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**USMLE®  
STEP 1**

**2021**

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# FIRST AID FOR THE®

# USMLE STEP 1 2021

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## **First Aid for the® USMLE Step 1 2021: A Student-to-Student Guide**

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## **Dedication**

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To all healthcare workers and first responders worldwide leading the fight against COVID-19. We salute your ongoing efforts and honor those who have lost their lives in service to others.

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# Contents

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

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

► SECTION I SUPPLEMENT	SPECIAL SITUATIONS	27
------------------------	--------------------	----

► SECTION II	HIGH-YIELD GENERAL PRINCIPLES		29
How to Use the Database	30	Pathology	205
Biochemistry	33	Pharmacology	231
Immunology	95	Public Health Sciences	259
Microbiology	123		

► SECTION III	HIGH-YIELD ORGAN SYSTEMS	283	
Approaching the Organ Systems	284	Neurology and Special Senses	503
Cardiovascular	287	Psychiatry	575
Endocrine	333	Renal	601
Gastrointestinal	367	Reproductive	635
Hematology and Oncology	413	Respiratory	683
Musculoskeletal, Skin, and Connective Tissue	455	Rapid Review	713

► SECTION IV	TOP-RATED REVIEW RESOURCES	737	
How to Use the Database	738	Biochemistry	742
Question Banks	740	Cell Biology and Histology	743
Web and Mobile Apps	740	Microbiology and Immunology	743
Comprehensive	741	Pathology	743
Anatomy, Embryology, and Neuroscience	741	Pharmacology	744
Behavioral Science	742	Physiology	744
Abbreviations and Symbols	745	Index	775
Image Acknowledgments	753	About the Editors	842

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# Foreword

*“If you see something that is not right, not fair, not just, you have a moral obligation to do something.”*

Congressman John Lewis

*First Aid for the USMLE Step 1* began over 30 years ago as a resource to prepare aspiring physicians for their first medical board exam. Since then, it has become one of the most well-known textbooks used by medical students worldwide. While we closely follow the USMLE’s lead in most respects, the widespread use of our book also provides an opportunity for us to be leaders in medical education.

In prior editions, there has been an unfortunate absence of diversity in both the text and images. This year, we strongly affirm that representing a broad spectrum of patients is essential for preparing for a successful medical career. The practice of medicine is inextricably intertwined with social determinants of health, and sociocultural understanding complements scientific knowledge for the future physician. Failing to provide representation of a diversity of people limits the educational experience and is to the detriment of future patients. We here describe our approach to improving the representation of race, ethnicity, sex, and gender, recognizing that we are neither experts nor authorities on diversity, equity, and inclusion.

We first surveyed our existing visual depictions of patients and pathologies. Of nearly 70 illustrations showing skin tone or sex in the 2020 edition, every single one showed pink/light beige skin, and all but one was male-appearing, excluding reproductive anatomy illustrations. To address this lack of diversity, we revised our illustrations to better reflect Fitzpatrick skin types I-VI and introduced more female-appearing and gender-neutral illustrations.

We also reviewed our use of language in the text. With respect to race and ethnicity, we transitioned from using “African-American” to “Black,” as not all Black patients are American or have African ancestry. We now capitalize “Black” in accordance with major journalistic organizations. We also switched from “Caucasian” to “White,” which we hope will be more accurate and inclusive.

We found many opportunities to improve the language used to describe disabled and ill patients as well. We now use person-first language such as “patients with diabetes” instead of “diabetic patients.” Dated references to “mental retardation” have been replaced with “intellectual disability.” We also removed other stigmatizing terms such as “alcoholics,” “smokers,” “epileptics,” and “bulimics” and replaced with appropriate person-first language.

Finally, we reviewed our use of terminology surrounding sex and gender identity. We opted for more neutral language by changing most uses of gendered pronouns to “they/them/theirs,” as well as changing “mother” to “pregnant patient.” We also removed gendered terms such as “girl,” “boy,” “woman,” and “man” in favor of “female” and “male” when referring to biological sex.

We acknowledge that our approach is imperfect and challenges remain. We also recognize that there may be differing perspectives that need to be addressed and balanced. However, just as the medical community learns invaluable lessons from its patients, we greatly value input from our peers and colleagues. We enthusiastically encourage feedback on our efforts to better represent all people. If you have comments or suggestions, please submit them via our website at [www.firstaidteam.com](http://www.firstaidteam.com). Alternatively, you can email us at [firstaid@scholarrx.com](mailto:firstaid@scholarrx.com). Thank you for your help in making *First Aid for the USMLE Step 1* an increasingly inclusive and useful resource.

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# Preface

With the 31st 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:

- 104 entirely new or heavily revised high-yield topics reflecting evolving trends in the USMLE Step 1.
- Updated ethics section and introduction of new communications skills section to reflect the recently changed Step 1 exam.
- Extensive text revisions, new mnemonics, clarifications, and corrections curated by a team of 25 medical student and resident physician authors who excelled on their Step 1 examinations and verified by a team of expert faculty advisors and nationally recognized USMLE instructors.
- Updated with 179 new and revised diagrams and illustrations as part of our ongoing collaboration with USMLE-Rx and ScholarRx (MedIQ Learning, LLC).
- Updated with 62 new and revised photos to help visualize various disorders, descriptive findings, and basic science concepts. Additionally, revised imaging photos have been labeled and optimized to show both normal anatomy and pathologic findings.
- Updated exam preparation advice for USMLE Step 1 pass/fail, Step 1 blueprint changes, and COVID-19 impacts.
- Revised language to support diversity, equity, and inclusion.
- Updated study tips on the opening page of each chapter.
- Improved organization and integration of text, illustrations, clinical images, and tables throughout for focused review of high-yield topics.
- Revised and expanded ratings of current, high-yield review resources, with clear explanations of their relevance to USMLE review.
- Real-time Step 1 updates and corrections can be found exclusively on our blog, [www.firstaidteam.com](http://www.firstaidteam.com).

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

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# General Acknowledgments

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

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# How to Contribute

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

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

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

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

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

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

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

Alternatively, you can email us at: [firstaid@scholarrx.com](mailto:firstaid@scholarrx.com).

Contributions submitted by **May 15, 2021**, receive priority consideration for the 2022 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/ScholarRx* team is pleased to offer paid editorial and coaching positions. We are looking for passionate, experienced, and dedicated medical students and recent graduates. Participants will have an opportunity to work on a wide variety of projects, including the popular *First Aid* series and the growing line of USMLE-Rx/ScholarRx products, including Rx Bricks. Please use our webform at <https://www.usmle-rx.com/join-the-first-aid-team/> to apply, and include a CV and writing examples.

For 2021, we are actively seeking passionate medical students and graduates with a specific interest in improving our medical illustrations, expanding our database of photographs (including clinical images depicting diverse skin types), and developing the software that supports our crowdsourcing platform. We welcome people with prior experience and talent in these areas. Relevant skills include clinical imaging, digital photography, digital asset management, information design, medical illustration, graphic design, tutoring, and software development.

# How to Use This Book

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

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

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

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

**INTEGRATE STUDY WITH CASES, FLASH CARDS, AND QUESTIONS:** To broaden your learning strategy, consider integrating your *First Aid* study with case-based reviews (eg, *First Aid Cases for the USMLE Step 1*), flash cards (eg, USMLE-Rx Step 1 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, ScholarRx Bricks and USMLE-Rx Step 1 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)	10–40 U/L	10–40 U/L
* Alkaline phosphatase	25–100 U/L	25–100 U/L
Amylase, serum	25–125 U/L	25–125 U/L
* Aspartate aminotransferase (AST, GOT at 30°C)	12–38 U/L	12–38 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	2.1–2.6 mmol/L
* Cholesterol, serum (Total)	Rec: < 200 mg/dL	< 5.2 mmol/L
* Creatinine, serum (Total)	0.6–1.2 mg/dL	53–106 µmol/L
Electrolytes, serum		
Sodium ( $\text{Na}^+$ )	136–146 mEq/L	136–146 mmol/L
Chloride ( $\text{Cl}^-$ )	95–105 mEq/L	95–105 mmol/L
* Potassium ( $\text{K}^+$ )	3.5–5.0 mEq/L	3.5–5.0 mmol/L
Bicarbonate ( $\text{HCO}_3^-$ )	22–28 mEq/L	22–28 mmol/L
Magnesium ( $\text{Mg}^{2+}$ )	1.5–2 mEq/L	0.75–1.0 mmol/L
Gases, arterial blood (room air)		
$\text{P}_{\text{O}_2}$	75–105 mm Hg	10.0–14.0 kPa
$\text{P}_{\text{CO}_2}$	33–45 mm Hg	4.4–5.9 kPa
pH	7.35–7.45	[ $\text{H}^+$ ] 36–44 nmol/L
* Glucose, serum	Fasting: 70–100 mg/dL	3.8–6.1 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 mOsmol/kg $\text{H}_2\text{O}$	275–295 mOsmol/kg $\text{H}_2\text{O}$
* Phosphorus (inorganic), serum	3.0–4.5 mg/dL	1.0–1.5 mmol/L
Prolactin, serum (hPRL)	Male: < 17 ng/mL Female: < 25 ng/mL	< 17 µg/L < 25 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
Thyroid-stimulating hormone, serum or plasma	0.4–4.0 µU/mL	0.4–4.0 mIU/L
* Urea nitrogen, serum (BUN)	7–18 mg/dL	25–64 nmol/L
* Uric acid, serum	3.0–8.2 mg/dL	0.18–0.48 mmol/L

(continues)

<b>Cerebrospinal Fluid</b>	<b>Reference Range</b>	<b>SI Reference Intervals</b>
Cell count	0–5/mm <sup>3</sup>	0–5 × 10 <sup>6</sup> /L
Glucose	40–70 mg/dL	2.2–3.9 mmol/L
Proteins, total	< 40 mg/dL	< 0.40 g/L
<b>Hematologic</b>		
Erythrocyte count	Male: 4.3–5.9 million/mm <sup>3</sup> Female: 3.5–5.5 million/mm <sup>3</sup>	4.3–5.9 × 10 <sup>12</sup> /L 3.5–5.5 × 10 <sup>12</sup> /L
Erythrocyte sedimentation rate (Westergen)	Male: 0–15 mm/hr Female: 0–20 mm/hr	0–15 mm/hr 0–20 mm/hr
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	135–175 g/L 120–160 g/L
Hemoglobin, plasma	< 4 mg/dL	< 0.62 μmol/L
Leukocyte count and differential		
Leukocyte count	4,500–11,000/mm <sup>3</sup>	4.5–11.0 × 10 <sup>9</sup> /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	25–35 pg/cell	0.39–0.54 fmol/cell
Mean corpuscular hemoglobin concentration	31%–36% Hb/cell	4.8–5.6 mmol Hb/L
Mean corpuscular volume	80–100 μm <sup>3</sup>	80–100 fL
Partial thromboplastin time (activated)	25–40 sec	25–40 sec
Platelet count	150,000–400,000/mm <sup>3</sup>	150–400 × 10 <sup>9</sup> /L
Prothrombin time	11–15 sec	11–15 sec
Reticulocyte count	0.5–1.5% of RBCs	0.005–0.015
<b>Urine</b>		
Creatinine clearance	Male: 97–137 mL/min Female: 88–128 mL/min	97–137 mL/min 88–128 mL/min
Osmolality	50–1200 mOsmol/kg H <sub>2</sub> O	50–1200 mOsmol/kg H <sub>2</sub> O
Proteins, total	< 150 mg/24 hr	< 0.15 g/24 hr
<b>Other</b>		
Body mass index	Adult: 19–25 kg/m <sup>2</sup>	19–25 kg/m <sup>2</sup>

