hemorrhage
as child abuse sign, 510
hypertensive emergency and, 284
retinal vein occlusion as cause, 485
Roth spots as, 633
- Retinal vein, 482
- Retinal vein occlusion, **485**
- Retinitis, **484, 486**
cidofovir for, 185
foscarnet for, 185
HIV and, 160
- Retinitis pigmentosa, **486**
- Retinoblastomas
osteosarcomas and, 429
tumor suppressor genes and, 230
- Retinoids, 440
- Retinopathy
Alport syndrome as cause, 547
chloroquine as cause, 183
diabetes mellitus as cause, 330
hypertension as cause, 284
of prematurity, 221, 607
sorbitol as cause, 92
- Retrognathia, in Potter sequence, 530
- Retrograde amnesia, 512
- Retroperitoneal fibrosis, 550
- Retroperitoneal structures, **339**
- Retrospective studies, 36
- Retroviruses
characteristics of, 151
genomes of, 147
- Rett syndrome, 511
X-linked dominant inheritance of, 70
- Reverse transcriptase, 158
- Reverse transcriptase inhibitors, 184
- Reye syndrome, **366**
- Rhabdomyolysis
daptomycin as cause, 178
hyperkalemia caused by, 542
- Rhabdomyomas, 295, 642
nomenclature for, 228
tuberous sclerosis as cause, 495
- Rhabdomyosarcomas
dactinomycin for, 410
desmin stain for, 60
nomenclature for, 228
- Rhabdoviruses
characteristics of, 151
as negative-stranded, 152
- Rhagades, in congenital syphilis, 131
- Rh blood classification, 382
- Rheumatic fever, **294**
criteria for, 120
heart murmur caused by, 273
Streptococcus pyogenes as cause, 120
streptolysin O and, 117
as type II hypersensitivity reactions, 204
- Rheumatic heart disease, 644
- Rheumatoid arthritis, **430**
AA amyloidosis and, 225
anatomy of, 430
anemia of chronic disease and, 391
autoantibody associated with, 207
azathioprine for, 212, 409
biliary cirrhosis and, 371
carpal tunnel syndrome and, 418
celecoxib for, 447

- cyclosporine for, 212
 etanercept for, 448
 HLA-DR4 and, 193, 643
 infliximab/adalimumab for, 448
 lab findings in, 634
 leflunomide for, 447
 methotrexate for, 409
 rituximab for, 214, 412
 therapeutic antibodies for, 214
 uveitis and, 484
- Rheumatoid factor, 207
- Rh hemolytic disease of the newborn, **382**
- Rhinitis
 phenylephrine for, 246
 as type I hypersensitivity reaction, 204
- Rhinosinusitis, **616**
- Rhinovirus, 151, **152**
 as picornavirus, 152
 receptors for, 150
- Rhizopus* spp., **137**, 630
- RhoGAM, **382**
- Rhombencephalon, 450
- Rhomboid crystals, 637
- Ribavirin
 for hepatitis, 639
 for hepatitis C, 187
 in pregnancy, avoiding, 187
 purine synthesis, effect on, 49
- Rib notching, 637
- Ribose, 90
- Ribosomes, 58
- Rice-water diarrhea, 162
 arsenic toxicity as cause, 87
 cholera toxin as cause, 116
Vibrio cholerae as cause, 129
- Richter transformation, 402
- Rickets, **427**
 Fanconi syndrome as cause, 633
 hypophosphatemia as cause, 542
 lab values in, 428
 treatments for, 640
 vitamin D deficiency as cause, 81, 313
 X-linked dominant inheritance of, 70
- Rickettsia* spp.
 Giemsa stain for, 110
 as intracellular organism, 112
 tetracyclines for, 175
- Rickettsial diseases, **133**
 morphology of, 109
- Rickettsia prowazekii*, 133
 animal transmission of, 132
 lice transmission of, 145
- Rickettsia rickettsii*, 133
 animal transmission of, 132
 chloramphenicol for, 175
 treatments for, 640
- Rickettsia typhi*, 132, 133
- Riedel thyroiditis, 322
- Rifabutin, 179
- Rifampin, 170, 179
 acute interstitial nephritis caused by, 554
 cytochrome P-450 and, 254
- for *Haemophilus influenzae* type B, 639
 for Hansen disease, 125
 hepatitis caused by, 252
 for *Mycobacterium leprae*, 179
 for *Mycobacterium tuberculosis*, 179, 640
 for *Neisseria meningitidis*, 640
 as prophylaxis, 181
 protease inhibitors and, 186
 RNA polymerase inhibition by, 54
- Rifamycins, **179**
- Rifaximin, 93, 367
- Rift Valley fever, 151
- Right anopia, 489
- Right anterior cardinal vein, 262
- Right bundle branch, 276
- Right bundle branch block, 271
- Right common cardinal vein, 262
- Right coronary artery, 265
 myocardial infarction and, 288
- Right external iliac artery, 342
- Right gastroepiploic artery, 343
- Right horn of sinus venosus, 262
- Right inferior phrenic artery, 342
- Right internal iliac artery, 342
- Right lower quadrant (RLQ) pain, 361
- Right lymphatic duct, 190
- Right marginal artery, 265
- Right recurrent laryngeal nerve, 568
- Right renal artery, 342
- Right subclavian artery, 568
- Right-to-left shunts, 282
- Right upper quadrant (RUQ) pain, 372
- Right ventricular hypertrophy (RVH)
 high altitude and, 615
 pulmonary hypertension as cause, 622
- Rigidity, in Parkinson disease, 633
- Riluzole, **505**
 for amyotrophic lateral sclerosis, 474
- Rimantadine, 184
- Ringed sideroblasts, 387
- Ringworm
 griseofulvin for, 183
 tinea corporis as cause, 136
- Risedronate, 447
- Risk, quantifying, **34**
- Risperidone, 514, 525
- Ristocetin, 385
- Risus sardonius
Clostridium tetani as cause, 122
 tetanospasmin as cause, 116
- Ritodrine, **602**
- Ritonavir, 184
 cytochrome P-450 and, 254
 for HIV, 186
- Rituximab, 214, **412**, 493
- Rivaroxaban, 407
 as anticoagulant, 383
 for deep venous thrombosis, 616
 for long-term anticoagulation, 640
- Rivastigmine, 244
 for Alzheimer disease, 505
- River blindness, 143
- RNA
 interference, 68
 microRNAs, **55**
 processing (eukaryotes), **54**
 protein synthesis direction, **53**
- RNA polymerases, **54**
- RNA viruses, **151**
 genome of, **147**
 replication of, 147
- Robertsonian translocation, **75**
- Rocker-bottom feet
 Edwards syndrome as cause, 74, 632
 Patau syndrome as cause, 74
- Rocky Mountain spotted fever, **133**
 animal transmission of, 132
 chloramphenicol for, 175
 presentation of, 633
- Rocuronium, 503
- Rod bacteria, 109
- Romaña sign, 142
- Romano-Ward syndrome, 277
- Romberg sign, 131, 474
- Romiplostim, 213
- Root cause analysis, for medical errors, 46
- Rooting reflex, 476
- Rosacea, 440
- Rose gardener's disease, 138
- Rosenthal fibers, 497
- Roseola
 HHV-6/HHV-7 as cause, 149
 rash caused by, 166
- Rosiglitazone, 334
- Rostral fold closure defects, 338
- Rosuvastatin, 300
- Rotator cuff muscles, **417**
- Rotavirus, **152**
 diarrhea caused by, 151, 162
 live attenuated vaccine for, 146
- Rotenone, 89
- Roth spots, 293, 633
- Rotor syndrome, 369
- Rough endoplasmic reticulum, **58**
- Rouleaux formation, 401, 638
- Round ligament of uterus, 574
- Rovsing sign, 360, 633
- Rubella, 151, **153**
 cardiac defects associated with, 284
 cataracts and, 483
 heart murmur caused by, 273
 rash caused by, 166
 as ToRCHeS infection, 165
 in unvaccinated children, 169
- Ruffini corpuscles, 454
- Russell sign, 520
- Ryanodine receptor, 424
- S**
- Saber shins
 congenital syphilis as cause, 131
 syphilis as cause, 165
- Sabin polio vaccine, 146
- Sabouraud agar, 111, 137
- Saccular aneurysms, 468
 Ehlers-Danlos syndrome and, 63
 renal cyst disorders and, 555
- Saccular lung development, 606
- Sacroccygeal teratomas, 598
- Saddle nose
 congenital syphilis as cause, 131
 Laron syndrome as cause, 327
 syphilis as cause, 165
- Safety culture, **45**
- Salicylates
 metabolic acidosis caused by, 543
 respiratory alkalosis caused by, 543
 toxicity treatment for, 251
- Saline, for β -blocker overdose, 303
- Saliva, effect of pilocarpine on, 244
- Salivary gland tumors, **353**
- Salk polio vaccine, 146
- Salmeterol, 246, 628
- Salmonella* spp.