## 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.

- |                       |  |
|-----------------------|--|
| <b>Years Prior</b>    | <ul style="list-style-type: none"><li><input type="checkbox"/> Use top-rated review resources for first-year medical school courses.</li><li><input type="checkbox"/> Ask for advice from those who have recently taken the USMLE Step 1.</li></ul>  |
| <b>Months Prior</b>   | <ul style="list-style-type: none"><li><input type="checkbox"/> Review computer test format and registration information.</li><li><input type="checkbox"/> Register six months in advance.</li><li><input type="checkbox"/> Carefully verify name and address printed on scheduling permit. Make sure the name on scheduling permit matches the name printed on your photo ID. Be familiar with COVID-19 cancellation and rescheduling policies.</li><li><input type="checkbox"/> Go online for test date ASAP.</li><li><input type="checkbox"/> Define your exam goals (pass comfortably, beat the mean, ace the test)</li><li><input type="checkbox"/> Set up a realistic timeline for study. Cover less crammable subjects first.</li><li><input type="checkbox"/> Evaluate and choose study materials (review books, question banks).</li><li><input type="checkbox"/> Use a question bank to simulate the USMLE Step 1 to pinpoint strengths and weaknesses in knowledge and test-taking skills.</li></ul> |
| <b>Weeks Prior</b>    | <ul style="list-style-type: none"><li><input type="checkbox"/> Do test simulations in question banks.</li><li><input type="checkbox"/> Assess how close you are to your goal.</li><li><input type="checkbox"/> Pinpoint remaining weaknesses. Stay healthy (exercise, sleep).</li><li><input type="checkbox"/> Verify information on admission ticket (eg, location, date).</li></ul>  |
| <b>One Week Prior</b> | <ul style="list-style-type: none"><li><input type="checkbox"/> Remember comfort measures (loose clothing, earplugs, etc).</li><li><input type="checkbox"/> Work out test site logistics (eg, location, transportation, parking, lunch).</li><li><input type="checkbox"/> Print or download your Scheduling Permit and Scheduling Confirmation to your phone.</li></ul>   |
| <b>One Day Prior</b>  | <ul style="list-style-type: none"><li><input type="checkbox"/> Relax.</li><li><input type="checkbox"/> Lightly review short-term material if necessary. Skim high-yield facts.</li><li><input type="checkbox"/> Get a good night's sleep.</li></ul>  |
| <b>Day of Exam</b>    | <ul style="list-style-type: none"><li><input type="checkbox"/> Relax.</li><li><input type="checkbox"/> Eat breakfast.</li><li><input type="checkbox"/> Minimize bathroom breaks during exam by avoiding excessive morning caffeine.</li></ul>  |
| <b>After Exam</b>     | <ul style="list-style-type: none"><li><input type="checkbox"/> Celebrate, regardless of how well you feel you did.</li><li><input type="checkbox"/> Send feedback to us on our website at <a href="http://www.firstaidteam.com">www.firstaidteam.com</a>.</li></ul>  |

## SECTION I

# Guide to Efficient Exam Preparation

*“One important key to success is self-confidence. An important key to self-confidence is preparation.”*

—Arthur Ashe

*“Wisdom is not a product of schooling but of the lifelong attempt to acquire it.”*

—Albert Einstein

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

—Miguel de Cervantes Saavedra, *Don Quixote*

*“Sometimes the questions are complicated and the answers are simple.”*

—Dr. Seuss

*“He who knows all the answers has not been asked all the questions.”*

—Confucius

*“The expert in anything was once a beginner.”*

—Helen Hayes

*“It always seems impossible until it’s done.”*

—Nelson Mandela

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

## ► INTRODUCTION

Relax.

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

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

### ► The test at a glance:

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

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 would normally 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 domestically and internationally for those seeking medical licensure in the United States.

The Step 1 exam includes test items that can be grouped by the organizational constructs outlined in Table 1 (in order of tested frequency). In late 2020, the NBME increased the number of items assessing communication skills. While pharmacology is still tested, they are focusing on drug mechanisms rather than on pharmacotherapy. You will generally not be required to identify specific medications indicated for a specific condition. Instead, you will be asked more about mechanisms and side effects.

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

Competency	Range, %	System	Range, %
Medical knowledge: applying foundational science concepts	60–70	General principles	12–16
Patient care: diagnosis	20–25	Behavioral health & nervous systems/special senses	9–13
Communication and interpersonal skills	6–9	Respiratory & renal/urinary systems	9–13
Practice-based learning & improvement	4–6	Reproductive & endocrine systems	9–13
Discipline	Range, %		
Pathology	44–52	Blood & lymphoreticular/immune systems	7–11
Physiology	25–35	Multisystem processes & disorders	6–10
Pharmacology	15–22	Musculoskeletal, skin & subcutaneous tissue	6–10
Biochemistry & nutrition	14–24	Cardiovascular system	5–9
Microbiology	10–15	Gastrointestinal system	5–9
Immunology	6–11	Biostatistics & epidemiology/population health	4–6
Gross anatomy & embryology	11–15	Social sciences: communication skills/ethics	6–9
Histology & cell biology	8–13		
Behavioral sciences	8–15		
Genetics	5–9		

\*Percentages are subject to change at any time. [www.usmle.org](http://www.usmle.org)

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

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

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

### What Is the CBT Like?

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

For security reasons, examinees are not allowed to bring any personal electronic equipment into the testing area. This includes both digital and analog watches, cell phones, tablets, and calculators. 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*
- *Esc—exit pop-up Calculator and Notes windows*

► **Heart sounds are tested via media questions.**

*Make sure you know how different heart diseases sound on auscultation.*

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

► **Familiarize yourself with the commonly tested lab values (eg, Hb, WBC, platelets, Na<sup>+</sup>, K<sup>+</sup>).**

► **Illustrations on the test include:**

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

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

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

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

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

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

The same USMLE Step 1 sample test items (120 questions) available on the USMLE website, [www.usmle.org](http://www.usmle.org), are used at these sessions. **No new items will be presented.** The practice session is available at a cost of \$75 (\$155 if taken outside of the US and Canada) and is divided into a short tutorial and three 1-hour blocks of ~40 test items each. Students receive a printed percent-correct score after completing the session. **No explanations of questions are provided.**

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

You may register for a practice session online at [www.usmle.org](http://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.

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

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

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

- Be familiar with Prometric's policies for cancellation and rescheduling due to COVID-19.

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. Be aware that your exam may be canceled because of circumstances related to the COVID-19 pandemic or other unforeseen events. If that were to happen, you should receive an email from Prometric containing notice of the cancellation and instructions on rescheduling. Visit [www.prometric.com](http://www.prometric.com) for updates regarding their COVID-19 cancellation and rescheduling policies.

- Test scheduling is done on a "first-come, first-served" basis. It's important to schedule an exam date as soon as you receive your scheduling permit.

Although requests for taking the exam may be completed more than six months before the test date, examinees will not receive their scheduling permits earlier than six months before the eligibility period. The eligibility period is the three-month period you have chosen to take the exam. Most medical students choose the April–June or June–August period. Because exams are scheduled on a "first-come, first-served" basis, it is recommended that you book an exam date on the Prometric website as soon as you receive your permit. Prometric will provide appointment confirmation on a print-out and by email. Be sure to read the latest *USMLE Bulletin of Information* for further details.

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

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

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

### When Should I Register for the Exam?

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

### Where Can I Take the Exam?

Your testing location is arranged with Prometric when you book your test date (after you receive your scheduling permit). For a list of Prometric locations nearest you, visit [www.prometric.com](http://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 online for ~120 days after score notification, after which scores can only be obtained through requesting an official USMLE transcript. Additional information about score timetables and accessibility is available on the official USMLE website.

## What About Time?

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

15 minutes	Tutorial (skip if familiar with test format and features)
7 hours	Seven 60-minute question blocks
45 minutes	Break time (includes time for lunch)

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

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

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

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

► Gain extra break time by skipping the tutorial, or utilize the tutorial time to add personal notes to your scratch paper.

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

### 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?

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

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

### How Is the Test Scored?

- *Determine if the impending transition to Pass/Fail scoring impacts your optimal testing date.*

The USMLE will be transitioning to a Pass/Fail scoring system no earlier than January 1, 2022. Results from Step 1 exams taken prior to the transition date will be reported using a three-digit test score. Changes will not be made to transcripts containing a three-digit test score after the switch to Pass/Fail grading. Should you consider delaying your exam until Pass/Fail scoring is implemented? At the moment, we don't think so in most situations. First, at press time, the actual implementation date has not been announced. Second, and more importantly, the test date should be driven by your readiness relative to your curriculum and school schedule. On the other hand, there are a number of possible reasons that you might want to consider taking your exam in 2021 and getting a 3-digit score. These may include interest in a competitive specialty, IMG status, and enrollment at a less competitive medical school. In these situations, the USMLE Step 2 CK can provide an additional opportunity to score well and demonstrate a strong fund of knowledge. Consult with your school advisors and follow us on social media for timely updates.

Examinees taking the current test will receive an electronic report that includes the examinee's pass/fail status, a three-digit test score, a bar chart comparing the examinee's performance to that of other examinees', and a

graphic depiction of the examinee's performance by physician task, discipline and organ system.

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

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

Since some questions may be experimental and are not counted, it is possible to get different scores for the same number of correct answers. In 2018, the mean score was 231 with a standard deviation of 19.

► The mean Step 1 score for US medical students continues to rise, from 200 in 1991 to 231 in 2018.