 animal transmission of, 132
 bloody diarrhea caused by, 162
 as encapsulated bacteria, 112
 food poisoning caused by, 161
 in Gram-negative algorithm, 125
 in immunodeficient patients, 210
 as intracellular organism, 112
 morphology of, 109
 osteomyelitis and, 163, 644
 penicillinase-sensitive penicillins for, 171
 reactive arthritis and, 433
 vs. *Shigella* spp., **129**
 splenic dysfunction and, 191
 TMP-SMX for, 177
 type III secretion system of, 113
- Salmonella typhi*, 129
- Salpingitis
 ectopic pregnancy and, 589
 pelvic inflammatory disease as cause, 167
- Sampling bias in studies, 36
- Sandflies, as disease vectors, 142
- Sandfly fever, 151
- Saquinavir, 184, 186
- Sarcoidosis, **435**
 acute interstitial nephritis caused by, 554
 cardiomyopathy caused by, 291
 erythema nodosum and, 444
 facial nerve palsy caused by, 480
 as granulomatous disease, 223
 hypervitaminosis D caused by, 428
 macrophages and, 379
 presentation of, 630
 restrictive/infiltrative
 cardiomyopathy caused by, 291
 as restrictive lung disease, 619
 uveitis and, 484
- Sarcoma botryoides, 591
- Sarcoma
 metastases of, 233
 methotrexate for, 409
 nomenclature of, 228
 vimentin stain for, 60
- Sarcoplasmic reticulum, 424
- Sargramostim, 213
- SARS (sudden acute respiratory syndrome), 151

- Sartorius muscle, 347
 Saturday night palsy, 419
 Saxagliptin, 335
 Scabies, 145, 183
 Scalded skin syndrome
 Staphylococcus aureus as cause, 119
 toxic shock syndrome toxin as cause, 117
 Scales, skin, 438
 Scaling, in tinea capitis, 136
 Scaphoid bone, 418
 Scar formation, 219, **222**
 Scarlet fever
 presentation of, 120, 634
 rash caused by, 166
 Streptococcus pyogenes as cause, 120
 S cells, 350
 Schiller-Duval bodies, 593, 636
 Schilling test, 390
 Schistocytes, 387
 in HELLP syndrome, 590
 in intravascular hemolysis, 391
 in microangiopathic anemia, 393
Schistosoma spp., **144**, 145
Schistosoma haematobium, 144
 diseases associated with, 145
 as oncogenic microbe, 231
 squamous cell carcinoma of bladder and, 551
Schistosoma mansoni, 144
 Schistosomiasis
 calcification and, 220
 as granulomatous disease, 223
 portal hypertension caused by, 365
 pulmonary arterial hypertension caused by, 622
 Schizoaffective disorder, 514
 Schizoid personality disorder, 519
 Schizophrenia, **514**
 antipsychotic drugs for, 525
 atypical antipsychotics for, 525
 drug therapy for, 524
 genetic risk of, 510
 neurotransmitter changes in, 511
 neurotransmitters for, 455
 readmissions caused by, 45
 treatments for, 640
 Schizophreniform disorder, 514
 Schizotypal personality disorder, 519
 Schüffner stippling, 141
 Schwann cells, **453**
 in Guillain-Barré syndrome, 493
 origin of, 450
 Schwannomas, 453, 496, 642
 Sciatic nerve, 422
 SCID (severe combined immunodeficiency disease), 209
 adenosine deaminase deficiency as cause, 50
 hypoplastic thymus in, 191
 lymphopenia caused by, 394
 Sclerae, 482
 blue, in osteogenesis imperfecta, 63
 Scleritis, in rheumatoid arthritis, 430
 Sclerodactyly, 437
 Scleroderma, **437**
 autoantibody associated with, 207
 lab findings in, 634, 635
 Sclerodermal esophageal dysmotility, 354
 Sclerosing adenosis, 595
 Sclerosing cholangitis, 369, 371
 ulcerative colitis as cause, 359
 Scombroid poisoning, 250
 Scopolamine, 245
 Scoring of USMLE Step 1 exam, 7, 9–10
 Scorpion sting, pancreatitis caused by, 373
 Scotoma, 489
 Scrotum, 575
 female homolog of, 572
 lymphatic drainage of, 573
 masses in, **598**
 varicoceles in, 597
 Scurvy
 collagen synthesis and, 62
 presentation of, 634
 vitamin C deficiency as cause, 80
 Seafood toxins, **250**
 Seborrheic keratosis, 440
 Sebum, 440
 Secobarbital, 501
 Secondary adrenal insufficiency, 318
 Secondary biliary cirrhosis, 371
 Secondary glomerular disease, 544
 Secondary hyperaldosteronism, 318
 Secondary hyperparathyroidism, 325, 326
 Secondary hypertension, 643
 Secondary spontaneous pneumothorax, 623
 Secondary syphilis, 634
 Second-wind phenomenon, 99
 Secretin, 350
 location of, 351
 somatostatinomas and, 332
 Secretion rate, **535**
 Secretory phase of menstrual cycle, 579
 Secretory vesicles, 59
 Segmental artery, 532
 Segmented viruses, **152**
 Seizures, **494**
 aluminum hydroxide as cause, 375
 amphetamines as cause, 522
 Angelman syndrome as cause, 69
 barbiturates for, 501
 benzodiazepine withdrawal as cause, 522
 β -blockers as cause, 249
 bupropion as cause, 528
 cytomegalovirus as cause, 165
 delirium tremens as cause, 524
 as drug reaction, 253
 hyperosmolar hyperglycemia nonketotic syndrome as cause, 332
 hypocalcemia as cause, 542
 hyponatremia as cause, 542
 lupus as cause, 434
 medium-chain acyl-CoA dehydrogenase deficiency as cause, 101
 meningiomas as cause, 496
 meropenem as cause, 173
 PCP as cause, 523
 phenylketonuria as cause, 95
 serotonin syndrome as cause, 527
 Taenia solium and, 145
 tramadol and, 499
 tuberous sclerosis as cause, 495
 Selection bias in studies, 36
 Selective estrogen receptor modulators (SERMs), 413, 426, **601**
 Selective IgA deficiency, 208
 Selective media, 110
 Selective serotonin reuptake inhibitors (SSRIs), **527**
 for adjustment disorder, 517
 for anxiety disorders, 516
 for atypical depression, 515
 for binge eating disorder, 520
 conditions used for, 524
 for depression, 639
 diarrhea caused by, 252
 for generalized anxiety disorder, 517, 639
 for major depressive disorder, 515
 mechanism of, 526
 naming convention for, 255
 for obsessive-compulsive disorder, 517
 for panic disorder, 517
 for phobias, 517
 for postpartum depression, 516
 for PTSD, 517
 sexual dysfunction caused by, 520
 SIADH caused by, 253
 Selegiline, 504, **505**, 528
 Selenium sulfide, 136
 Self-fulfilling prophecies, 36
 Seminal vesicles, 571, 575
 Seminiferous tubules, 575, **576**
 spermatogenesis in, 583
 Seminomas, 598, 645
 Semustine, 410
 Senile plaques, 636
 Sensitivity equation, 646
 Sensitivity, in diagnostic tests, 33
 Sensorineural hearing loss, 481
 Sensory cortex, 467
 Sensory receptors, **454**
 thalamus and, 458
 Separation anxiety disorder, 511
 Separation anxiety in infants, 43
 Sepsis
 acute respiratory distress syndrome as cause, 621
 acute tubular necrosis caused by, 554
 findings associated with, 643
 in immunodeficient patients, 210
 lymphopenia caused by, 394
 neutropenia caused by, 394
 Pseudomonas aeruginosa and, 127
 shock caused by, 292
 Streptococcus agalactiae as cause, 121
 Septate uterus, 572
 Septation of heart chambers, 262
 Septic arthritis, **432**
 gonococci as cause, 126
 Staphylococcus aureus as cause, 119
 Septicemia
 Listeria monocytogenes as cause, 123
 readmissions caused by, 45
 Waterhouse-Friderichsen syndrome and, 318
 Septic shock
 diffuse cortical necrosis and, 552
 macrophages and, 379
 norepinephrine for, 246
 Septum primum, 262
 Septum secundum, 262
 Sequence, in organogenesis, 563
 Serine, 230
 Seronegative spondyloarthritis, **433**
 Serosa, 341
 Serositis, 434
 Serotonin, 455
 in carcinoid syndrome, 332
 derivatives of, 94
 vitamin B₆ and, 78
 Serotonin-norepinephrine reuptake inhibitors (SNRIs), **527**
 conditions used for, 524
 for fibromyalgia, 435
 for generalized anxiety disorder, 517, 639
 for major depressive disorder, 515
 mechanism of, 526
 serotonin syndrome caused by, 527
 Serotonin syndrome, **527**
 dextromethorphan as cause, 627
 MAO inhibitors as cause, 528
 MDMA as cause, 523
 oxazolindiones as cause, 176
 tramadol as cause, 499
 Serous cystadenocarcinomas, 592, 593, 644
 Serous cystadenomas, 592, 644
 Serous papillary cystadenocarcinomas of ovary, 232
 Serrated colonic polyps, 363
Serratia spp.
 as catalase-positive organism, 112
 chronic granulomatous disease and, 209
 in Gram-negative algorithm, 125
 in immunodeficient patients, 210
 lactose fermentation by, 126
 morphology of, 109
Serratia marcescens
 cephalosporins for, 172
 pigment produced by, 113
 UTIs caused by, 164
 Serratus anterior muscle, 420
 Sertoli cells, 571, 576
 Sertoli cell tumors, 598
 Sertraline, 527
 Serum amyloid A, 198

- Serum lactate, 330
- Serum markers of liver pathology, **366**
- Serum osmolarity
- antidiuretic hormone regulation of, 311
 - in hyperosmolar hyperglycemia nonketotic syndrome, 332
- Serum sickness, 205
- Serum tumor markers, **232**
- 17 α -hydroxylase, 312
- Sevoflurane, 502
- Sex chromosome disorders, **585**
- Sex hormone-binding globulin (SHBG), 316
- Sex hormones
- adrenal cortex secretion of, 306
 - disorders of, **586**
- Sex pilus, in bacterial genetics, 114
- Sex steroids, for hypopituitarism, 329
- Sexual abuse, 512
- Sexual development stages, 584
- Sexual dysfunction, **520**
- β -blockers as cause, 249, 303
 - cimetidine as cause, 374
 - Lambert-Eaton myasthenic syndrome as cause, 436
 - PDE-5 inhibitors for, 603
 - Peyronie disease and, 597
 - sildenafil for, 627
 - treatments for, 639
 - tuberoinfundibular pathway and, 458
- Sexually transmitted infections (STIs), **167**
- key associations, 645
 - parental consent for minors and, 40
 - sexual dysfunction caused by, 520
- Sexual response, innervation of, 575
- Sézary syndrome, 400, 631
- SGLT-2 inhibitors, 335
- Shagreen patches, 495
- “Shawl and face” rash, 436
- SHBG. *See* Sex hormone-binding globulin (SHBG)
- Sheehan syndrome, 329, 588, 632
- Sheep, as disease vectors, 144
- Shield chest, in Turner syndrome, 585
- Shiga-like toxin, 116, 128
- Shiga toxin, 114, 116
- Shigella* spp.
- bloody diarrhea caused by, 162
 - exotoxin produced by, 116
 - morphology of, 109
 - penicillinase-sensitive penicillins for, 171
 - reactive arthritis and, 433
 - vs. *Salmonella* spp., **129**
 - TMP-SMX for, 177
 - type III secretion system of, 113
- Shigella boydii*, 129
- Shigella dysenteriae*, 129
- Shigella flexneri*, 129
- Shigella sonnei*, 129
- Shingles, 149
- Shock, **292**
- acute respiratory distress syndrome as cause, 621
 - acute tubular necrosis caused by, 554
 - dopamine for, 246
 - Ebola as cause, 156
 - norepinephrine for, 246
 - placental abruption as cause, 588
 - pulmonary anthrax as cause, 121
 - Waterhouse-Friderichsen syndrome and, 318
- Short gastric arteries, 343
- Shortness of breath, in panic disorder, 517
- Shuffling gait, in Parkinson disease, 461
- SIADH, **328**
- ADH antagonists for, 336
 - carbamazepine as cause, 500
 - demeclocycline for, 336
 - as drug reaction, 253
 - key associations, 645
 - markers in, 542
 - small cell lung cancer as cause, 626
 - treatments for, 640
- Sialyl-Lewis^x, 221
- Sibling studies, 32
- Sickle cell anemia, 392
- in anemia taxonomy, 388
 - ESR in, 224
 - hydroxyurea for, 411
 - sickle cells in, 387
- Sickle cell disease
- autosplenectomy and, 641
 - chromosome associated with, 75
 - focal segmental glomerulosclerosis and, 548
 - lab findings in, 636
 - missense mutation as cause, 52
 - osteomyelitis and, 163
 - osteonecrosis caused by, 427
 - priapism caused by, 597
 - renal papillary necrosis and, 554
 - treatments for, 641
- Sickle cells, 387
- Sideroblastic anemia, 387, 389
- in anemia taxonomy, 388
 - lab findings in, 635
 - lead poisoning as cause, 389
 - vitamin B₆ deficiency as cause, 78
- Sigmoid colon, 360, 645
- Sigmoid sinus, 470
- Signaling pathways
- of endocrine hormones, **316**
 - of steroid hormones, **316**
- Signal recognition particle (SRP), 59
- Signet cell adenocarcinomas, 593
- Signet ring cells, 356
- Sign of Leser-Trélat, 229
- Sildenafil, 603
- for erectile dysfunction, 639
 - priapism caused by, 597
 - for pulmonary arterial hypertension, 640
 - for pulmonary hypertension, 627
- Silencers, in gene expression, **54**
- Silent mutations, **52**
- Silicosis, 619, **620**
- Silver stain, 110, 127
- Simeprevir
- for hepatitis, 639
 - for hepatitis C, 187
- Simple pneumothorax, 622
- Simple renal cysts, 555
- Simvastatin, 300
- Single nucleotide polymorphisms (SNPs), 66