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

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

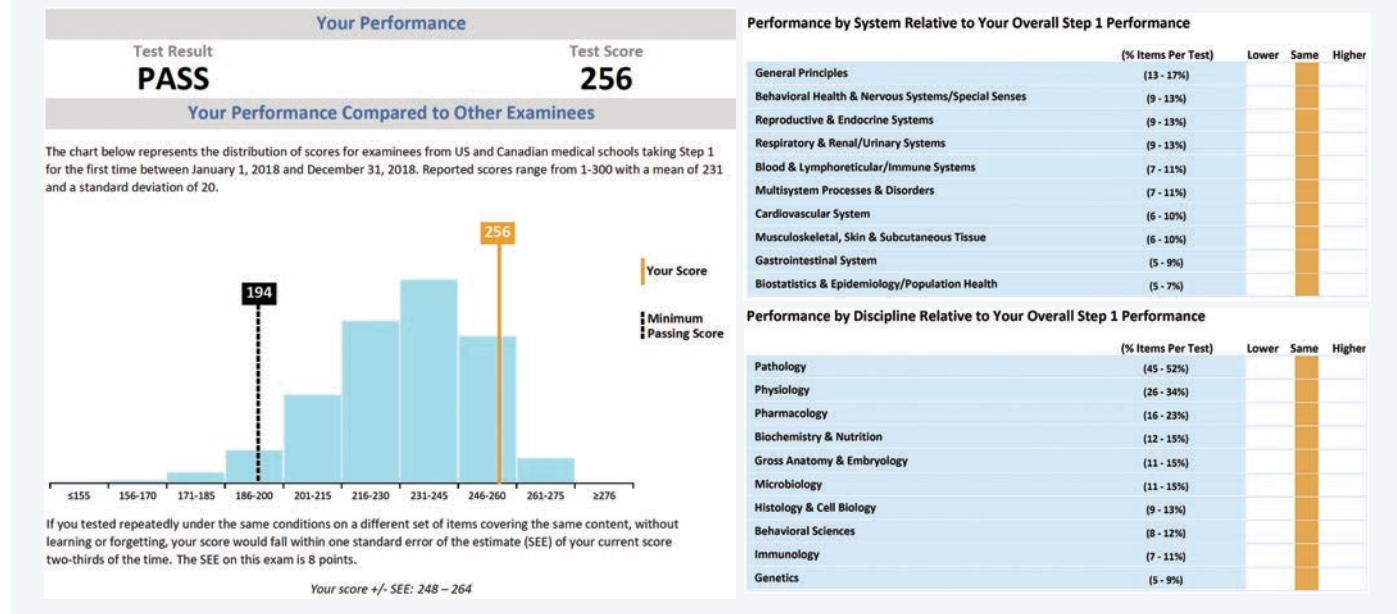
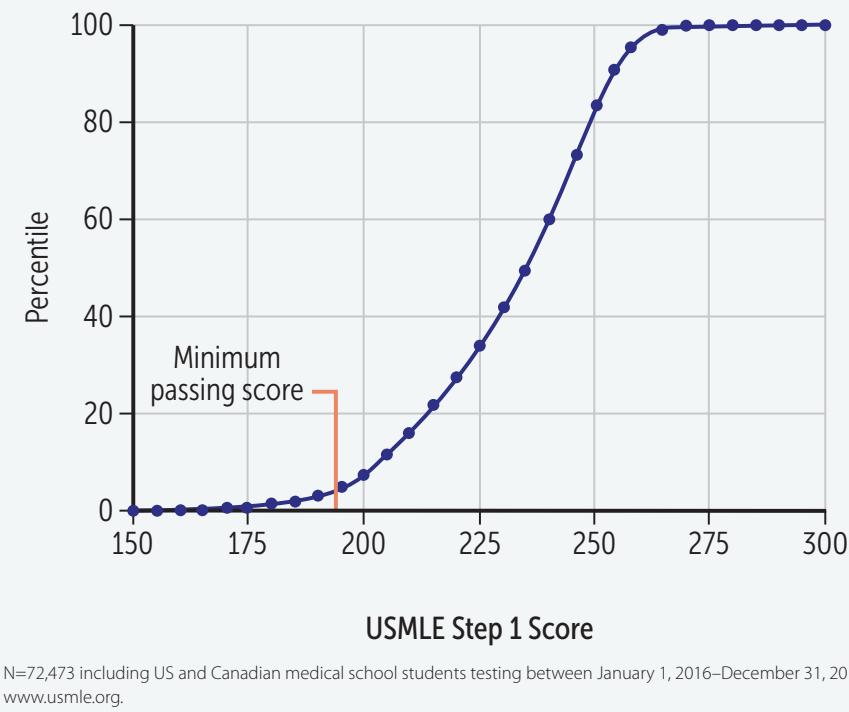


FIGURE 2. Score and Percentile for First-time Step 1 Takers.



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.

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

TABLE 2. Passing Rates for the 2018–2019 USMLE Step 1.<sup>2</sup>

	2018	2019		
	No. Tested	% Passing	No. Tested	% Passing
Allopathic 1st takers	20,670	96%	21,308	97%
Repeating	941	67%	838	66%
Allopathic total	21,611	95%	22,146	96%
Osteopathic 1st takers	4,092	96%	4,794	96%
Repeating	44	73%	43	67%
Osteopathic total	4,136	96%	4,837	96%
Total US/Canadian	25,747	94%	26,983	96%
IMG 1st takers	14,332	80%	14,046	82%
Repeating	2,111	44%	2,019	45%
IMG total	16,443	75%	16,065	78%
Total Step 1 examinees	42,190	87%	43,048	89%

## What Does My Score Mean?

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

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

## Official NBME/USMLE Resources

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

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

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

Keep in mind that this bank of questions is available only on the web. The NBME requires that users start and complete the exam within 90 days of purchase. Once the assessment has begun, users are required to complete the sections within 20 days. Following completion of the questions, the

► Practice questions may be easier than the actual exam.

TABLE 3. CBSE to USMLE Score Prediction.

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

**TABLE 4. CBSSA to USMLE Score Prediction.**

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

CBSSA provides a performance profile indicating the user's relative strengths and weaknesses, much like the report profile for the USMLE Step 1 exam. The profile is scaled with an average score of 500 and a standard deviation of 100. In addition to the performance profile, examinees will be informed of the number of questions answered incorrectly. You will have the ability to review the text of the incorrect question with the correct answer. Explanations for the correct answer, however, will not be provided. The NBME charges \$60 for assessments with expanded feedback. The fees are payable by credit card or money order. For more information regarding the CBSE and the CBSSA, visit the NBME's website at [www.nbme.org](http://www.nbme.org).

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

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

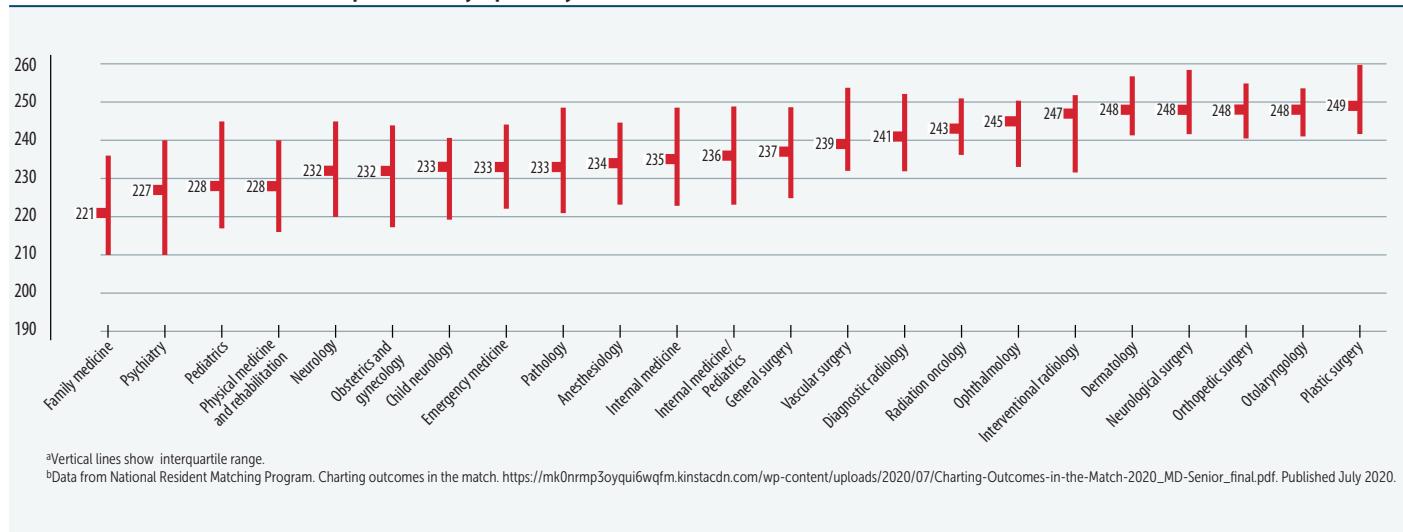
## ► DEFINING YOUR GOAL

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

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

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

The value of the USMLE Step 1 score in selecting residency applicants remains controversial, and some have called for less emphasis to be placed on the score when selecting or screening applicants.<sup>3</sup> For the time being, however, it continues to be an important part of the residency application, and it is not uncommon for some specialties to implement filters that screen out applicants who score below a certain cutoff. This is more likely to be seen in competitive specialties (eg, orthopedic surgery, ophthalmology, dermatology, otolaryngology). Independent of your career goals, you can maximize your future options by doing your best to obtain the highest score possible (see Figure 3). At the same time, your Step 1 score is only one of a number of

**FIGURE 3.** Median USMLE Step 1 Score by Specialty for Matched US Seniors.<sup>a,b</sup>

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.

## ► LEARNING STRATEGIES

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

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

## HIGH EFFICACY

### Practice Testing

Also called “retrieval practice,” practice testing has both direct and indirect benefits to the learner.<sup>4</sup> Effortful retrieval of answers does not only identify weak spots—it directly strengthens long-term retention of material.<sup>5</sup> The more effortful the recall, the better the long-term retention. This advantage has been shown to result in higher test scores and GPAs.<sup>6</sup> In fact, research has shown a positive correlation between the number of boards-style practice questions completed and Step 1 scores among medical students.<sup>7</sup>

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

TABLE 5. Effective Learning Strategies.

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

Practice testing should be done with “interleaving” (mixing of questions from different topics in a single session). Question banks often allow you to intermingle topics. Interleaved practice helps learners develop their ability to focus on the relevant concept when faced with many possibilities. Practicing topics in massed fashion (eg, all cardiology, then all dermatology) may seem intuitive, but there is strong evidence that interleaving correlates with longer-term retention and increased student achievement, especially on tasks that involve problem solving.<sup>5</sup>

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

### Distributed Practice

Also called “spaced repetition,” distributed practice is the opposite of massed practice or “cramming.” Learners review material at increasingly spaced out

intervals (days to weeks to months). Massed learning may produce more short-term gains and satisfaction, but learners who use distributed practice have better mastery and retention over the long term.<sup>5,9</sup>

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

► *Studies have linked spaced repetition learning with flash cards to improved long-term knowledge retention and higher exam scores.*

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

## MODERATE EFFICACY

### Mnemonics

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

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

### Elaborative Interrogation/Self-Explanation

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

► *Elaborative interrogation and self-explanation prompt learners to generate explanations for facts, which improves recall and problem solving.*

### Concept Mapping

Concept mapping is a method for graphically organizing knowledge, with concepts enclosed in boxes and lines drawn between related concepts. Creating or studying concept maps may be more effective than other activities (eg, writing or reading summaries/outlines). However, studies have reached mixed conclusions about its utility, and the small size of this effect raises doubts about its authenticity and pedagogic significance.<sup>14</sup>

### LOW EFFICACY

#### Rereading

While the most commonly used method among surveyed students, rereading has not been shown to correlate with grade point average.<sup>9</sup> Due to its popularity, rereading is often a comparator in studies on learning. Other strategies that we have discussed (eg, practice testing) have been shown to be significantly more effective than rereading.

#### Highlighting/Underlining

Because this method is passive, it tends to be of minimal value for learning and recall. In fact, lower-performing students are more likely to use these techniques.<sup>9</sup> Students who highlight and underline do not learn how to actively recall learned information and thus find it difficult to apply knowledge to exam questions.

### Summarization

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

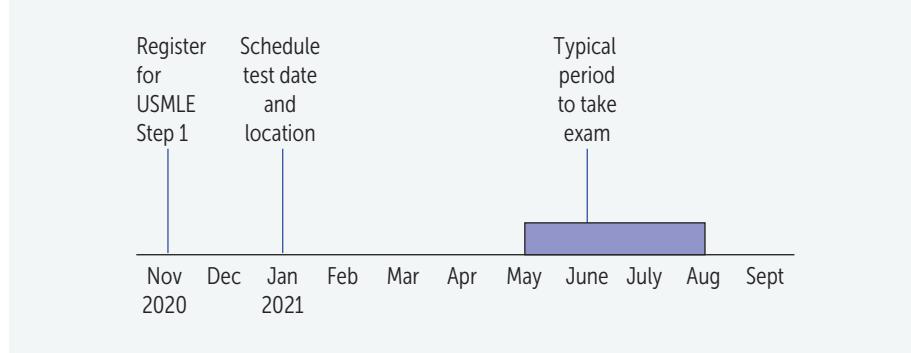
## ► TIMELINE FOR STUDY

#### Before Starting

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

#### Make a Schedule

After you have defined your goals, map out a study schedule that is consistent with your objectives, your vacation time, the difficulty of your ongoing

**FIGURE 4.** Typical Timeline for the USMLE Step 1.

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

coursework, and your family and social commitments (see Figure 4). Determine whether you want to spread out your study time or concentrate it into 14-hour study days in the final weeks. Then factor in your own history in preparing for standardized examinations (eg, SAT, MCAT). Talk to students at your school who have recently taken Step 1. Ask them for their study schedules, especially those who have study habits and goals similar to yours. Sample schedules can be found at <https://firstaidteam.com/schedules/>.

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

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

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

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

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.<sup>16</sup> Moreover, undergraduate science GPAs as well as MCAT scores are strong predictors of performance on the Step 1 exam.<sup>17</sup>

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

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](http://www.firstaidteam.com/bonus)).

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

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

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

#### Weeks Prior (Dedicated Preparation)

Your dedicated prep time may be one week or two months. You should have a working plan as you go into this period. Finish your schoolwork strong, take a day off, and then get to work. Start by simulating a full-length USMLE Step 1 if you haven’t yet done so. Consider doing one NBME CBSSA and the free questions from the NBME website. Alternatively, you could choose 7 blocks of randomized questions from a commercial question bank. Make sure you get feedback on your strengths and weaknesses and adjust your studying

accordingly. Many students study from review sources or comprehensive programs for part of the day, then do question blocks. Also, keep in mind that reviewing a question block can take upward of two hours. Feedback from CBSSA exams and question banks will help you focus on your weaknesses.

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

### 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

- ▶ 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.

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.

## ► 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.

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

## Apps

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

## Practice Tests

Taking practice tests provides valuable information about potential strengths and weaknesses in your fund of knowledge and test-taking skills. Some students use practice examinations simply as a means of breaking up the monotony of studying and adding variety to their study schedule, whereas other students rely almost solely on practice. You should also subscribe to one or more high-quality question banks.

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

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

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

► *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

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

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

### Pacing

► *Time management is an important skill for exam success.*

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

### Dealing with Each Question

There are several established techniques for efficiently approaching multiple choice questions; find what works for you. One technique begins with identifying each question as easy, workable, or impossible. Your goal should be to answer all easy questions, resolve all workable questions in a reasonable amount of time, and make quick and intelligent guesses on all impossible questions. Most students read the stem, think of the answer, and turn immediately to the choices. A second technique is to first skim the answer choices to get a context, then read the last sentence of the question

(the lead-in), and then read through the passage quickly, extracting only information relevant to answering the question. This can be particularly helpful for questions with long clinical vignettes. Try a variety of techniques on practice exams and see what works best for you. If you get overwhelmed, remember that a 30-second time out to refocus may get you back on track.

### Guessing

There is **no penalty** for wrong answers. Thus, **no test block should be left with unanswered questions**. If you don't know the answer, first eliminate incorrect choices, then guess among the remaining options. **Note that dozens of questions are unscored experimental questions** meant to obtain statistics for future exams. Therefore, some questions will seem impossible simply because they are part of the development process for future exams.

### Changing Your Answer

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

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

## ► CLINICAL VIGNETTE STRATEGIES

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

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

### What Is a Clinical Vignette?

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

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

### Strategy

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

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.

### ► 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.

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

Make sure you know both your school's and the NBME's policies regarding retakes. The NBME allows a maximum of six attempts to pass each Step examination.<sup>18</sup> You may take Step 1 no more than three times within a 12-month period. Your fourth and subsequent attempts must be at least 12 months after your first attempt at that exam and at least six months after your most recent attempt at that exam. No earlier than July 1, 2021, the total number of attempts an examinee may take per Step examination will be reduced to four attempts.

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.

## ► TESTING AGENCIES

- **National Board of Medical Examiners (NBME) / USMLE Secretariat**  
Department of Licensing Examination Services  
3750 Market Street  
Philadelphia, PA 19104-3102  
(215) 590-9500 (operator) or  
(215) 590-9700 (automated information line)  
Email: webmail@nbme.org  
[www.nbme.org](http://www.nbme.org)
- **Educational Commission for Foreign Medical Graduates (ECFMG)**  
3624 Market Street  
Philadelphia, PA 19104-2685  
(215) 386-5900  
Email: info@ecfmg.org  
[www.ecfmg.org](http://www.ecfmg.org)

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## SECTION I SUPPLEMENT

# Special Situations

Please visit [www.firstaidteam.com/bonus/](http://www.firstaidteam.com/bonus/) to view this section.

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

## ► NOTES

## SECTION II

# High-Yield General Principles

*“I’ve learned that I still have a lot to learn.”*

—Maya Angelou

*“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

*“Success is the maximum utilization of the ability that you have.”*

—Zig Ziglar

▶ How to Use the Database	30
▶ Biochemistry	33
▶ Immunology	95
▶ Microbiology	123
▶ Pathology	205
▶ Pharmacology	231
▶ Public Health Sciences	259

## ► HOW TO USE THE DATABASE

The 2021 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 biochemistry, microbiology, immunology, basic pathology, basic pharmacology, and public health sciences. Section III focuses on organ systems, with subsections covering the embryology, anatomy and histology, physiology, clinical pathology, and clinical pharmacology relevant to each. Each subsection is then divided into smaller topic areas containing related facts. Individual facts are generally presented in a three-column format, with the **Title** of the fact in the first column, the **Description** of the fact in the second column, and the **Mnemonic or Special Note** in the third column. Some facts do not have a mnemonic and are presented in a two-column format. Others are presented in list or tabular form in order to emphasize key associations.

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

The database of high-yield facts is not comprehensive. Use it to complement your core study material and not as your primary study source. The facts and notes have been condensed and edited to emphasize the high-yield 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. Determine your most efficient methods for learning the material, and do not be afraid to abandon a strategy if it is not working for you.

Our database of high-yield facts is updated 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

All images and diagrams marked with Rx are © USMLE-Rx.com (MedIQ Learning, LLC) and reproduced here by special permission. All images marked with RU are © Dr. Richard P. Usatine, author of *The Color Atlas of Family Medicine*, *The Color Atlas of Internal Medicine*, and *The Color Atlas of Pediatrics*, and are reproduced here by special permission ([www.usatinemedia.com](http://www.usatinemedia.com)). Images and diagrams marked with \* are adapted or reproduced with permission of other sources as listed on page 753. Images and diagrams with no acknowledgment are part of this book.

### Disclaimer

The entries in this section reflect student opinions on 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](http://www.firstaidteam.com) or directly by email to [firstaid@scholarrx.com](mailto:firstaid@scholarrx.com).

▶ NOTES

# Biochemistry

*The nitrogen in our DNA, the calcium in our teeth, the iron in our blood, the carbon in our apple pies were made in the interiors of collapsing stars. We are made of starstuff.*

—Carl Sagan

*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

*DNA was the first three-dimensional Xerox machine.*

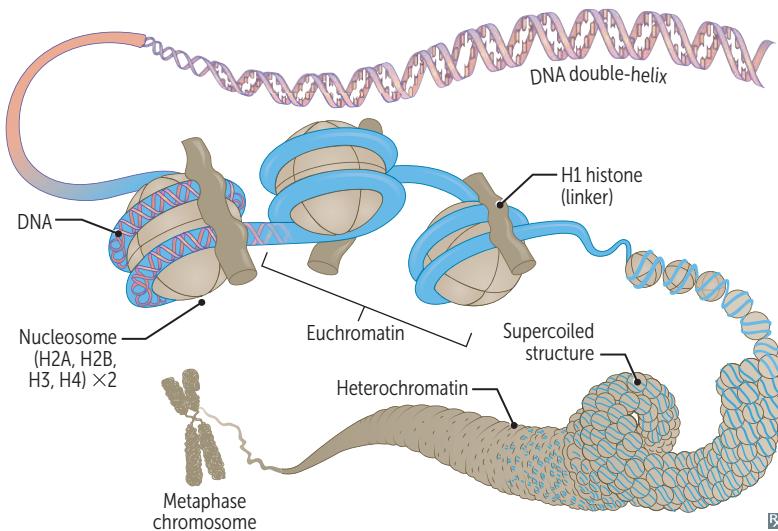
—Kenneth Ewart Boulding

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

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

► Molecular	34
► Cellular	46
► Laboratory Techniques	52
► Genetics	56
► Nutrition	65
► Metabolism	73

## ► BIOCHEMISTRY—MOLECULAR

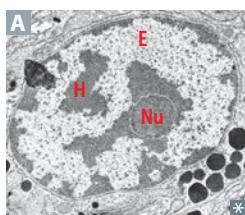
**Chromatin structure**

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

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

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

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

**Heterochromatin**

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

**Heterochromatin = highly condensed.**

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

**Euchromatin**

Less condensed, appears lighter on EM (labeled E in **A**). Transcriptionally active, sterically accessible.

*Eu* = true, “truly transcribed.”

Euchromatin is **expressed**.

**DNA methylation**

Changes the expression of a DNA segment without changing the sequence. Involved with aging, carcinogenesis, genomic imprinting, transposable element repression, and X chromosome inactivation (lyonization).

DNA is methylated in imprinting.

Methylation within gene promoter (CpG islands) typically represses (silences) gene transcription. CpG **methylation makes DNA mute**.

**Histone methylation**

Usually causes reversible transcriptional suppression, but can also cause activation depending on location of methyl groups.

Histone **methylation mostly makes DNA mute**.