- Single-stranded binding proteins, 51
- Sinusitis
- brain abscesses caused by, 163
 - C3 deficiency and, 199
 - Kartagener syndrome as cause, 60, 633
 - Wegener granulomatosis as cause, 296
- Sinusoids of spleen, **191**
- Sinus venosus, 262
- Sirolimus
- as immunosuppressant, 212
 - targets of, 213
- Sister Mary Joseph nodules, 356
- Sitagliptin, 335
- Situs inversus, 60, 633
- 6-mercaptopurine, 409
- allopurinol and, 448
 - azathioprine and, 212
 - in cell cycle, 408
 - purine synthesis and, 49
 - targets of, 408
 - toxicities of, 413
 - for ulcerative colitis, 359, 641
- 6-thioguanine, 408
- Sjögren syndrome, 244, **432**
- acute interstitial nephritis caused by, 554
 - autoantibody associated with, 207
 - biliary cirrhosis and, 371
 - pilocarpine for, 244
 - presentation of, 631
 - rheumatoid arthritis as cause, 430
- Skeletal muscles
- ACh receptors in, 241
 - autoregulation of, 280
 - glycogen metabolism in, 98
 - in nervous system, 241
- Skin
- autoregulation of, 280
 - collagen in, 61
 - dermatology, 437–445
 - morphology of, **438**
 - vascular tumors of, **441**
 - wrinkles of aging, 64
- Skin cancer, **445**
- albinism and, 439
 - Lynch syndrome and, 363
 - sunburn and, 444
- Skin disorders, **440, 443, 444**
- Skin drug reactions, **253**
- Skin flora, 161
- Skin infections, 127, **442**
- Skin layers, **437**
- Skin lesions
- Crohn disease as cause, 359
 - kwashiorkor as cause, 82
 - ulcerative colitis as cause, 359
- Skin ulcers, 142
- Skip lesions, 359, 641
- Slapped cheek rash, 166, 630
- Sleep apnea, **621**
- pulse pressure in, 266
 - pulsus paradoxus in, 294
- Sleep physiology, **457**
- Sleep problems
- apnea, 621
 - benzodiazepines and, 457, 522
 - β -blockers as cause, 249
 - delirium and, 512
 - generalized anxiety disorder as cause, 517
 - in geriatric patients, 44
 - ghrelin in, 311
 - leptin in, 311
 - major depressive disorder as cause, 515
 - menopause as cause, 582
 - paroxysmal nocturnal dyspnea, 292
 - stimulant withdrawal as cause, 522
 - varenicline as cause, 528
- Sleep terror disorder, **520**
- Sleepwalking, 457, 501
- Sliding hiatal hernias, 349
- Slipped capital femoral epiphysis, 427
- Slow twitch muscle fibers, 424
- Small bowel disease, 352
- Small cell lung cancer, **626, 645**
- carcinogens causing, 231
 - Cushing syndrome and, 229
 - hyponatremia and, 229
 - Lambert-Eaton myasthenic syndrome and, 436
 - neuromuscular paraneoplastic syndromes and, 229
 - topotecan for, 411
- Small intestine, 350
- Small lymphocytic lymphoma (SLL), 402
- Small nuclear ribonucleoproteins (snRNPs), 55
- Smallpox, 146, 148
- Smoke inhalation, 222
- Smoking
- abdominal aortic aneurysms and, 286
 - angina caused by, 287
 - atherosclerosis and, 286
 - Buerger disease and, 296, 639
 - bupropion for cessation, 528
 - carcinogenic nature of, 231
 - cataracts and, 483
 - cervical cancer and, 591
 - colorectal cancer and, 364
 - emphysema and, 618
 - esophageal cancer and, 355
 - head and neck cancer and, 616
 - hormonal contraception contraindication, 602
 - Legionnaires' disease and, 127
 - lung cancer and, 626
 - pancreatic cancer and, 373
 - placental abruption and, 588
 - renal cell carcinoma and, 550
 - renal tumors and, 645
 - saccular aneurysms and, 468

- Smoking (*continued*)
 squamous cell carcinoma of
 bladder and, 551
 stomach cancer and, 356
 teratogenic effects of, 564
 transitional cell carcinoma
 and, 551
 varenicline for cessation, 528
- Smooth endoplasmic reticulum, **58**
- Smooth muscle
 autoantibody to, 207
 contraction of, **425**
 in nervous system, 241
 in respiratory tree, 608
 tumor nomenclature in, 228
- Snuffles, in congenital syphilis, 131
- Soap bubble on X-ray, 638
- Social anxiety disorder, 517
 drug therapy for, 524
 Selective serotonin reuptake
 inhibitors (SSRIs)
 for, 527
 venlafaxine for, 527
- Sodium channel blockers, **302**
- Sodium channels
 cystic fibrosis and, 72
 epilepsy drug effects on, 500
 glucose and, 308
 local anesthetic effects on, 503
 pacemaker action potential
 and, 275
 permethrin and, 183
- Sodium oxybate, 521
- Sodium-potassium channels, 241
- Sodium-potassium pump, **61**
 cell injury and, 218
- Sodium stibogluconate, 183
 for leishmaniasis, 142
- Sofosbuvir, 187, 639
- Solifenacin, 245
- Solitary functioning kidney, **531**
- Solitary nucleus of medulla, 279
- Somatic hypermutation, 193
- Somatic mosaicism, 69
- Somatic symptom disorder, **518**
- Somatosensory cortex, 462
- Somatostatin, 309, 336, 350
 glucagon and, 309
 location of, 351
 production of, 307
- Somatostatinomas, **332**
- Somatotroph hyperplasia, 496
- Somatotropic adenomas, 644
- Somatotropin. *See* Growth hormone
 (GH)
- Sonic hedgehog gene, 562
- Sonic hedgehog signaling
 pathway, 451
- Sorbitol, **92**
- Sorbitol dehydrogenase, 92
- Sotalol, 303
- Southern blot, 65
- Southwestern blot, 65
- Space of Disse, 346
- Spaghetti and meatballs appearance
 of tinea versicolor, 136
- Spasticity, 501
- Spastic paralysis, 473
Clostridium tetani as cause, 122
 tetanospasmin as cause, 116
- Specificity equation, 33, 646
- Spectrin, 71
- Spermatic cord, 348
- Spermatoceles, 598
- Spermatocytes, 576
- Spermatogenesis, 576, **583**
 cryptorchidism and, 597
 prolactin effect on, 310
 Sertoli cells and, 576
- Spermatogonia, 576
- Sperm, ejaculation pathway, 575
- Sphenomandibular ligament, 569
- Sphenoparietal sinus, 470
- Spherical bacteria, 109
- Spherocytes, 387
 in extravascular hemolysis, 391
- Sphincter of Oddi, 347, 350
- Sphingolipidoses, 100
- Sphingomyelin, 100
- Sphingomyelinase, 100
- Spider angiomas
 ataxia-telangiectasia as cause, 209
 cirrhosis as cause, 365
- “Spike and dome” cells, 548
- Spikes on basement membrane, 638
- Spina bifida
 Dandy-Walker syndrome and, 451
 lab findings in, 636
- Spina bifida occulta, 451
- Spinal cord, **472**
 embryologic derivatives of, 563
 hemisection of, 475
 lesions of, **474**
 lower extent, **472**
- Spinal nerves, **472**
- Spinal tap, bloody/yellow, 635, 638
- Spinal tract anatomy and
 functions, **473**
- Spindle cells, 496
- Spinothalamic tract, 473
- Spiral bacteria, 109
- Spirochetes, **130**
- Spiroonolactone, 558, 603
 gynecomastia caused by, 595
 for heart failure, 292
 for hyperaldosteronism, 639
 metabolic acidosis caused by, 543
 for PCOS, 591
 reproductive hormones and, 600
- Splay, in glucose clearance, 536
- Spleen
 blood supply and innervation
 of, 342
 diagram of, 191
 embryology, 339
 in gastrointestinal anatomy, 340
 ischemia susceptibility, 218
 sinusoids of, **191**
 thrombocytes in, 378
- Splenectomy, 71, 392
- Splenic artery, 343
- Splenomegaly
 amyloidosis and, 225
 anemia as cause, 141
 cirrhosis as cause, 365
 hairy cell leukemia as cause, 402
 hereditary spherocytosis as
 cause, 392
 rheumatoid arthritis as cause, 430
- Splenorenal ligament, 340
- Spliceosome, 55
- Splice site mutations, **52**
- Splicing of pre-mRNA, **55**
- Splinter hemorrhages, 293, 634
- Splitting, as ego defense, 509
 in borderline personality
 disorder, 519
- Splitting, in heart sounds, **271**
- Spondyloarthropathy, 225
- Spongiform cortex, in Creutzfeldt-
 Jakob disease, 491
- Spongiosis, 439
- Spontaneous abortion
 antiphospholipid syndrome as
 cause, 434
 fibroid tumors as cause, 594
Listeria monocytogenes as
 cause, 123
 syphilis as cause, 165
 Vitamin A overdose as cause, 564
 warfarin as cause, 564
- Spore-forming bacteria, **114**
- Spores, 108
- Sporothrix schenckii*, **138, 641**
- Sporotrichosis, 138
- Sprue
 fat-soluble vitamin deficiencies
 and, 76
 vitamin B₁₂ deficiency caused
 by, 80
- Squalene epoxidase, 181, 182
- Squamous cell carcinomas
 of bladder, 144, **551**
 carcinogens causing, 231
 of cervix, 591
 cytokeratin stain for, 60
 of esophagus, 354, 355, 643
 of head and neck, 616
 HIV and, 160
 hypercalcemia and, 229
 lab findings in, 636
 of lungs, 626
 pectinate line and, 345
 of penis, 597
 of skin, 445
 sunburn and, 444
 of vagina, 591
- Squamous epithelium, 608
- SRY gene, **571**
- Stable angina, 287, 641
- Stable cells, 58
- Stab wounds, winged scapula caused
 by, 420
- Staghorn calculi, 549
- Stains, bacterial, **110**
- Standard deviation, 37
- Standard error of the mean, 37
- Stapedial artery, 568
- Stapedius muscle, 569
- Stapes bone, 481, 569
- Staphylococcal scalded skin
 syndrome, 442
- Staphylococcus* spp.
 antibiotic tests for, 118
 as catalase-positive organism, 112
 Chédiak-Higashi syndrome
 and, 209
 chronic granulomatous disease
 and, 209
 in Gram-positive algorithm, 118
 morphology of, 109
- Staphylococcus aureus*, **119**
 antimicrobial prophylaxis for, 181
 bacterial endocarditis caused
 by, 293
 β-hemolytic nature of, 119
 brain abscesses caused by, 163
 cephalosporins for, 172
 chronic granulomatous disease
 and, 643
 cystic fibrosis and, 72, 162
 dapsone for, 178
 exotoxin produced by, 117
 food poisoning caused by, 161, 643
 immunocompromised patients
 and, 162
 influenza and, 153
 IV drug use and, 162
 lactational mastitis caused by, 595
 lung abscesses caused by, 624
 as nosocomial infection, 162, 168
 osteomyelitis and, 163, 644
 penicillinase-resistant penicillins
 for, 171
 pigment produced by, 113
 pneumonia caused by, 624, 644
 as postviral infection, 162
 septic arthritis caused by, 432
 skin infections caused by, 442
 T cells, effect on, 202
 treatments for, 641
- Staphylococcus epidermidis*, **119**
 bacterial endocarditis caused
 by, 293
 Gram-positive testing, 118
 in vivo biofilm produced by, 113
 as normal flora, 161
 as nosocomial infection, 168
 novobiocin response, 637
 osteomyelitis caused by, 163
 vancomycin for, 173
- Staphylococcus gallolyticus*, 121
- Staphylococcus pneumoniae*, 616
- Staphylococcus saprophyticus*, **120**
 Gram-positive testing, 118
 kidney stones caused by, 549
 novobiocin response, 637
 as urease-positive organism, 112
 urinary tract infections caused
 by, 552, 646
 UTIs caused by, 164
- Starling curve, **268**
- Starling forces, 281
- “Starry sky” appearance of B cells, 400
- Start and stop codons, **53**
- Starvation, metabolism in, 103
- Statins
 for acute coronary syndromes, 290
 cholesterol synthesis and, 103

- hepatitis caused by, 252
for hypercholesterolemia, 640
myopathy caused by, 253
Statistical distribution, **37**
Statistical hypotheses, **37, 38, 39**
Statistical tests, **39**
Status epilepticus, 494
 benzodiazepines for, 501
 drug therapy for, 500
Stavudine, **184, 186**
Steady state, in dosage
 calculations, 237
Steatohepatitis, 365
Steatorrhea
 cystic fibrosis as cause, 72
 malabsorption syndromes as
 cause, 358
 octreotide as cause, 375
 orlistat as cause, 376
 somatostatinomas as cause, 332
Steeple sign on X-ray, 154, 638
Stellate cells, 346
Stellate infiltration of ductal
 carcinoma, 596
Stem cells, in aplastic anemia, 391
Stercobilin, 353
Steroid hormone signaling
 pathways, **316**
Steroids
 acute pancreatitis caused by, 373
 adrenal insufficiency caused
 by, 318
 for berylliosis, 620
 CRH levels in, 309
 for lupus, 434
 for multiple sclerosis, 492
 osteoporosis and, 426
 for polymyositis/
 dermatomyositis, 436
 for sarcoidosis, 435
 for temporal arteritis, 641
Steroid synthesis, 83
Stevens-Johnson syndrome, 443
 as drug reaction, 253
 epilepsy drugs causing, 500
 ethosuximide as cause, 500
 sulfa drug allergies as cause, 254
Stimulants, for ADHD, 511
St. John's wort, 254
St. Louis encephalitis, 151
Stomach
 cholecystokinin effect on, 350
 in gastrointestinal anatomy, 340
 histology of, 341
 sclerosis of, 437
 secretin effect on, 350
"Stone" bone appearance, 426
Straight sinus, 470
Stranger anxiety in infants, 43
Strawberry cervix, 142, 164, 167
Strawberry hemangiomas, 441, 645
Strawberry tongue
 causes of, 634
 Kawasaki disease as cause, 296
 in scarlet fever, 120
Streak ovaries, 634
Streptococcus spp.