**Histone acetylation**

Removal of histone’s  $\oplus$  charge  $\rightarrow$  relaxed DNA coiling  $\rightarrow$   $\uparrow$  transcription.

Thyroid hormone receptors alter thyroid hormone synthesis by acetylation. Dysregulated acetylation is implicated in Huntington disease. Histone **acetylation makes DNA active**.

**Histone deacetylation**

Removal of acetyl groups  $\rightarrow$  tightened DNA coiling  $\rightarrow$   $\downarrow$  transcription.

**Nucleotides**

Nucleoside = base + (deoxy)ribose (sugar).

Nucleotide = base + (deoxy)ribose + phosphate; linked by 3'-5' phosphodiester bond.

5' end of incoming nucleotide bears the triphosphate (energy source for the bond).  $\alpha$ -Phosphate is target of 3' hydroxyl attack.

**Purines (A,G)**—2 rings.

**Pyrimidines (C,U,T)**—1 ring

Deamination reactions:

Cytosine  $\rightarrow$  uracil

Adenine  $\rightarrow$  hypoxanthine

Guanine  $\rightarrow$  xanthine

5-methylcytosine  $\rightarrow$  thymine

Uracil found in RNA; thymine in DNA.

Methylation of uracil makes thymine.

**Pure As Gold.**

**CUT** the pyramid.

**Thy**mine has a **methyl**.

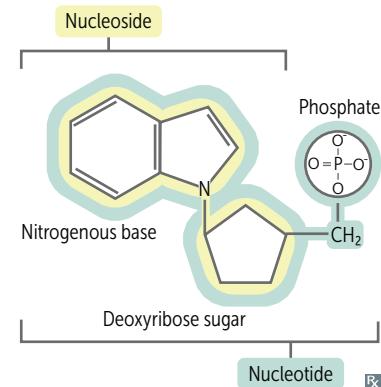
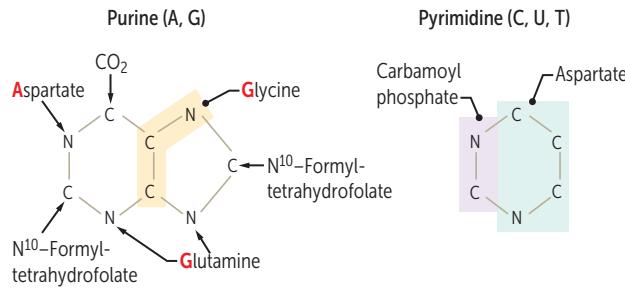
C-G bond (3 H bonds) stronger than A-T bond (2 H bonds).  $\uparrow$  C-G content  $\rightarrow$   $\uparrow$  melting temperature of DNA. “**C-G** bonds are like **Crazy Glue**.”

Amino acids necessary for **purine** synthesis (cats purr until they **GAG**):

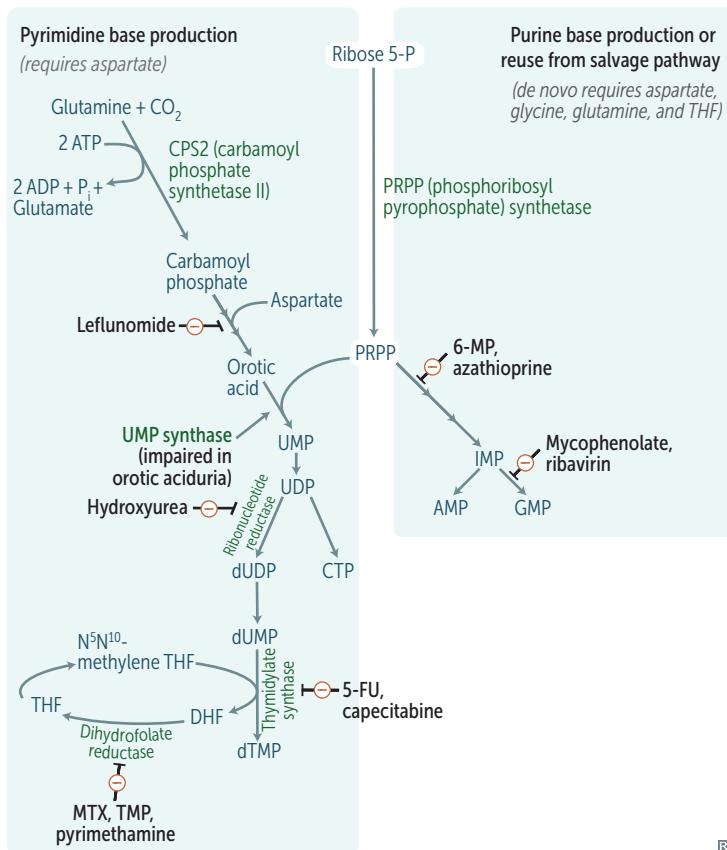
**Glycine**

**Aspartate**

**Glutamine**



**De novo pyrimidine and purine synthesis** Various immunosuppressive, antineoplastic, and antibiotic drugs function by interfering with nucleotide synthesis:



### Pyrimidine synthesis:

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

### Purine synthesis:

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

### Purine and pyrimidine synthesis:

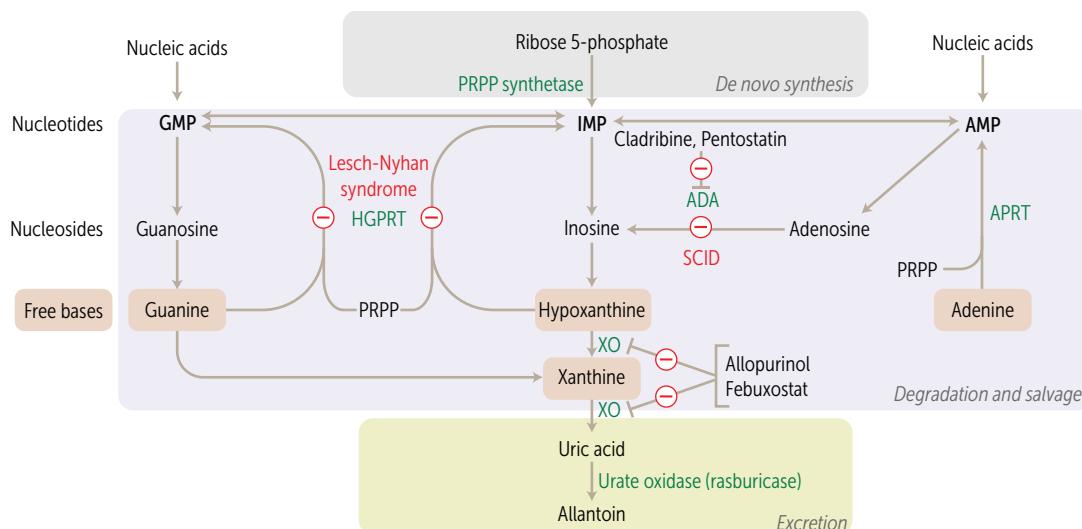
- Hydroxyurea:** inhibits ribonucleotide reductase
- Methotrexate (MTX), trimethoprim (TMP),** and **pyrimethamine:** inhibit dihydrofolate reductase ( $\downarrow$  deoxythymidine monophosphate [dTMP]) in humans, bacteria, and protozoa, respectively

CPS1 = mitochondria (urea cycle)

CPS2 = cytosol

Rx

### Purine salvage deficiencies



ADA, adenosine deaminase; APRT, adenine phosphoribosyltransferase; HGPRT, hypoxanthine guanine phosphoribosyltransferase; XO, xanthine oxidase; SCID, severe combined immune deficiency (autosomal recessive inheritance)

<b>Adenosine deaminase deficiency</b>	ADA is required for degradation of adenosine and deoxyadenosine. ↓ ADA → ↑ dATP → ↓ ribonucleotide reductase activity → ↓ DNA precursors in cells → ↓ lymphocytes.	One of the major causes of autosomal recessive SCID.
<b>Lesch-Nyhan syndrome</b>	Defective purine salvage due to absent HGPRT, which converts hypoxanthine to IMP and guanine to GMP. ↑ purine synthesis (↑ PRPP aminotransferase activity) → excess uric acid production. X-linked recessive.  Findings: intellectual disability, self-mutilation, aggression, hyperuricemia (red/orange “sand” [sodium urate crystals] in diaper), gout, dystonia, macrocytosis.	<b>HGPRT:</b> Hyperuricemia Gout Pissed off (aggression, self-mutilation) Red/orange crystals in urine Tense muscles (dystonia) Treatment: allopurinol or febuxostat (2nd line).

### Genetic code features

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

**DNA replication**

Occurs in  $5' \rightarrow 3'$  direction (“**Synth3sis**”) in continuous and discontinuous (Okazaki fragment) fashion. Semiconservative. More complex in eukaryotes than in prokaryotes, but shares analogous enzymes.

**Origin of replication A**

Particular consensus sequence in genome where DNA replication begins. May be single (prokaryotes) or multiple (eukaryotes).

AT-rich sequences (such as TATA box regions) are found in promoters and origins of replication.

**Replication fork B**

Y-shaped region along DNA template where leading and lagging strands are synthesized.

**Helicase C**

Unwinds DNA template at replication fork.

**Helicase halves DNA.**

Deficient in **Bloom syndrome** (**BLM** gene mutation).

**Single-stranded binding proteins D**

Prevent strands from reannealing or degradation by nucleases.

**DNA topoisomerases E**

Creates a **single-** (topoisomerase I) or **double-** (topoisomerase II) stranded break in the helix to add or remove supercoils (as needed due to underwinding or overwinding of DNA).

In eukaryotes: irinotecan/topotecan inhibit topoisomerase (TOP) I, etoposide/teniposide inhibit TOP II.

In prokaryotes: fluoroquinolones inhibit TOP II (DNA gyrase) and TOP IV.

**Primase F**

Makes an RNA primer on which DNA polymerase III can initiate replication.

**DNA polymerase III G**

Prokaryotes only. Elongates leading strand by adding deoxynucleotides to the  $3'$  end. Elongates lagging strand until it reaches primer of preceding fragment.

DNA polymerase III has  $5' \rightarrow 3'$  synthesis and proofreads with  $3' \rightarrow 5'$  exonuclease. Drugs blocking DNA replication often have a modified  $3'$  OH, thereby preventing addition of the next nucleotide (“chain termination”).

**DNA polymerase I H**

Prokaryotes only. Degrades RNA primer; replaces it with DNA.

Same functions as DNA polymerase III, also excises RNA primer with  $5' \rightarrow 3'$  exonuclease.

**DNA ligase I**

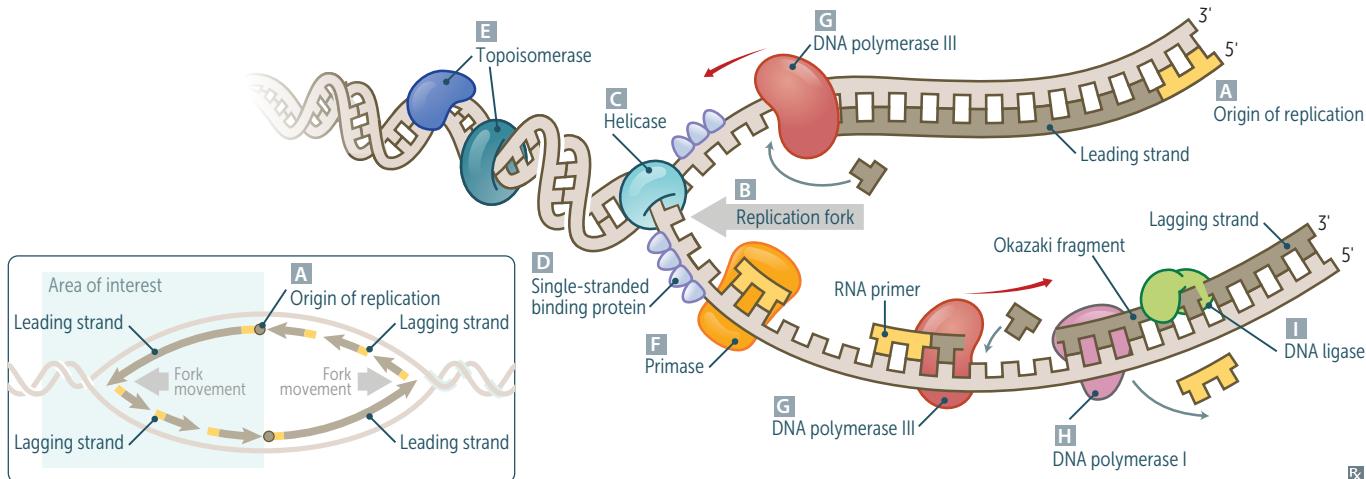
Catalyzes the formation of a phosphodiester bond within a strand of double-stranded DNA.

Joins Okazaki fragments. **Ligase** links DNA.

**Telomerase**

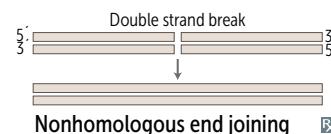
Eukaryotes only. A reverse transcriptase (RNA-dependent DNA polymerase) that adds DNA (**TTAGGG**) to  $3'$  ends of chromosomes to avoid loss of genetic material with every duplication.

Often upregulated in cancer, downregulated in aging and progeria. **Telomerase TAGs for Greatness and Glory.**

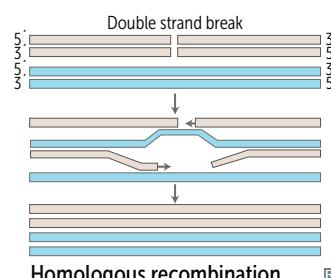


**DNA repair****Double strand****Nonhomologous end joining**

Brings together 2 ends of DNA fragments to repair double-stranded breaks.  
Defective in ataxia-telangiectasia.  
Homology not required. Some DNA may be lost.

**Homologous recombination**

Requires 2 homologous DNA duplexes. A strand from damaged dsDNA is repaired using a complementary strand from intact homologous dsDNA as a template.  
Defective in breast/ovarian cancers with *BRCA1* mutation and in Fanconi anemia.  
Restores duplexes accurately without loss of nucleotides.

**Single strand****Nucleotide excision repair**

Specific endonucleases release the oligonucleotides containing damaged bases; DNA polymerase and ligase fill and reseal the gap, respectively. Repairs bulky helix-distorting lesions.

Occurs in G<sub>1</sub> phase of cell cycle.  
Defective in *xeroderma pigmentosum* (inability to repair DNA pyrimidine dimers caused by UV exposure). Presents with dry skin, photosensitivity, skin cancer.

**Base excision repair**

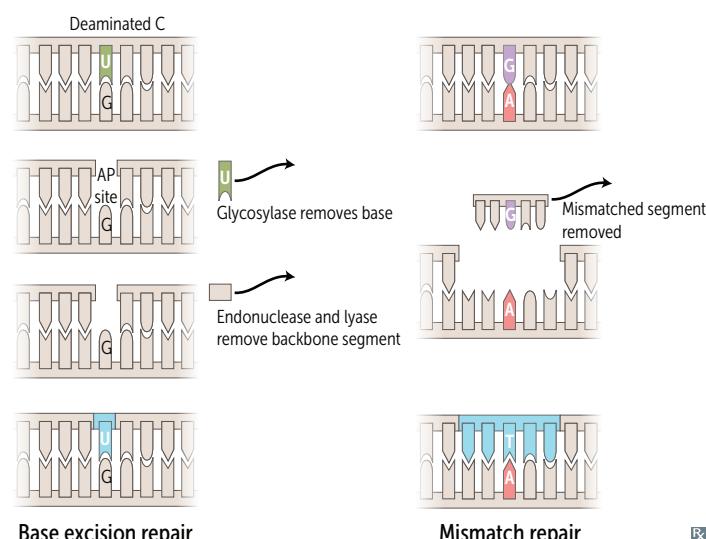
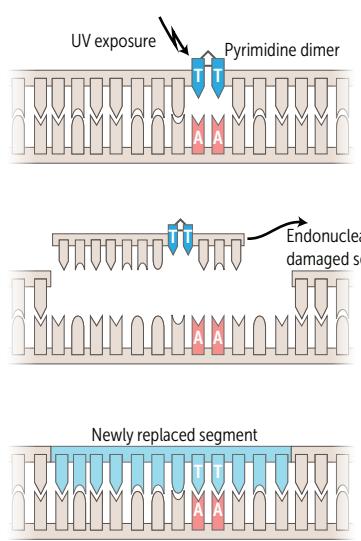
Base-specific Glycosylase removes altered base and creates AP site (apurinic/apurimidinic). One or more nucleotides are removed by AP-Endonuclease, which cleaves 5' end. AP-Lyase cleaves 3' end. DNA Polymerase-β fills the gap and DNA Ligase seals it.

Occurs throughout cell cycle.  
Important in repair of spontaneous/toxic deamination.  
“GEL Please.”

**Mismatch repair**

Mismatched nucleotides in newly synthesized (unmethylated) strand are removed and gap is filled and resealed.

Occurs predominantly in S phase of cell cycle.  
Defective in Lynch syndrome (hereditary nonpolyposis colorectal cancer [HNPCC]).

**Nucleotide excision repair****Base excision repair****Mismatch repair**

**Mutations in DNA**

Degree of change: silent << missense < nonsense < frameshift. Single nucleotide substitutions are repaired by DNA polymerase and DNA ligase. Types of single nucleotide (point) mutations:

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

**Single nucleotide substitutions****Silent mutation**

Codes for same (synonymous) amino acid; often involves 3rd position of codon (tRNA wobble).

**Missense mutation**

Results in changed amino acid (called conservative if new amino acid has similar chemical structure). Examples: sickle cell disease (substitution of glutamic acid with valine).

**Nonsense mutation**

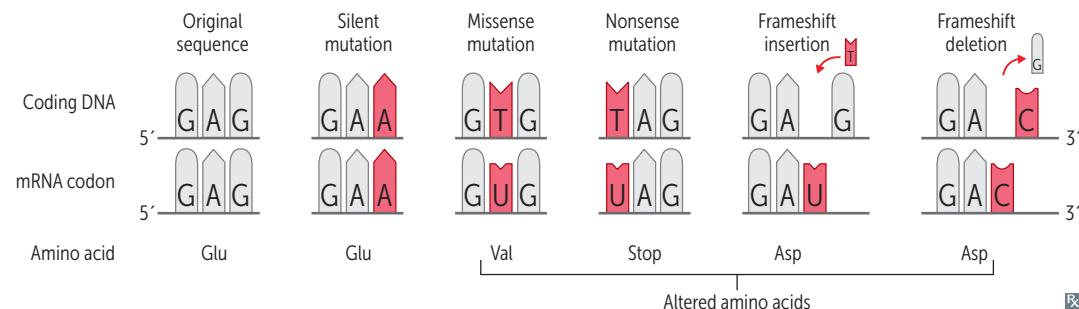
Results in early **stop** codon (UGA, UAA, UAG). Usually generates nonfunctional protein. **Stop the nonsense!**

**Other mutations****Frameshift mutation**

Deletion or insertion of any number of nucleotides not divisible by 3 → misreading of all nucleotides downstream. Protein may be shorter or longer, and its function may be disrupted or altered. Examples: Duchenne muscular dystrophy, Tay-Sachs disease.

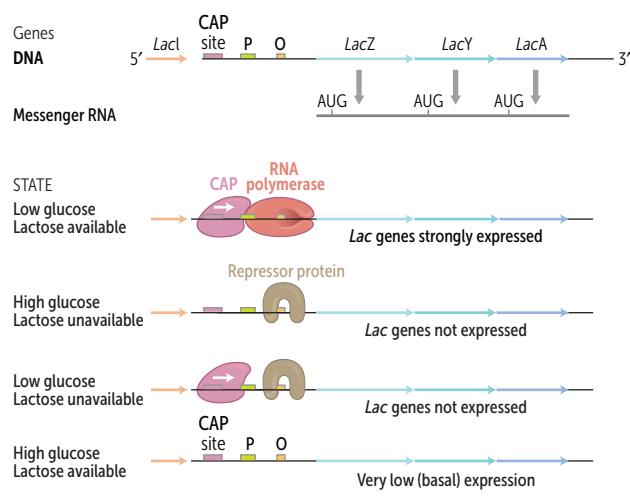
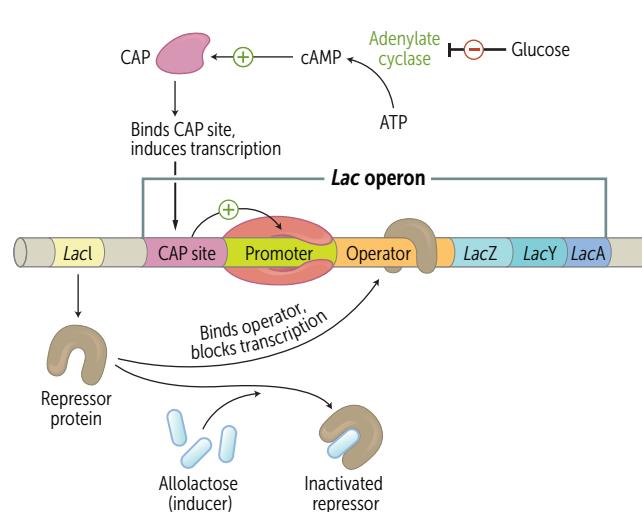
**Splice site mutation**

Retained intron in mRNA → protein with impaired or altered function. Examples: rare causes of cancers, dementia, epilepsy, some types of β-thalassemia, Gaucher disease, Marfan syndrome.