 antibiotic tests for, 118
 Chédiak-Higashi syndrome
 and, 209
 in Gram-positive algorithm, 118
 morphology of, 109
 septic arthritis caused by, 432
Streptococcus agalactiae (Group B
 strep), **121**
 antimicrobial prophylaxis for, 181
 bacitracin response, 635
 bacterial meningitis caused by, 642
 β -hemolytic nature of, 119
 as encapsulated bacteria, 112
 Gram-positive testing, 118
 in immunodeficient patients, 210
 meningitis caused by, 163
 in neonates, 165
 pneumonia caused by, 162
 splenic dysfunction and, 191
Streptococcus bovis, **121**
 bacterial endocarditis caused
 by, 293
 colon cancer and, 638
 colorectal cancer and, 364
 treatments for, 641
Streptococcus mitis, 120
Streptococcus mutans
 biofilm produced by, 113
 dental caries caused by, 120
 as normal flora, 161
 optochin response, 637
Streptococcus pneumoniae, **120**
 α -hemolytic nature of, 119
 bacterial meningitis caused by, 642
 chloramphenicol for, 175
 cystic fibrosis and, 162
 as encapsulated bacteria, 112
 Gram-positive testing, 118
 IgA protease and, 113
 in immunodeficient patients, 210
 influenza and, 153
 IV drug use and, 162
 meningitis caused by, 163
 optochin response, 637
 penicillin G/V for, 170
 pneumonia caused by, 162, 624
 as postviral infection, 162
 splenic dysfunction and, 191
 transformation in, 114
 treatments for, 641
Streptococcus pyogenes (Group A
 strep), **120**
 acute poststreptococcal
 glomerulonephritis and, 546
 bacitracin response, 635
 β -hemolytic nature of, 119
 clindamycin for, 175
 exotoxin produced by, 117
 Gram-positive testing, 118
 M protein and, 113
 penicillin G/V for, 170
 rash caused by, 166
 skin infections caused by, 442
 T cells, effect on, 202
 treatments for, 641
Streptococcus sanguinis, 113, 637
Streptogramins, 170, 181
Streptokinase, 383, 407
Streptolysin O, 117
Streptomycin, 170, 174, **180**
Streptozocin, 410
Stress, as asthma trigger, 618
Stress incontinence, 551
Striated muscle, 228
Striatum, 460, 467
"String sign" on barium swallow, 359
Stroke, **467**
 ADP receptor inhibitors for, 407
 atrial fibrillation as precursor, 278
 central post-stroke pain
 syndrome, 468
 cilostazol/dipyridamole for, 407
 direct factor Xa inhibitors for, 407
 eclampsia as cause, 590
 homocystinuria as cause, 96
 hypertension as cause, 284
 hypertensive emergency and, 284
 sickle cell anemia as cause, 392
 syphilis as cause, 131
 thrombolytics for, 407
 vertigo caused by, 495
 warfarin for, 406
Stroke volume, 267, 647
Stroma, diseases affecting, 595
Strongyloides spp., 142
Strongyloides stercoralis, 143
ST-segment elevation MI
 (STEMI), 287, **289**
 treatments for, 290
ST segment, in EKG, 276
Studies
 errors in, **36**
 types of, 32
Studying for USMLE Step 1 exam
 materials for, 18–19
 in preclinical years, 12–13
 timeline for, 14–17
Sturge-Weber syndrome, 495, 634
Stylohyoid ligament, 569
Stylohyoid muscle, 569
Styloid process, 569
Stylopharyngeus, 569
Subacute cerebellar
 degeneration, 626
Subacute combined degeneration, 80
Subacute endocarditis
 enterococci as cause, 121
 Staphylococcus gallolyticus as
 cause, 121
Subacute granulomatous
 thyroiditis, 322
Subacute sclerosing panencephalitis
 (SSPE), 154
Subacute thyroiditis, 223
Subarachnoid hemorrhage, 468, 469
 headache caused by, 494
 lab findings in, 635, 638
 nimodipine for, 298
 presentation of, 634
Subarachnoid space, 472
 in cavernous sinus, 481
 in neural tube defects, 451
Subclavian arteries, 466, 568
Subcutaneous fat, 437
 erythema nodosum in, 444
Subcutaneous nodules, 120
Subcutis, 437
Subdural hematomas, 469
 as child abuse sign, 510
 key associations, 643
Subendocardium, 218
Sublimation, as ego defense, 509
Submucosa, 341
Submucosal gland, 341
Subunit muscle, 417
Substance abuse
 adult T-cell lymphoma and, 400
 Candida albicans and, 137
 delirium caused by, 512
 dementia caused by, 513
 dissociative identity disorder
 and, 512
 loss of orientation caused by, 512
 parental consent for minors
 and, 40
 Pseudomonas aeruginosa and, 127
 stages of change in
 overcoming, **521**
 suicide and, 516
 torsades de pointes caused by, 277
 tricuspid valve endocarditis caused
 by, 293
Substance P, 499
Substance use disorder, **521**
Substantia nigra, 635
Substantia nigra pars compacta, 460
Subthalamic nucleus, 460
 lesions in, 464
Subunit vaccines, 146
Succimer
 for arsenic toxicity, 251
 for gold poisoning, 251
 for lead poisoning, 251, 389
 for mercury poisoning, 251
Succinate dehydrogenase, 78, 89
Succinylcholine, 503
Succinyl-CoA
 in gluconeogenesis, 89
 in TCA cycle, 88
Sucking reflex, 476
Sucralfate, **375**
Sudan stain, 358
Sudden cardiac death, 287
Sudden infant death syndrome
 (SIDS), 581
Suicidal patients, 42
 confidentiality exceptions and, 41
 elderly, 44
Suicide
 bipolar disorder and, 515
 borderline personality disorder
 and, 519
 as common cause of death, 45
 major depressive disorder and, 515
 physician-assisted, 42
 risk factors for, **516**
 schizophrenia and, 514
Sulbactam, 171
Sulci, in Alzheimer disease, 491
Sulfadiazine, 177
 functioning of, 170
 for *Toxoplasma gondii*, 140, 641

- Sulfa drugs, **254**
 acute pancreatitis caused by, 373
 erythema multiforme caused by, 443
 G6PD deficiency caused by, 392
 lupus-like syndrome caused by, 253
 megaloblastic anemia caused by, 252
 rash caused by, 253
- Sulfamethoxazole, 170, 177
- Sulfapyridine, 375
- Sulfasalazine, 254, **375**, 430
- Sulfatides, 124, 493
- Sulfisoxazole, 170, 177
- Sulfonamides, **177**
 acute interstitial nephritis caused by, 554
 cytochrome P-450 and, 254
 functioning of, 170
 hemolysis in G6PD deficiency caused by, 252
 hypothyroidism caused by, 252
 for *Nocardia* spp., 123
 photosensitivity caused by, 253
 in pregnancy, avoiding, 187
 trimethoprim and, 177
 vitamin B₉ deficiency caused by, 79
- Sulfonyleureas, 254, 334
 disulfiram-like reaction caused by, 254
 insulin and, 308
- Sulfur granules, 113, 123
- Sumatriptan, 505
 for cluster headaches, 494
 coronary vasospasm caused by, 251
 for migraines, 640
- Sunburn, 444
- Superficial inguinal lymph nodes, 190
- Superficial inguinal ring, 348
- Superior cerebellar artery, 466
- Superior colliculi, 477
- Superior gluteal nerve, 422
- Superior lobe, 609
- Superior mesenteric artery, 342
- Superior mesenteric artery (SMA) syndrome, 342
- Superior mesenteric lymph nodes, 190
- Superior mesenteric vein, 344
- Superior oblique muscle, 488
- Superior ophthalmic vein, 470
- Superior orbital fissure, 478
- Superior rectal artery, 345
- Superior rectal vein, 344
- Superior rectus muscle, 488
- Superior sagittal sinus, 470
- Superior sulcus tumors, 625
- Superior vena cava
 EKG and, 276
 embryological development of, 262
 in fetal circulation, 264
- Superior vena cava syndrome, **625**
 lung cancer and, 626
 Pancoast tumor as cause, 625
- Superoxide dismutase, 201
 free radical elimination by, 221
- Suppression, as ego defense, 509
- Suprachiasmatic nucleus, 456
 sleep physiology and, 457
- Supraclavicular node
 enlargement, 631
- Suprarenal arteries, 342
- Suprascapular nerve, 417
- Supraspinatus muscle, 417
 in Erb palsy, 420
- Supratentorial mass, 498
- Supraventricular tachycardia
 adenosine for diagnosing, 304
 β -blockers for, 249, 303
 calcium channel blockers for, 304
- Suramin, 140, 183
- Surface F protein, 153
- Surfactant, 611
- Surgical neck of humerus, 423
- Surrogate decision-maker, **41**
- Swan-Ganz catheter, 280
- Swarming, in *Pseudomonas aeruginosa*, 164
- Sweat, effect of pilocarpine on, 244
- Sweat glands
 embryologic derivatives of, 563
 in nervous system, 241
- Swiss cheese model, **46**
- Sydenham chorea, 120, 294
- Sylvian fissure, 462
- Sympathetic nervous system, 241
 male sexual response and, 575
- Sympathetic receptors, 242
- Sympatholytic drugs, **247**
- Sympathomimetic drugs, **246**
- Symphysis pubis, 575
- Syncope, 273
- Syncytiotrophoblasts, 566
 β -hCG and, 232
 choriocarcinomas and, 587
 hCG secretion by, 580
- Syndrome of apparent
 mineralocorticoid excess, 538
- Syndrome of inappropriate
 antidiuretic hormone secretion. *See* SIADH
- Synergistic drug interactions, 237
- Syngeneic grafts, 210
- Syphilis, **131**
 antimicrobial prophylaxis for, 181
 aortic aneurysms and, 641
 dementia caused by, 491
 as granulomatous disease, 223
 presentation of, 633, 634
 as STI, 167
 tabes dorsalis caused by, 474
 testing for, 131
 thoracic aortic aneurysms and, 286
 as ToRCHeS infection, 165
- Syphilitic heart disease, **294**
- Syringomyelia, **452**
 Horner syndrome and, 487
 spinal cord lesions in, 474
- Systemic mycoses, **135**
- Systemic primary carnitine deficiency, 101
- Systole, 270
 heart failure and, 292
 heart murmurs of, 272, 273
 heart sounds of, 272
- Systolic ejection, 270
- Systolic murmur, 291
- Systolic pressure, 266
- T**
- Tabes dorsalis
 lab findings in, 635
 spinal cord lesions in, 474
 syphilis as cause, 131, 167
- Tachyarrhythmia
 isoproterenol for evaluating, 246
 thyroid storm as cause, 323
- Tachycardia
 alcohol withdrawal as cause, 523
 amphetamines as cause, 522
 delirium tremens as cause, 524
 fenoldopam as cause, 298
 hydralazine as cause, 298
 MDMA as cause, 523
 metronidazole as cause, 178
 nitrates as cause, 299
 PCP as cause, 523
 phenoxybenzamine as cause, 248
 pulmonary embolism as cause, 617
 stimulants as cause, 522
 thyroid hormones as cause, 335
 tricyclic antidepressants as cause, 527
 Wolff-Parkinson-White syndrome as cause, 277
- Tachyphylactic drug interactions, 237
- Tachypnea
 asthma as cause, 618
 pulmonary embolism as cause, 617
- Tacrine, 505
- Tacrolimus
 hyperglycemia caused by, 252
 as immunosuppressant, 212
 targets of, 213
- Tactile hallucinations, 513
 cocaine as cause, 522
- Tadalafil, 603, 639
- Taenia solium*, 144, 145
- Takayasu arteritis, 223, **296**
- Talcosis, 223
- Talking, as developmental milestone, 43
- Tamoxifen, **413**, 601
 for breast cancer, 639
 hot flashes caused by, 252
- Tamsulosin, 248, 599, **603**
- Tanner stages of sexual development, **584**
- Tarasoff decision, 41
- Tardive dyskinesia, 525
 as drug reaction, 253
 metoclopramide for, 376
 nigrostriatal pathway and, 458
- Target cells, 191, 387
- Tarsal tunnel syndrome, 422
- TATA box, 54
- Tau proteins, 637
- Taxonomy, bacterial, **109**
- Tay-Sachs disease, 100
 frameshift mutation as cause, 52
 presentation of, 630
- Tazobactam, 171
- TBG. *See* Thyroid-binding globulin (TBG)
- TCA cycle, **88**
 diagram of, 85
 hyperammonemia and, 93
 location of in cell, 83
 pyruvate metabolism and, 88
 rate-determining enzyme for, 84
- T cells, **380**
 activation of, **195**
 adaptive immunity and, 192
 anergy, 202
 cell surface proteins, 202
 cytokines secreted by, 200