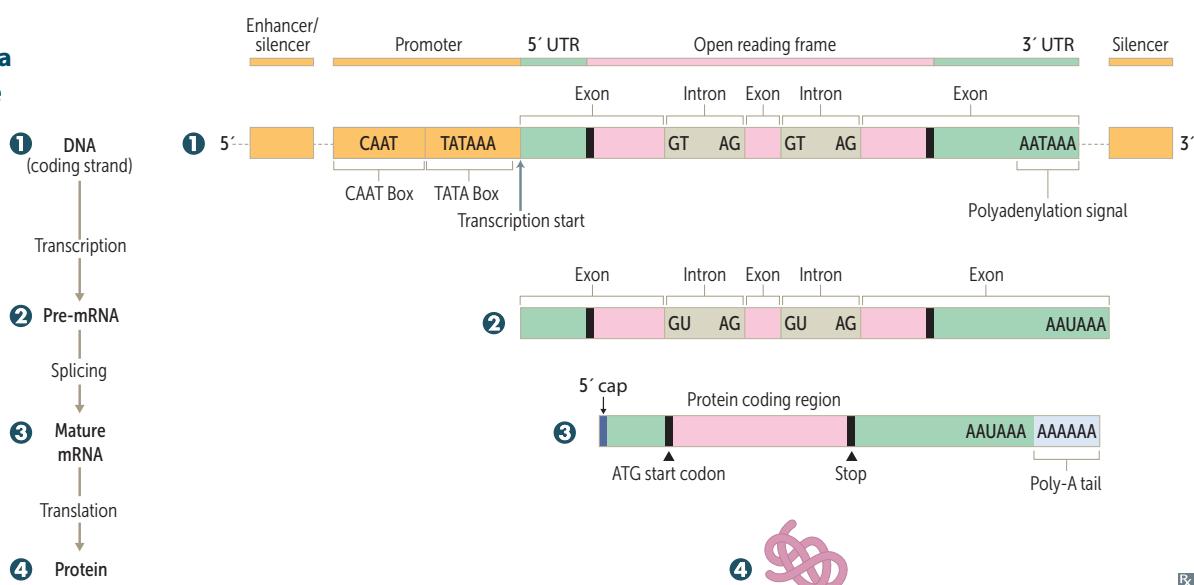
**Lac operon**

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

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



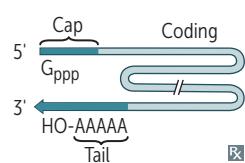
## Functional organization of a eukaryotic gene



## Regulation of gene expression

<b>Promoter</b>	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, which differ between eukaryotes and prokaryotes).	Promoter mutation commonly results in dramatic ↓ in level of gene transcription.
<b>Enhancer</b>	DNA locus where regulatory proteins (“activators”) bind, <b>increasing</b> expression of a gene on the same chromosome.	Enhancers and silencers may be located close to, far from, or even within (in an intron) the gene whose expression they regulate.
<b>Silencer</b>	DNA locus where regulatory proteins (“repressors”) bind, <b>decreasing</b> expression of a gene on the same chromosome.	

## RNA processing (eukaryotes)



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

The following processes occur in the nucleus:

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

Capped, tailed, and spliced transcript is called mRNA.

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

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

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

## RNA polymerases

### Eukaryotes

RNA polymerase I makes **rRNA**, the most common (**rampant**) type; present only in nucleolus.  
 RNA polymerase II makes **mRNA** (**massive**), **microRNA** (**miRNA**), and **small nuclear RNA** (**snRNA**).  
 RNA polymerase III makes 5S rRNA, **tRNA** (**tiny**).  
 No proofreading function, but can initiate chains. RNA polymerase II opens DNA at promoter site.

I, II, and III are numbered in the same order that their products are used in protein synthesis: rRNA, mRNA, then tRNA.

**α-amanitin**, found in *Amanita phalloides* (death cap mushrooms), inhibits RNA polymerase II. Causes dysentery and severe hepatotoxicity if ingested.

Actinomycin D, also called dactinomycin, inhibits RNA polymerase in both prokaryotes and eukaryotes.

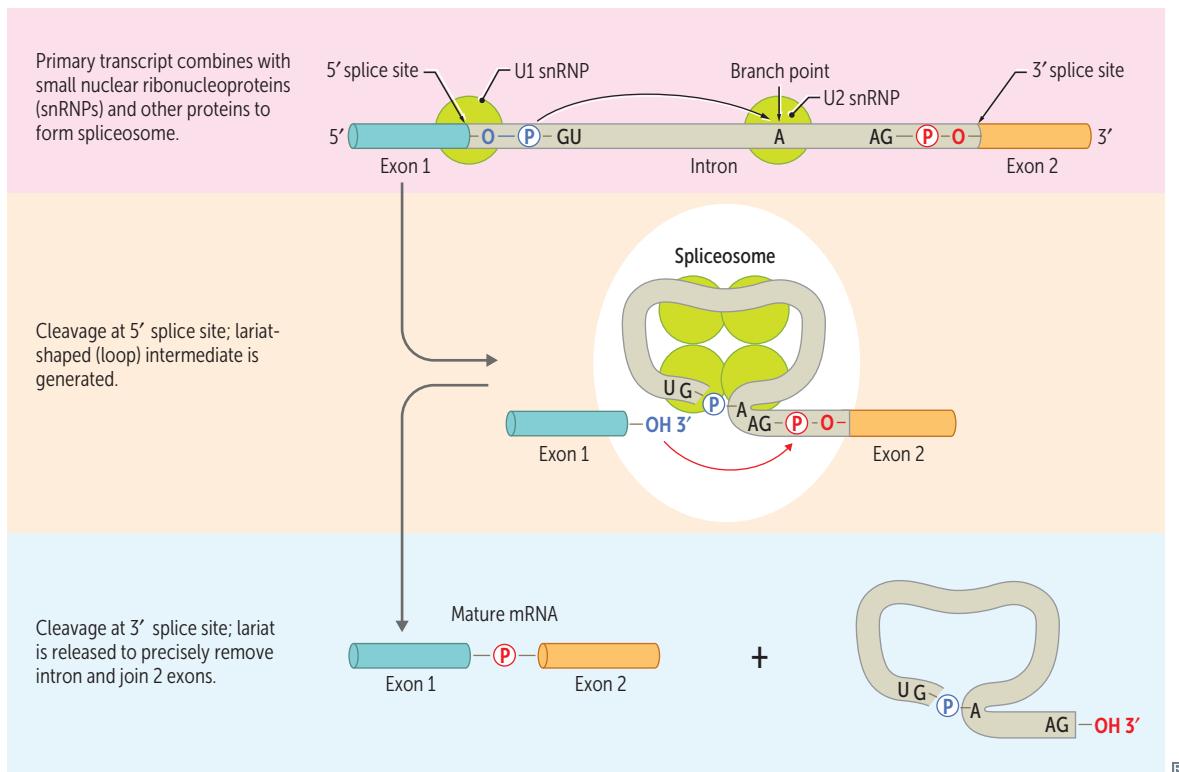
### Prokaryotes

1 RNA polymerase (multisubunit complex) makes all 3 kinds of RNA.

Rifamycins (rifampin, rifabutin) inhibit DNA-dependent RNA polymerase in prokaryotes.

## Splicing of pre-mRNA

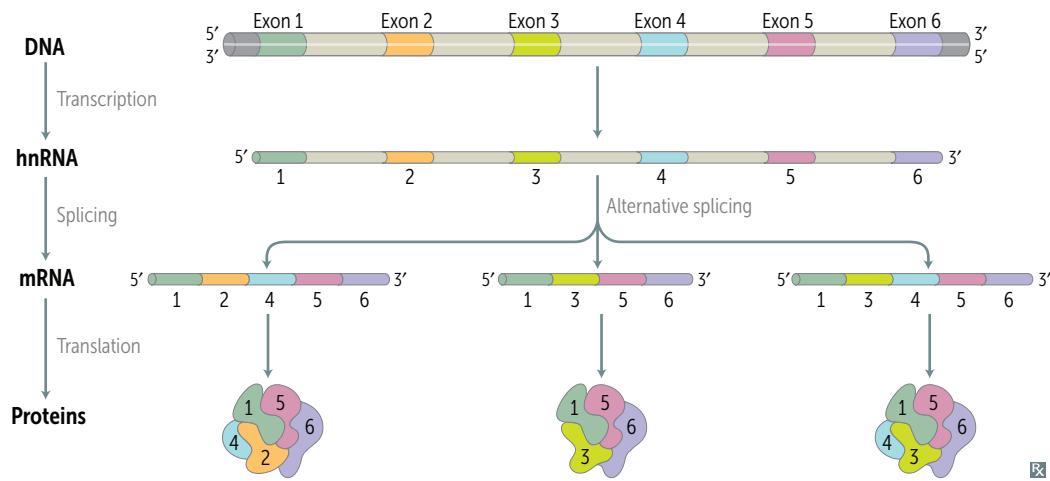
Part of process by which precursor mRNA (pre-mRNA) is transformed into mature mRNA.  
 Alterations in snRNP assembly can cause clinical disease; eg, in spinal muscular atrophy, snRNP assembly is affected due to ↓ SMN protein → congenital degeneration of anterior horns of spinal cord → symmetric weakness (hypotonia, or “floppy baby syndrome”).  
 Anti-U1 snRNP antibodies are associated with SLE, mixed connective tissue disease, other rheumatic diseases.



**Introns vs exons**

Exons contain the actual genetic information coding for protein.  
 Introns do not code for protein, but are important in regulation of gene expression.  
 Different exons are frequently combined by alternative splicing to produce a larger number of unique proteins.  
 Alternative splicing can produce a variety of protein products from a single hnRNA (heterogenous nuclear RNA) sequence (eg, transmembrane vs secreted Ig, tropomyosin variants in muscle, dopamine receptors in the brain, host defense evasion by tumor cells).

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



**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.**

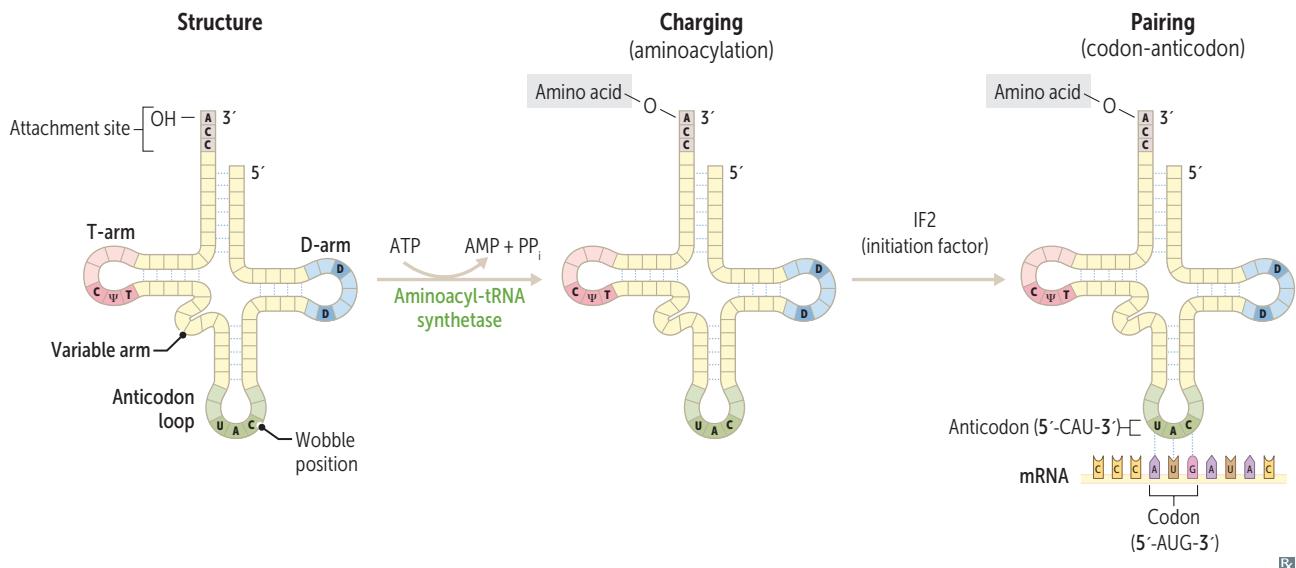
T-arm: contains the TΨC (ribothymidine, pseudouridine, cytidine) sequence necessary for tRNA-ribosome binding. **T-arm** Tethers tRNA molecule to ribosome.