 cytotoxic, 194
 differentiation of, **194**
 disorders of, 208, 209
 function of, 380
 glucocorticoids effect on, 212
 helper, 194
 in HIV, 159
 leflunomide effect on, 447
 in lymph node, 190
 major functions of, 193
 regulatory, 194
 sirolimus effect on, 212
 in spleen, 191
 in thymus, 191
- Tears, effect of pilocarpine on, 244
- Telangiectasias
 autosomal dominance of, 71
 in basal cell carcinomas, 445
 in CREST syndrome, 437
 Osler-Weber-Rendu syndrome as cause, 634
- Telencephalon, 450
- Tellurite agar, 111
- Telomerase, **51**
- Telophase, 58
- Temazepam, 501
- Temperature receptors, 454
- Temperature regulation, 456
- Temporal arteritis
 ESR in, 224
 as granulomatous disease, 223
 key associations, 645
 necrosis and, 217
 polymyalgia rheumatica and, 435
 treatments for, 641
- Temporalis muscle, 569
- Temporal lobe, 462, 467
- Temporal lobe encephalitis, 149
- Temporal retina, 487
- Tendinopathy of rotator cuff, 417
- Tendinous xanthomas, 285
 familial hypercholesterolemia as cause, 71, 105
- Tendonitis
 as drug reaction, 253
 fluoroquinolones as cause, 178
- Tendons, collagen in, 61
- Tenectplase, 383, 407

- Teniposide, **411**
 in cell cycle, 408
 as topoisomerase inhibitor, 51
- Tennis elbow, 417
- Tenofovir, **184**
 Fanconi syndrome caused by, 538
 for HIV, 186
- Tenosynovitis, 432
- Tension headaches, 494
- Tension pneumothorax, 622, 623
- Tensor fascia latae muscle, 422
- Tensor tympani muscle, 569
- Tensor veli palatini muscle, 569
- Tentorium cerebelli, 498
- Teratogens, **564**
 ACE inhibitors as, 559
 aminoglycosides as, 174
 angiotensin II receptor blockers as, 559
 carbamazepine as, 500
 griseofulvin as, 183, 187
 leftunomide as, 447
 lithium as, 526
 methimazole as, 335
 ribavirin as, 187
 vitamin A, 77
 warfarin as, 406
- Teratomas, 598
- Terazosin, 248, 599
- Terbinafine, 181, **182**
- Terbutaline, **602**
- Teres minor, 417
- Teriparatide, 426, **447**
- Terminal bronchioles, 606
- Terminal deoxynucleotidyl transferase (TdT), 196
- Terminal ducts (breast), diseases affecting, 595
- Termination of protein synthesis, 57
- Tertiary adrenal insufficiency, 318
- Tertiary hyperparathyroidism, 326
- Tertiary syphilis
 aortic aneurysms and, 641
 as granulomatous disease, 223
- Tesamorelin, 309
- Testes, 575
 descent of, **573**
 embryologic derivatives of, 563
 lymphatic drainage of, 573
 progesterone production in, 577
- Testicular atrophy
 alcoholism as cause, 523
 cirrhosis as cause, 365
 muscular dystrophy as cause, 73
- Testicular cancer
 bleomycin for, 410
 cisplatin/carboplatin for, 411
 gynecomastia caused by, 595
 key associations, 645
- Testicular lymphomas, 598
- Testicular/ovarian arteries, 342
- Testicular tumors, **598**
- Testosterone, 582, **603**
 in androgen insensitivity syndrome, 586
 in cryptorchidism, 597
 in Klinefelter syndrome, 585
 Leydig cell secretion of, 576
 pharmacologic control of, 600
 Sertoli cells and, 576
 SHBG effect on, 316
 signaling pathways for, 316
 in spermatogenesis, 576
- Testosterone-secreting tumors, 586
- Testosterone synthesis, 182
- Tetanospasmin, 116, 122
- Tetanus
 bacteria causing, 114
 exotoxins as cause, 115
 vaccine for, 122
- Tetanus toxin, 122, 203
- Tetany
 hypocalcemia as cause, 542
 hypoparathyroidism as cause, 325
 thymic aplasia as cause, 208
- Tetrabenazine
 for Huntington disease, 505
 for Tourette syndrome, 511, 524
- Tetracaine, 503
- Tetracyclines, 170, 175
 esophagitis caused by, 252
 Fanconi syndrome caused by, 253, 538
 photosensitivity caused by, 253
 as protein synthesis inhibitors, 174
 pseudotumor cerebri and, 471
 as teratogens, 187, 564
 tooth discoloration caused by, 253
- Tetrahydrofolic acid, 79, 177
- Tetralogy of Fallot, 263, 282
 22q11 syndromes as cause, 284
 cyanosis caused by, 642
 fetal alcohol syndrome as cause, 284
 lab findings in, 635
 thymic aplasia as cause, 208
- Tetrodotoxin, 250
- TGF- β
 regulatory T cells and, 194
 in wound healing, 223
- Thalamus, 450, **458**
- Thalassemia, 388
 in anemia taxonomy, 388
 lab findings in, 636
 target cells in, 387
- Thalidomide, 564
- Thayer-Martin agar, 110, 111
- Theca interna cells, 577
- Theca-lutein cysts, 587, 592
- Thecomas, 592
- Thenar muscles, 420, 421
- Theophylline, 628
 cytochrome P-450 and, 254
 therapeutic index value of, 240
- Therapeutic antibodies, **214**
- Therapeutic index, **240**
- Therapeutic privilege, and informed consent, 40
- Thermogenin, 89
- Thiazides, 254, **558**
 gout caused by, 253
 for heart failure, 292
 for hypertension, 298
 site of action, 556
- Thiazolidinediones, 334
- Thick ascending loop of Henle
 Bartter syndrome and, 538
 ethacrynic acid effect on, 557
 loop diuretics effect on, 557
 in nephron physiology, 537
- Thin descending loop of Henle, 537
- Thionamides, **335**
- Thiopental, 501, 502
- Thioridazine, 525
- Thirst
 hypothalamus and, 456
 renin-angiotensin-aldosterone system and, 540
- 30S inhibitors, 174
- Thoracentesis, 623
- Thoracic aortic aneurysm, 284, 286
- Thoracic duct, 190
- Thoracic outlet syndrome, 420
- Threadworms, 143
- Threonine, 92
- Threonine kinase, 230
- Thrombi
 atherosclerosis as cause, 286
 calcification and, 220
- Thrombin, 405
- Thrombocytes, **378**
 in essential thrombocythemia, 404
 as liver marker, 366
 in myeloproliferative disorders, 404
 in platelet plug formation, 385
 in wound healing, 223
- Thrombocytopenia, 378
 azathioprine as cause, 212
 blood transfusion therapy for, 399
 cirrhosis as cause, 365
 Class IA antiarrhythmics as cause, 302
 cytarabine as cause, 409
 as drug reaction, 252
 ganciclovir as cause, 185
 glycoprotein IIb/IIIa inhibitors as cause, 407
 heparin as cause, 405
 oxazolidinones as cause, 176
 recombinant cytokines for, 213
 sirolimus as cause, 212
 sulfa drug allergies as cause, 254
 ToRCHeS infections as cause, 165
 Wiskott-Aldrich syndrome as cause, 209
- Thrombocytosis, 191
- Thrombogenesis, **385**
- Thrombolytic drugs, 383, **407**
- Thrombomodulin
 in thrombogenesis, 385
- Thrombophlebitis
 pancreatic cancer as cause, 373
 vancomycin as cause, 173
- Thrombopoietin receptor agonists, 213
- Thrombopoietin signaling pathways, 316
- Thrombosis
 celecoxib as cause, 447
 essential thrombocythemia as cause, 404
 homocystinuria as cause, 96
- Thrombotic complications, 252
- Thrombotic endocarditis, 642
- Thrombotic stroke, 470
- Thrombotic thrombocytopenic purpura (TTP), 387
- Thromboxane, 446
- Thrush
Candida albicans as cause, 137
 vs. hairy leukoplakia, 442
 HIV and, 160
 nystatin for, 182
 SCID as cause, 209
- Thumbprint sign on X-ray, 126
- Thumb sign on X-ray, 638
- Thymic aplasia, 76, 208, 570
 22q11 deletion syndromes as cause, 76
 chromosome associated with, 75
 DiGeorge syndrome as cause, 570
 hypoparathyroidism caused by, 325
 hypoplastic thymus in, 191
 lymphopenia caused by, 394
- Thymic cortex
 T cell selection in, 194
- Thymic hyperplasia, 436
- Thymic shadow, 209
- Thymidine, 177
- Thymidine kinase, 184
- Thymidylate, 49
- Thymomas
 Good syndrome and, 229
 myasthenia gravis and, 229, 436
 pure red cell aplasia and, 229
- Thymus, **191**
 in fetal development, 306
 T cell differentiation in, 194
 T cell origination in, 380
- Thymus-dependent antigens, 197
- Thymus-independent antigens, 197
- Thyroglobulin
 autoantibody to, 207
 function of, 315
- Thyroglossal duct cyst, 306
- Thyroid adenomas, 321, **324**
- Thyroid cancer, **324**
 bone metastases in, 644
 carcinogens causing, 321
 goiter caused by, 231
 key associations, 645
 MEN 2B and, 634
 metastases of, 233
 Psammoma bodies in, 232
- Thyroid cartilage, 569
- Thyroid cysts, 321
- Thyroid development, 306
- Thyroidectomy, 324
- Thyroid hormones, **315**
 signaling pathways for, 316
 in toxic multinodular goiter, 323
- Thyroiditis, 223
- Thyroid lymphomas, 324
- Thyroid peroxidase
 function of, 315
 thionamide effect on, 335
 thyroid hormones and, 315
- Thyroid-regulating hormone (TRH)
 signaling pathways for, 316
 thyroid hormones and, 315

- Thyroid replacement therapy, 426
- Thyroid-stimulating hormone (TSH)
- Graves disease and, 323
 - in hyperthyroidism, 321
 - in hypothyroidism, 321
 - secretion of, 307
 - signaling pathways of, 316
- Thyroid-stimulating hormone (TSH) receptor, 207
- Thyroid-stimulating immunoglobulin (TSI), 315, 323
- Thyroid storm, 323
- Thyrotropin-releasing hormone (TRH), 309, 310
- Thyroxine, 329
- Thyroxine-binding globulin (TBC), 315
- Tiagabine, 500
- TIBC
- in anemia, 394
 - in anemia of chronic disease, 391
 - lab values in anemia, 394
- Tibial nerve, 422
- Ticagrelor, 407
- Ticarcillin, 170
- characteristics of, 171
 - for *Pseudomonas aeruginosa*, 127
- Ticks, as disease vectors, 132, 141, 133
- Ticlopidine, 385, 407
- Tics, in Tourette syndrome, 511
- Tidal volume (TV), 610
- Tigecycline, 181
- Tight junctions, 438, 455
- Time course of untreated HIV infection, 159
- Timolol, 249, 303, 498
- Tinea, 136, 183
- Tinea capitis, 136
- Tinea corporis, 136
- Tinea cruris, 136
- Tinea pedis, 136
- Tinea unguium, 136
- Tinea versicolor, 136
- Tinel sign, 419
- Tinnitus
- Meniere disease as cause, 631
 - streptomycin as cause, 180
- Tiotropium, 245
- Tirofiban, 385, 407
- Tissue factor pathway, 383
- Tissue plasminogen activator (tPA)
- for ischemic stroke, 470
- TMP-SMX, 177
- as HIV prophylaxis, 181
 - hyperkalemic renal tubular acidosis caused by, 544
 - for *Pneumocystis jirovecii*, 138, 640
 - as prophylaxis, 181
 - as UTI prophylaxis, 641
- TNF- α , 200
- endotoxins and, 117
 - extrinsic pathway and, 216
 - in granulomatous diseases, 223
 - Graves disease and, 323
- TNF- α inhibitors, 430, 448
- TNF (tumor necrosis factor), 232
- TNM staging system, 228
- Tobramycin, 170, 174
- Togaviruses
- characteristics of, 151
 - genomes of, 147
 - rubella as, 153
- Tolbutamide, 334
- Tolcapone, 504
- Toll-like receptors (TLRs), 192
- Tolterodine, 245
- Tolvaptan, 328, 336, 640
- Tone, as motor neuron sign, 473
- Tongue development, 452
- Tonic-clonic seizures, 494
- drug therapy for, 500
 - treatments for, 641
- Tonic seizures, 494
- Tonsils, in X-linked agammaglobulinemia, 208
- Tooth problems
- bulimia nervosa as cause, 520
 - congenital syphilis as cause, 131
 - demeclocycline as cause, 336
 - dental caries, 120
 - dentinogenesis imperfecta, 63
 - discoloration, from
 - tetracyclines, 175, 187, 253
 - fetal tetracycline exposure as cause, 564
 - Gardner syndrome as cause, 363
 - primary teeth retention, in Job syndrome, 208
 - Sjögren syndrome as cause, 432
- Tophi, in gout, 634
- Topiramate
- for epilepsy, 500
 - for migraine headaches, 494, 640
 - for pseudotumor cerebri, 471
- Topoisomerase inhibitors, 408
- Topoisomerases, 178
- Topotecan, 408, 411
- ToRCHeS infections, 165
- cataracts and, 483
 - rubella as, 153
- Torsades de pointes, 277
- Class IA antiarrhythmics as cause, 302
 - as drug reaction, 251
 - hypomagnesemia as cause, 542
 - ibutilide as cause, 303
 - magnesium for, 304
 - sotalol as cause, 303
- Torsemeide, 557
- Total anomalous pulmonary venous return (TAPVR), 282
- Total lung capacity (TLC), 610
- in flow volume loops, 619
- Total parenteral nutrition (TPN), 372
- Total peripheral resistance, 266, 269
- Tourette syndrome, 511
- antipsychotic drugs for, 525
 - atypical antipsychotics for, 525
 - drug therapy for, 524
 - obsessive-compulsive disorder and, 517
 - sympatholytic drugs for, 247
- Toxic dose, 240
- Toxic epidermal necrolysis, 443
- Toxicities, 251
- Toxic multinodular goiter, 323
- Toxic shock-like syndrome, 120
- Toxic shock syndrome, 117
- exotoxin A as cause, 117
 - presentation of, 119
 - Staphylococcus aureus* as cause, 119
- Toxic shock syndrome toxin, 117
- Toxocara* spp., 142
- Toxocara canis*, 143
- Toxoplasma* spp., 163
- Toxoplasma gondii*, 140
- HIV and, 160
 - lab findings in, 637
 - as ToRCHeS infection, 165
 - treatments for, 641
- Toxoplasmosis, 140
- antimicrobial prophylaxis for, 181
 - calcification and, 220
 - congenital, presentation of, 630
 - vs. PCL, 400
 - pyrimethamine for, 183
 - trimethoprim prophylaxis for, 177
- TP53 gene, 230
- Trabecula
- in lymph node, 190
 - in spleen, 191
- Trabecular outflow, 483
- Trachea
- anatomy of, 609
 - bifurcation of, 609
 - in fetal development, 306
 - in respiratory tree, 608
- Tracheoesophageal anomalies, 338
- Tracheoesophageal fistula, 338
- Tramadol, 499
- seizures caused by, 253
- Transcortical aphasia, 463
- Transcription factor, 230
- Transduction, 114
- Transference, 508
- Transferrin
- as acute-phase reactant, 198
 - in anemia, 394
 - free radical elimination by, 221
 - lab values in anemia, 394
- Transformation, 114
- Transformation zone, 574
- Transient arthritis, 130
- Transient ischemic attacks (TIAs), 407, 470
- Transitional cell carcinomas, 231, 551
- Transition metals, free radical injuries and, 221
- Transition (mutation), 52
- Transjugular intrahepatic portosystemic shunt (TIPS), 344
- Transketolase
- in metabolic pathways, 85
 - vitamin B₁ and, 77
- Transpeptidases, 170
- Transposition, 114
- Transposition of great vessels, 263, 282
- cyanosis caused by, 642
 - diabetes in pregnancy as cause, 284
- Transsexualism, 520
- Transtentorial herniation, 498
- Transthyretin gene, 225
- Transudate pleural effusion, 623
- Transudate, vs. exudate, 224
- Transversalis fascia, 339, 348
- Transverse sinus, 470
- Transversion (mutation), 52
- Transversus abdominis muscle, 348
- Transvestism, 520
- Tr antigens, 229
- Tranlycypromine, 528
- Trapezium bone, 418
- Trapezoid bone, 418
- TRAP stain, 402
- Trastuzumab, 214, 413
- for breast cancer, 639
 - toxicities of, 413
- Trauma
- DIC and, 643
 - pneumothorax caused by, 623
- Traumatic aortic rupture, 286
- Traumatic pneumothorax, 623
- Travelers' diarrhea, 128
- Trazodone, 528
- mechanism of, 526
 - priapism caused by, 597
- Treacher Collins syndrome, 569
- Trematodes, 144
- Tremor
- immunosuppressants as cause, 212
 - resting, 461, 633
- Trench fever, 145
- Trendelenburg sign, 422
- Treponema* spp., 130
- Treponema pallidum*
- granulomatous diseases caused by, 223
 - penicillin G/N for, 170
 - presentation of, 632
 - as STI, 167
 - syphilis caused by, 131
 - treatments for, 641
- TRH. *See* Thyrotropin-releasing hormone (TRH)
- Triamcinolone, 336, 446. *See also* Glucocorticoids
- Triamterene, 537, 558
- Triazolam, 501
- Triceps reflex, 476
- Trichinella* spp., 142
- Trichinella spiralis*, 143, 145
- Trichinosis, 143
- Trichomonas* spp.
- metronidazole for, 178
 - vaginitis caused by, 164
- Trichomonas vaginalis*, 142
- as STI, 167
 - treatments for, 641
- Trichomoniasis, 167
- Trichophyton* spp., 136
- Tricuspid atresia, 263, 282
- Tricuspid insufficiency, 270
- Tricuspid regurgitation
- carcinoid syndrome as cause, 332
 - Ebstein anomaly and, 282
 - heart murmurs caused by, 273
 - holosystolic murmur and, 643
 - pansystolic murmur in, 272

- Tricuspid stenosis, 272
 Tricuspid valve endocarditis, 293, 643
 Tricyclic antidepressants (TCAs), **527**
 antimuscarinic reaction caused by, 254
 for fibromyalgia, 435
 for generalized anxiety disorder, 517
 mechanism of, 526
 naming convention for, 255
 as noradrenergic drug, 243
 serotonin syndrome caused by, 527
 torsades de pointes caused by, 251
 toxicity treatment for, 251
 as weak bases, 238
 Trientine, 371
 Trifluoperazine, 525
 Trigeminal nerve (5th cranial nerve), **479**
 as branchial arch derivative, 569
 lesion in, 480
 location in brain stem, 477
 migraine headaches and, 494
 pathway for, 478
 in tongue, 452
 Trigeminal neuralgia, 494
 pain produced by, 494
 treatments for, 641
 Triglycerides, 105
 in chylothorax, 623
 insulin and, 308
 in Von Gierke disease, 99
 Trigone, 532
 Triiodothyronine, **335**. *See* also Thyroid hormones
 Trimethoprim, 170, **177**
 folate deficiency caused by, 390
 pyrimidine synthesis and, 49
 as teratogen, 564
 Trimming, in protein synthesis, 57
 Trinucleotide repeat expansion diseases, **73**
 Triose kinase, 91
 Triple-blinded studies, 32
 Triptans, **505**
 angina caused by, 287
 for migraine headaches, 494
 Triquetrum bone, 418
 tRNA, **56**
 Trochlea, 488
 Trochlear nerve (4th cranial nerve), **479**
 in cavernous sinus, 481
 location in brain stem, 477
 ocular motility and, 488
 palsy of, 489
 pathway for, 478
Tropheryma whipplei, 110, 358
 Tropical sprue, 358
 Tropicamide, 245
 Troponin C, 424
 Troponins
 in MI, 289
 in myocardial infarction, 287
 Trousseau sign, 325, 542
 Trousseau syndrome
 lab findings in, 636
 pancreatic cancer as cause, 373
 as paraneoplastic syndrome, 229
 True-negative rate, 33
 True-positive rate, 33
 Truncal ataxia, 459
 Truncus arteriosus, 262
 22q11 syndromes as cause, 284
 cyanosis caused by, 642
 thymic aplasia as cause, 208
Trypanosoma brucei, **140**, 183
Trypanosoma cruzi, **142**
 achalasia and, 354
 nifurtimox for, 183
 Trypanosomes, stain for, 110
 Trypsin, 352
 Trypsinogen, 352
 Trypsase, 379
 Tryptophan, 92, 94
TSC1/TSC2 genes, 230
 Tsetse flies, as disease vectors, 140
 TSH. *See* Thyroid-stimulating hormone (TSH)
t-tests, 39
 T-tubule membrane, 424
 Tubal ligation, 592
 Tuberculoid Hansen disease, 125
 Tuberculosis, **124**
 Addison disease caused by, 318
 calcification in, 220
 constrictive pericarditis and, 642
 corticosteroids and, 313
 erythema nodosum and, 444
 as granulomatous disease, 223
 isoniazid for, 180
 macrophages and, 379
 necrosis and, 217
 presentation of, 124
 primary and secondary, **124**
 silicosis and, 620
 V/Q mismatch and, 614
 Tuberin protein, 230
 Tuberoinfundibular pathway, 458
 Tuberosus sclerosis, 495
 autosomal dominance of, 71
 tumor suppressor genes and, 230
 Tubocurarine, 503
 Tubular necrosis, 553
 Tubulointerstitial inflammation
 WBC casts in, 544
 Tularemia, 132
 Tumor lysis syndrome
 gout and, 431
 hyperkalemia caused by, 542
 lab findings in, 636
 rasburicase for, 448
 Tumor markers, **232**
 for acute lymphoblastic leukemia, 402
 for pancreatic adenocarcinomas, 373
 Tumors
 benign vs. malignant, 228
 grade vs. stage, **228**
 nomenclature of, **228**
 TNM staging system for, 228
 Tumor suppressor genes, **230**
 Tumor suppressors, 58
 Tunica albuginea, 575, 597
 Tunica muscularis externa, 341
 Tunica serosa, 341
 Tunica submucosa, 341
 Tunica vaginalis, 573
 Turcot syndrome, 363
 Turner syndrome, **585**
 amenorrhea caused by, 645
 cardiac defects associated with, 284
 coarctation of aorta and, 283
 cystic hygromas and, 441
 GH for, 336
 horseshoe kidney and, 531
 presentation of, 634
 T wave, in ECG, 276
 21-hydroxylase, 312
 21-hydroxylase deficiency, 642
 22q11 deletion syndromes, **76**, 284
 Twin concordance studies, 32
 Twinning, **565**
 2-naphthylamine, 231
 TXA₂
 aspirin effect on, 447
 in platelet plug formation, 385
 in thrombogenesis, 385
 Type 1 muscle fibers, 424
 Type 2 muscle fibers, 424
 Type I errors in statistical hypothesis testing, 38
 Type I hypersensitivity reactions, 204
 to helminths, 142
 IgE antibodies and, 197
 mast cells and, 379
 Type II errors in statistical hypothesis testing, 38
 Type II hypersensitivity reactions, 204
 to blood transfusions, 206
 to helminths, 142
 to organ transplants, 211
 rheumatic fever as, 294
 Type III hypersensitivity reactions, 205
 acute poststreptococcal glomerulonephritis as, 546
 C3 deficiency and, 199
 to organ transplants, 211
 Type III secretion system, **113**
 Type IV hypersensitivity reactions, 205
 allergic contact dermatitis as, 440
 graft-versus-host disease as, 211
 Typhoid fever, 129
 Typhus, **133**
 animal transmission of, 132
 lice transmission of, 145
 Tyramine, **243**
 Tyrosinase, 439
 Tyrosine
 derivatives of, 94
 as noradrenergic drug, 243
 Tyrosine catabolism, **95**
 Tyrosine kinase
 as endocrine hormone messenger, 316
 in glycogen regulation, 97
 insulin and, 308
 as oncogene product, 230
 Tyrosinemia, 538
 Tyrosine phosphorylation, 308
 Tzanck test, 150
U
 Ubiquitination, 57
 UDP-glucose pyrophosphorylase, 98
 UDP-glucuronosyl-transferase, 353
 Ulcerative colitis, 359
 HLA-B27 and, 643
 lab findings in, 636
 spondyloarthritis and, 433
 sulfasalazine for, 375
 treatments for, 641
 Ulcers
 bismuth/sucralfate for, 375
 complications of, **357**
 glucocorticoids as cause, 336
 Helicobacter pylori as cause, 130
 Ulipristal, 602
 Ulnar claw, 419, 421
 Ulnar nerve, 418, 419
 Ulnar nerve injury, 418, 421
 Umbilical artery, 264, 566, 567
 Umbilical cord, **567**
 Umbilical vein, 566, 567
 blood in, 264
 postnatal derivative of, 264
 Umbilicus, 344
 Umbilical cord separation delay, 209
 UMP synthase, 390
 Unambiguous genetic code, **50**
 Uncal herniation, 498
 Uncinate process, 339
 Unconjugated
 hyperbilirubinemia, 369
 Uncoupling agents, 89
 Uncus, 498
 Undifferentiated thyroid carcinomas, 324
 Undulant fever, 132
 “Unhappy triad” in knee injuries, 417
 Unilateral renal agenesis, **531**
 Uniparental disomy, **69**
 Universal electron acceptors, **86**
 Universal genetic code, **50**
 Unnecessary procedures desired by patient, 42
 Unstable angina, 287, 290
 Unvaccinated children, 169
 Upper extremity nerves, **419**
 Upper motor neuron (UMN)
 lesions, 480, 632
 Upper respiratory infections (URIs)
 asthma triggered by, 618
 rhinosinusitis caused by, 616
 Urachal cysts, 567
 Urachus, 264, **567**
 Uracil, 49
 Urea, 94
 Urea cycle, **93**
 diagram of, 85
 location of in cell, 83
 ornithine transcarbamylase deficiency and, 94
 rate-determining enzyme for, 84

- Ureaplasma* spp.
 morphology of, 109
 as urease-positive organism, 112
- Urease, 164
- Urease-positive organisms, **112**
- Uremia
 acute pericarditis caused by, 294
 acute respiratory distress syndrome
 as cause, 621
 metabolic acidosis as cause, 543
 renal failure as cause, 553
- Ureter, 532, 571, 575
 anatomy of, 574
 constriction of, 535
 course of, **532**
 in horseshoe kidney, 531
 transitional cell carcinoma in, 551
 Y-shaped bifid, 531
- Ureteral orifice, 532
- Ureteric bud
 bifurcation of, 531
 development problems, 531
- Ureteropelvic junction
 obstruction, 531
- Urethra, 575
 benign prostatic hyperplasia
 and, 599
 injury to, **575**
- Urethral orifice, 532
- Urethritis
 chlamydia as cause, 134, 167
Chlamydia trachomatis as
 cause, 134
 gonorrhoea as cause, 167
 LMN facial nerve palsy as
 cause, 634
 in reactive arthritis, 433
- Ureteropelvic junction, 530
- Urge incontinence, 551
 drug therapy for, 245
- Uric acid
 in gout, 448
 in Von Gierke disease, 99
- Urinary incontinence, **551**
 drug therapy for, 245
 ephedrine for, 246
 hydrocephalus as cause, 471
 multiple sclerosis as cause, 492
- Urinary retention
 atropine as cause, 245
 bethanechol for, 244
 delirium caused by, 512
 neostigmine for, 244
 tricyclic antidepressants as
 cause, 527
- Urinary tract infections (UTIs), **164**,
552
 antimicrobial prophylaxis for, 181
 BPH as cause, 599
 duplex collecting system and, 531
 enterococci as cause, 121
 key associations, 646
Klebsiella as cause, 128
 organisms causing, **164**
 prophylaxis for, 641
Pseudomonas aeruginosa and, 127
 pyelonephritis caused by, 552
- SGLT-2 inhibitors as cause, 335
Staphylococcus saprophyticus as
 cause, 120
 sulfa drug allergies as cause, 254
 sulfonamides for, 177
 TMP-SMX for, 177
- Urinary tract obstructions, 644
- Urine
 bilirubin and, 353
 casts in, **544**
 concentration of, 537
 diuretics, effect on, 558
- Urine pH, and drug elimination, **238**
- Urobilin, 353
- Urobilinogen
 in extravascular hemolysis, 391
 intravascular hemolysis as
 cause, 391
- Urogenital fold, 572
- Urogenital sinus, 530
- Uroporphyrinogen decarboxylase, 395
- Urosepsis, 552
- Ursodiol, **376**
- Urticaria, 440
 ethosuximide as cause, 500
 scombroid poisoning as cause, 250
 serum sickness as cause, 205
 as skin wheals, 438
 sulfa drug allergies as cause, 254
 as type I hypersensitivity
 reaction, 204
- USMLE Step 1 exam
 check-in process, 8
 clinical vignette strategies, 20
 content areas covered in, 3
 failing, 21–22
 goal-setting for, 12
 leaving exam early, 8
 overview of, 2
 passing rates for, 10
 practice exams for, 10, 18–19
 registering for, 5–6, 7
 rescheduling, 6
 score notifications for, 7
 scoring of, 9–10
 studying for, 12–13, 14–17, 18–19
 testing agencies, 22
 testing locations, 7
 test-taking strategies, 19–20
 time budgeting during, 7–8
 types of questions on, 8
- Uterine artery, 532, 574
- Uterine fibroids, 640
- Uteroplacental insufficiency, 590
- Uterus
 anomalies of, **572**
 collagen in, 61
 epithelial histology of, 574
 in genital embryology, 571
 zygote implantation in, 580
- Uterus didelphys, 572
- Uveitis, **484**
 Crohn disease as cause, 359
 sarcoidosis as cause, 435, 630
 seronegative spondyloarthritis as
 cause, 433
 ulcerative colitis as cause, 359
- Uveoscleral outflow, 483
- Uvula, in cleft palate, 570
- U wave, in ECG, 276
- V**
- Vaccines, **203**
 for *Bordetella pertussis*, 127
 for diphtheria, 123
 for encapsulated bacteria, 112
 for *Haemophilus influenzae*, 126,
 163
 inactivated, 203
 live attenuated, 146, 203
 organisms affecting unvaccinated
 children, 169
 for rabies, 155
 for rotavirus, 152
 for *Salmonella typhi*, 129
 for tetanus, 122
 viral, 146
- Vagal nuclei, **479**
- Vagina
 anatomy of, 574
 epithelial histology of, 574
 in genital embryology, 571
- Vaginal atrophy
 hormone replacement therapy
 for, 601
 menopause as cause, 582
- Vaginal bleeding
 cervical cancer as cause, 591
 endometrial cancer as cause, 594
 endometrial hyperplasia as
 cause, 594
 endometriosis as cause, 594
 granulosa cell tumors as cause, 593
 hydatidiform moles as cause, 587
 thecomas as cause, 592
- Vaginal candidiasis
 nystatin for, 182
 SGLT-2 inhibitors as cause, 335
- Vaginal clear cell
 adenocarcinomas, 564
- Vaginal epithelial stippling, 638
- Vaginal infections, **164**
- Vaginal tumors, **591**
- Vaginismus, 520
- Vaginitis, 142
 treatment for, 639
Trichomonas as cause, 164
 trichomoniasis as cause, 167
- Vagus nerve (10th cranial nerve), **479**
 baroreceptors/chemoreceptors
 and, 279
 as branchial arch derivative, 569
 lesion in, 480
 location in brain stem, 477
 location of in gastrointestinal
 system, 351
 pathway for, 478
 in tongue, 452
- Valacyclovir, **184**
- Validity, 35
- Valine, 92, 95
- Valproate
 for migraine headaches, 494
 as teratogen, 564
 for tonic-clonic seizures, 641
- Valproic acid
 for bipolar disorder, 515, 524, 638
 for epilepsy, 500
 necrosis caused by, 252
 pancreatitis caused by, 252
- Valsalva maneuver, effect on
 auscultation, 272
- Valsartan, 559
- Valvular dysfunction, 292
- Vancomycin, **173**
 for *Clostridium difficile*, 122, 639
 cutaneous flushing caused by, 251
 for enterococci, 639
 functioning of, 170
 for meningitis, 163
 for MRSA, 181
 for *Staphylococcus aureus*, 641
 for *Streptococcus pneumoniae*, 641
 toxicity caused by, 254
- Vanillylmandelic acid (VMA)
 in neuroblastomas, 319
 in tyrosine catabolism, 95
- Vanishing bile duct syndrome, 211
- Vardenafil, 603, 639
- Varenicline, 522, 528
- Variable expressivity, **68**
- Variance, 37
- Variant angina, 287
- Variceal bleeding, 249
- Varicella zoster virus (VZV), 146,
 149, 442
 guanosine analogs for, 184
 in immunodeficient patients, 210
 live attenuated vaccine for, 146
 meningitis caused by, 163
 passive antibodies for, 203
 rash caused by, 166
 Reye syndrome and, 366
 as skin vesicles, 438
 vaccine for, 203
- Varices, in Budd-Chiari
 syndrome, 368
- Varicocele, 597
- Varicoceles, 576, **597**
- Vasa previa, 589
- Vasa vasorum
 aortic aneurysms and, 641
 syphilis and, 131
- Vascular dementia, 491
- Vascular function curves, **269**
- Vascular inflammation, 219
- Vascular tumors of skin, **441**
- Vasculitides, **296–297**
- Vasculitis
 intraparenchymal hemorrhage
 caused by, 469
 methotrexate for, 409
- Vas deferens, 532, 571, 575
- Vasoactive intestinal polypeptide
 (VIP), 350
- Vasoconstriction, 540
- Vasoconstrictors, 503
- Vasodilation
 cilostazol/dipyridamole for, 407
 sympathetic receptors and, 242
- Vasodilators
 afterload, effect on, 267

- for aortic dissections, 287
atrial natriuretic peptide as, 279
for coronary steal syndrome, 287
nitrates as, 299
- Vasogenic edema, 455
- Vasopressin. *See* Antidiuretic hormone (ADH)
- Vasopressin receptors, 242
- V(D)J recombination, 192
- VDRL false positives, 131
- Vecuronium, 503
- Veganism, B₁₂ deficiency caused by, 80, 390
- VEGF (vascular endothelial growth factor), 223
- Velocardiofacial syndrome, 76
- Vemurafenib, 413, 445
- Venlafaxine, 527
conditions used for, 524
for panic disorder, 517
for phobias, 517
for PTSD, 517
- Venodilators, 267
- Venous gonadal drainage, 573
- Venous return, 269
- Venous sinus thrombosis, 470
- Venous thromboembolism, 406
- Venous thrombosis, 392
- Ventilation, 610
high altitude and, 615
perfusion and, 614
- Ventral lateral (VL) nucleus, 458
- Ventral pancreatic bud, 339
- Ventral posterolateral (VPL) nucleus, 458
- Ventral posteromedial (VPM) nucleus, 458
- Ventricles
embryology, 262
morphogenesis of, 263
- Ventricular arrhythmia, 288
- Ventricular fibrillation
ECG tracing for, 278
torsades de pointes as precursor, 277
- Ventricular septal defect (VSD), 263, 283, 642
congenital rubella as cause, 284
cri-du-chat syndrome as cause, 75
cyanosis caused by, 642
Down syndrome as cause, 284
fetal alcohol syndrome as cause, 284
heart murmurs caused by, 273
holosystolic murmur and, 643
pansystolic murmur in, 272
- Ventricular system, 471
- Ventriculomegaly, 514
- Ventromedial area of hypothalamus, 456
- Verapamil, 298, 299, 304, 494
- Vermal cortex lesions, 459
- Verrucae, 440
- Vertebrae, and diaphragm, 609
- Vertebral artery, 466
- Vertebral compression fractures, 426, 646
- Vertigo, 495
Meniere disease as cause, 631
streptomycin as cause, 180
- Vesamicol, 243
- Vesicles, 438
- Vesicourachal diverticulum, 567
- Vesicoureteral reflux
hydronephrosis caused by, 550
pyelonephritis and, 552
- Vesicular trafficking proteins, 59
- Vestibular bulbs, 572
- Vestibular schwannomas, 453
- Vestibulocochlear nerve (8th cranial nerve), 479
acoustic neuromas and, 453
location in brain stem, 477
pathway for, 478
schwannomas and, 496
- VHL gene, 230
pheochromocytomas and, 320
von Hippel-Lindau disease and, 71
- Vibrio spp., 109
- Vibrio cholerae*, 129
exotoxin produced by, 116
in Gram-negative algorithm, 125
watery diarrhea caused by, 162
- Vibrio parahaemolyticus*, 161
- Vibrio vulnificus*, 161
- Vigabatrin, 500
- Vimentin
as cytoskeletal element, 60
as stain, 60
- Vinblastine, 411
in cell cycle, 408
microtubules and, 60
- Vinca alkaloids, 408
- Vincristine, 411
in cell cycle, 408
microtubules and, 60
toxicities of, 413
- Vinyl chloride
angiosarcomas caused by, 368, 441
as carcinogen, 231
- VIPomas, 350
MEN I syndrome as cause, 333
octreotide for, 375
- Viral encephalitis, 646
- Viral envelopes, 147
- Virchow nodes, 356, 631
- Virchow triad, 616, 643
- Viridans streptococci, 118, 120
 α -hemolytic nature of, 119
bacterial endocarditis caused by, 293
biofilm produced by, 113
brain abscesses caused by, 163
as normal flora, 161
- Virilization, 312
- Virology, 146–161
- Viruses, 146–161
enveloped, 146
genetics of, 146
immunocompromised patients and, 162
negative-stranded, 152
pneumonia caused by, 162
receptors for, 150
replication of, 147
segmented, 152
structure of, 146
vaccines for, 146
watery diarrhea caused by, 162
- Visceral larva migrans, 143
- Visceral leishmaniasis, 142
- Vision loss
hyperammonemia as cause, 93
retinal detachment as cause, 485
- Visual cortex, 462, 467
- Visual field defects, 489
- Visual hallucinations, 513
- Vital capacity (VC), 610
- Vitamin A (retinol), 77
fat solubility of, 76
free radical elimination by, 221
pseudotumor cerebri and, 471
as teratogen, 564
- Vitamin B₁ deficiency
brain lesions and, 464
dementia caused by, 491
Korsakoff syndrome caused by, 512
Wernicke-Korsakoff syndrome caused by, 523
- Vitamin B₁ (thiamine), 77
pyruvate dehydrogenase complex and, 87
water solubility of, 76
- Vitamin B₂ (riboflavin), 78
pyruvate dehydrogenase complex and, 87
water solubility of, 76
- Vitamin B₃ deficiency, 491
- Vitamin B₃ (niacin), 78
derivatives of, 94
as lipid-lowering agent, 300
pyruvate dehydrogenase complex and, 87
water solubility of, 76
- Vitamin B₅ (pantothenic acid), 78
pyruvate dehydrogenase complex and, 87
water solubility of, 76
- Vitamin B₆ deficiency, 389
isoniazid as cause, 180
- Vitamin B₆ (pyridoxine), 76, 78
- Vitamin B₇ (biotin), 76, 79
- Vitamin B₉ deficiency, 390
in anemia taxonomy, 388
neutrophils in, 378
- Vitamin B₉ (folate), 79
absorption of, 352
deficiency in, 646
water solubility of, 76
- Vitamin B₁₂ (cobalamin), 80
absorption of, 352
water solubility of, 76
- Vitamin B₁₂ deficiency, 390
in anemia taxonomy, 388
dementia caused by, 491, 513
Diphyllobothrium latum as cause, 144, 145
neutrophils in, 378
spinal cord lesions in, 474
- Vitamin B₁ (thiamine)
for maple syrup urine disease, 95
- Vitamin B₆
isoniazid and, 180
for sideroblastic anemia, 389
- Vitamin C (ascorbic acid), 80
free radical elimination by, 221
for methemoglobinemia, 612
for methemoglobin toxicity, 251
water solubility of, 76
- Vitamin D, 81, 313. *See* also Cholecalciferol
fat solubility of, 76
function of, 314
for osteomalacia/rickets, 640
for osteoporosis prophylaxis, 426
for osteoporosis, 640
PTH and, 314
signaling pathways for, 316
- Vitamin D deficiency, 313, 325
hyperparathyroidism caused by, 428
osteomalacia/rickets caused by, 427
- Vitamin deficiencies, 646
- Vitamin E, 81
fat solubility of, 76
free radical elimination by, 221
- Vitamin K, 81
in coagulation cascade, 384
fat solubility of, 76
for warfarin reversal, 641
for warfarin toxicity, 251, 406
- Vitamin K deficiency, 384, 396
cephalosporins as cause, 172
- Vitamin/mineral absorption, 352
- Vitamins, 76–82
fat-soluble, 76
water-soluble, 76
- Vitelline duct, 567
- Vitelline fistula, 567
- Vitiligo, 439
- Vitreous bodies, collagen in, 61
- Vitreous chamber, 482
- VLDL (very low-density lipoprotein), 105
- Volume of distribution, 237, 646
- Volvulus, 362
malrotation as cause, 361
Meckel diverticulum as cause, 361
- Vomiting
arsenic toxicity as cause, 87
diabetic ketoacidosis as cause, 331
fructose intolerance as cause, 91
hyperammonemia as cause, 93
iron poisoning as cause, 396
Mallory-Weiss syndrome as cause, 354
maple syrup urine disease as cause, 95
medium-chain acyl-CoA dehydrogenase deficiency as cause, 101
metabolic alkalosis caused by, 543
metoclopramide for, 376
MI as cause, 288
in neonates, 339
ondansetron for, 376
Reye syndrome as cause, 366
trichinosis as cause, 143
vitamin C toxicity as cause, 80

- Von Gierke disease, 99
gout and, 431
presentation of, 632
- Von Hippel-Lindau disease, 495
autosomal dominance of, 71
chromosome associated with, 75
hemangioblastomas and, 496
presentation of, 633
renal cell carcinoma and, 550
renal tumors and, 645
tumor suppressor genes and, 230
- Von Willebrand disease, 385, 643
- Voriconazole, 181, 182
- V/Q mismatch, 614, 617
- V/Q ratio, 615
- VRE (vancomycin-resistant enterococci), 121
antimicrobials for, 181
daptomycin for, 178
oxazolidinones for, 176
- V_{max} , 236
- Vulnerable child syndrome, 510
- Vulva, lymphatic drainage of, 573
- Vulvovaginitis, 137, 164
- vWF
in platelet plug formation, 385
receptor for, 378
in thrombocytes, 378
in thrombogenesis, 385
- W**
- WAGR complex, 551
- “Waiter’s tip” (Erb palsy), 420
- Waiver to informed consent, 40
- Waiving right to confidentiality, 41
- Waldenström macroglobulinemia
lab findings in, 637
vs. multiple myeloma, 401
- Walking, as developmental milestone, 43
- Walking pneumonia, 134
- Wallenberg syndrome, 467
- Wallerian degeneration of neurons, 453
- Wall tension, 267
- Warfarin, 406
in coagulation cascade, 384
cytochrome P-450 and, 254
for deep venous thrombosis, 616
griseofulvin and, 183
vs. heparin, 406
for long-term anticoagulation, 640
reversal of, 641
as teratogen, 564
therapeutic index value of, 240
toxicity treatment for, 251, 399
as vitamin K antagonist, 81
- Warm autoimmune hemolytic anemia, 393
- Warthin-Finkeldey giant cells, 154
- Warthin tumors, 353
- WAS gene, 209
- Waterhouse-Friderichsen syndrome, 318
meningococci as cause, 126
presentation of, 630
- Watershed zones, 218, 466
- Water-soluble vitamins, 76
- Waxy casts, 544, 638
- Weakness, as motor neuron sign, 473
- Wegener granulomatosis, 296
autoantibody associated with, 207
as granulomatous disease, 223
lab findings in, 634, 637
as restrictive lung disease, 619
RPGN and, 546
treatments for, 639
- Weibel-Palade bodies
in platelet plug formation, 385
- Weight gain
atypical antipsychotics as cause, 525
Cushing syndrome as cause, 317
danazol as cause, 602
duodenal ulcers as cause, 357
glitazone/thiazolidinediones as cause, 334
hypothyroidism as cause, 321
major depressive disorder as cause, 515
mirtazapine as cause, 528
prednisone as cause, 412
sulfonylureas as cause, 334
valproic acid as cause, 500
- Weight loss
adrenal insufficiency as cause, 318
anorexia nervosa as cause, 520
cholelithiasis and, 372
chronic mesenteric ischemia as cause, 362
colorectal cancer as cause, 364
diabetes mellitus as cause, 330
esophageal cancer as cause, 355
gastric ulcers as cause, 357
hyperthyroidism as cause, 321
lymphoma as cause, 631
major depressive disorder as cause, 515
malabsorption syndromes as cause, 358
metformin as cause, 334
orlistat for, 376
pancreatic cancer as cause, 373
for PCOS, 591
polyarteritis nodosa as cause, 296
polymyalgia rheumatica as cause, 435
for pseudotumor cerebri, 471
renal cell carcinoma as cause, 550
for sleep apnea, 621
stomach cancer as cause, 356
for stress incontinence, 551
tuberculosis as cause, 124
Whipple disease as cause, 634
- Weil disease, 130
- Wenckebach AV block, 278
- Wernicke aphasia, 463
- Wernicke area, 462
aphasia and, 463
stroke effects, 467
- Wernicke encephalopathy, 523
mammillary bodies and, 641
- Wernicke-Korsakoff syndrome, 464, 523
vitamin B₁ deficiency as cause, 77
- Western blot, 65
HIV diagnosis with, 158
- Western equine encephalitis, 151
- West Nile virus, 151
meningitis caused by, 163
- Wet beriberi, 77
presentation of, 631
- Wharton jelly, 567
- Wheals, 438
- Wheezing
asthma as cause, 618
bronchial carcinoid tumor as cause, 626
lung cancer as cause, 626
- Whipple disease, 358
periodic acid-Schiff stain for, 110
presentation of, 634
- Whipple procedure
for pancreatic cancer, 373
- White pulp, in spleen, 191
- Whooping cough
Bordetella pertussis as cause, 127
pertussis toxin and, 116
- Wickham striae, 444
- Wide splitting, 271
- Williams syndrome, 75
cardiac defects associated with, 284
chromosome associated with, 75
- Wilms tumor, 551
chromosome associated with, 75
dactinomycin for, 410
vs. neuroblastomas, 319
tumor suppressor genes and, 230
- Wilson disease, 371
chromosome associated with, 75
dementia caused by, 491
Fanconi syndrome caused by, 538
free radical injury and, 221
lab findings in, 637
liver cancer and, 645
presentation of, 631
- Winged scapula, 420
- Winters formula, 543, 647
- Wiskott-Aldrich syndrome, 209
lab findings in, 637
as X-linked recessive disorder, 72
- Wnt-7* gene, 562
- Wobble, tRNA, 56
- Wolff-Chaikoff effect, 315, 322.
See also Jod-Basedow phenomenon
- Wolffian duct, 571
- Wolff-Parkinson-White syndrome, 277, 635
- Wound healing, 223
- Woven bone, 425
- Wright-Giemsa stain, 378
- Wright stain, 130
- Wrinkles of aging, 64
- Wrist bones, 418
- Wrist drop
lead poisoning as cause, 389
radial nerve injury as cause, 419
- Writer’s cramp, 461
- Written advance directives, 41
- WT1/WT2* genes, 230
- Wuchereria bancrofti*, 142, 143
- X**
- Xanthine, 448
- Xanthine oxidase, 448
- Xanthine oxidase inhibitors, 431, 639
- Xanthochromia, 638
- Xanthochromic spinal tap, 469
- Xanthogranulomatous pyelonephritis, 552
- Xanthomas
hyperchylomicronemia as cause, 105
hyperlipidemia as cause, 285
- Xenografts, 210
- Xeroderma pigmentosum, 53
- Xerosis cutis, 77
- Xerostomia, 244
- Xerostomia, in Sjögren syndrome, 432
- X-linked agammaglobulinemia, 208
- X-linked dominant inheritance, 70
- X-linked recessive inheritance, 70
- X-rays, teratogenic effects of, 564
- Y**
- Yellow cerebrospinal fluid, 638
- Yellow fever, 151, 152
live attenuated vaccine for, 146
liver anatomy and, 346
vaccine for, 203
- Yellow spinal tap, 635
- Yersinia* spp.
in Gram-negative algorithm, 125
morphology of, 109
reactive arthritis and, 433
- Yersinia enterocolitica*, 129, 162
- Yersinia pestis*
animal transmission of, 132
as intracellular organism, 112
- Yo antigens, 229
- Yolk sac tumors, 593, 598
- Z**
- Zafirlukast, 628
arachidonic acid pathway and, 446
- Zaleplon, 501
- Zanamivir, 184
for influenza, 640
- Zenker diverticulum, 361, 643
- Zero-order elimination, 238
- Zidovudine, 184, 186
- Ziehl-Neelsen stain, 110
- Zileuton, 446, 628
- Zinc, 82
for Wilson disease, 371
- Ziprasidone, 525
- Zoledronic acid, 447
- Zollinger-Ellison syndrome, 332, 645
duodenal ulcers caused by, 357
gastrin in, 350
MEN 1 syndrome as cause, 333
proton pump inhibitors for, 374
- Zolpidem, 501
- Zona fasciculata, 306, 313
- Zona glomerulosa, 306
- Zona reticularis, 306
- Zonular fibers, 482
- Zoonotic bacteria, 132
- Zymogens, 352

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