D-arm: contains **Dihydrouridine** residues necessary for tRNA recognition by the correct aminoacyl-tRNA synthetase. **D-arm** allows **Detection** of the tRNA by aminoacyl-tRNA synthetase.

Attachment site: 3'-ACC-5' is the amino acid **ACCeptor** site.

**Charging**

Aminoacyl-tRNA synthetase (uses ATP; 1 unique enzyme per respective amino acid) and binding of charged tRNA to the codon are responsible for the accuracy of amino acid selection. Aminoacyl-tRNA synthetase matches an amino acid to the tRNA by scrutinizing the amino acid before and after it binds to tRNA. If an incorrect amino acid is attached, the bond is hydrolyzed. A mischarged tRNA reads the usual codon but inserts the wrong amino acid.

**Start and stop codons****mRNA start codons**

AUG.

**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 Go Away.**

**UAA** = **U Are Away.**

**UAG** = **U Are G**one.

## Protein synthesis

### Initiation

- Eukaryotic initiation factors (eIFs) identify the 5' cap.
- eIFs help assemble the 40S ribosomal subunit with the initiator tRNA.
- eIFs released when the mRNA and the ribosomal 60S subunit assemble with the complex. Requires GTP.

### Elongation

- Aminoacyl-tRNA binds to A site (except for initiator methionine, which binds the P site), requires an elongation factor and GTP.
- rRNA ("ribozyme") catalyzes peptide bond formation, transfers growing polypeptide to amino acid in A site.
- Ribosome advances 3 nucleotides toward 3' end of mRNA, moving peptidyl tRNA to P site (translocation).

### Termination

Eukaryotic release factors (eRFs) recognize the stop codon and halt translation → completed polypeptide is released from ribosome. Requires GTP.

**Eukaryotes:**  $40S + 60S \rightarrow 80S$  (even).

**Prokaryotes:**  $30S + 50S \rightarrow 70S$  (prime).

Synthesis occurs from N-terminus to C-terminus.

**ATP-tRNA Activation (charging).**

**GTP-tRNA Gripping and Going places (translocation).**

Think of "going APE":

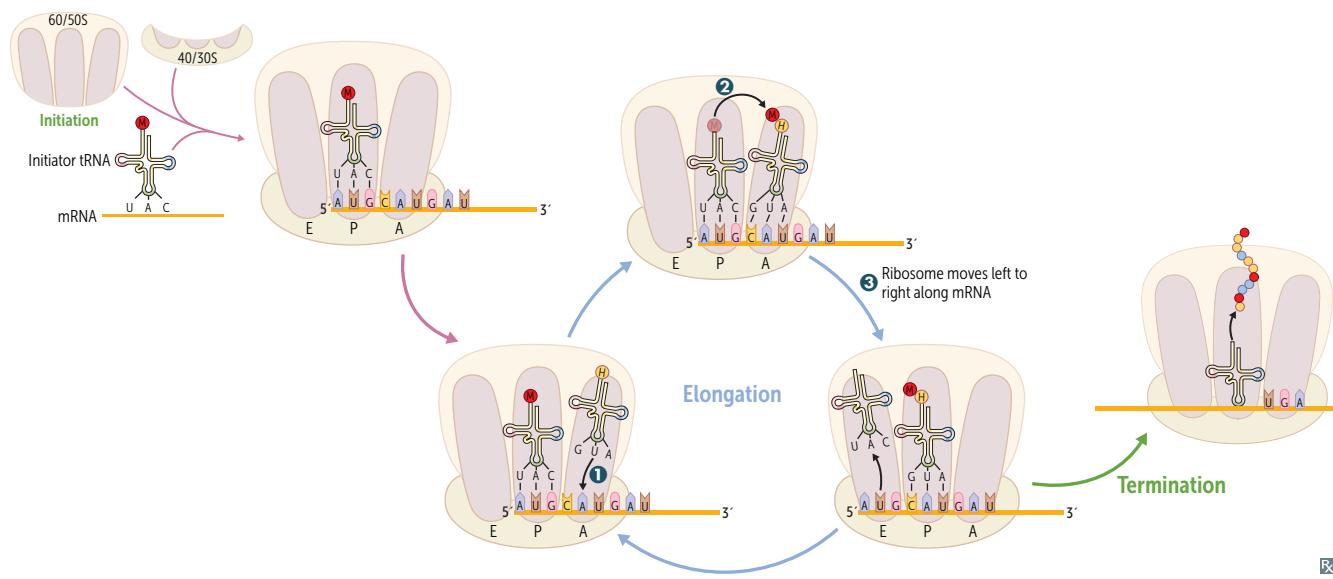
**A** site = incoming **A**minoacyl-tRNA.

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

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

Elongation factors are targets of bacterial toxins (eg, *Diphtheria*, *Pseudomonas*).

**Shine-Dalgarno sequence**—ribosomal binding site in prokaryotic mRNA. Enables protein synthesis initiation by aligning the ribosome with the start codon so that code is read correctly.



## Posttranslational modifications

### Trimming

Removal of N- or C-terminal propeptides from zymogen to generate mature protein (eg, trypsinogen to trypsin).

### Covalent alterations

Phosphorylation, glycosylation, hydroxylation, methylation, acetylation, and ubiquitination.

### Chaperone protein

Intracellular protein involved in facilitating and maintaining protein folding. In yeast, heat shock proteins (eg, HSP60) are constitutively expressed, but expression may increase with high temperatures, acidic pH, and hypoxia 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<sub>1</sub> and G<sub>0</sub> are of variable duration.

## REGULATION OF CELL CYCLE

**Cyclin-dependent kinases**

Constitutively expressed but inactive when not bound to cyclin.

**Cyclin-CDK complexes**

Cyclins are phase-specific regulatory proteins that activate CDKs when stimulated by growth factors. The cyclin-CDK complex can then phosphorylate other proteins (eg, Rb) to coordinate cell cycle progression. This complex must be activated/inactivated at appropriate times for cell cycle to progress.

**Tumor suppressors**

p53 → p21 induction → CDK inhibition → Rb hypophosphorylation (activation) → G<sub>1</sub>-S progression inhibition. Mutations in tumor suppressor genes can result in unrestrained cell division (eg, Li-Fraumeni syndrome). Growth factors (eg, insulin, PDGF, EPO, EGF) bind tyrosine kinase receptors to transition the cell from G<sub>1</sub> to S phase.

## CELL TYPES

**Permanent**

Remain in G<sub>0</sub>, regenerate from stem cells.

Neurons, skeletal and cardiac muscle, RBCs.

**Stable (quiescent)**

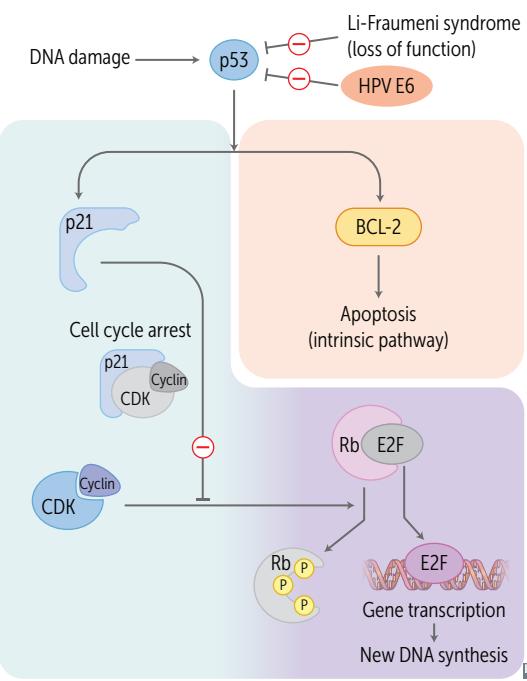
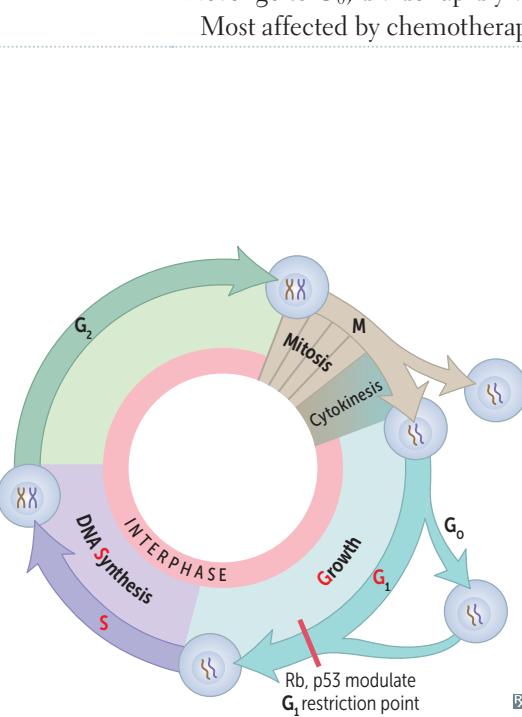
Enter G<sub>1</sub> from G<sub>0</sub> when stimulated.

Hepatocytes, lymphocytes, PCT, periosteal cells.

**Labile**

Never go to G<sub>0</sub>, divide rapidly with a short G<sub>1</sub>.

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 lysosomal and other proteins.  
Nissl bodies (RER in neurons)—synthesize peptide neurotransmitters for secretion.  
Free ribosomes—unattached to any membrane; site of synthesis of cytosolic, peroxisomal, and mitochondrial proteins.

N-linked glycosylation occurs in the endoplasmic reticulum.  
Mucus-secreting goblet cells of small intestine and antibody-secreting plasma cells are rich in RER.  
Proteins within organelles (eg, ER, Golgi bodies, lysosomes) are formed in RER.

**Smooth endoplasmic reticulum**

Site of steroid synthesis and detoxification of drugs and poisons. Lacks surface ribosomes.  
Location of glucose-6-phosphatase (last step in both glycogenolysis and gluconeogenesis).

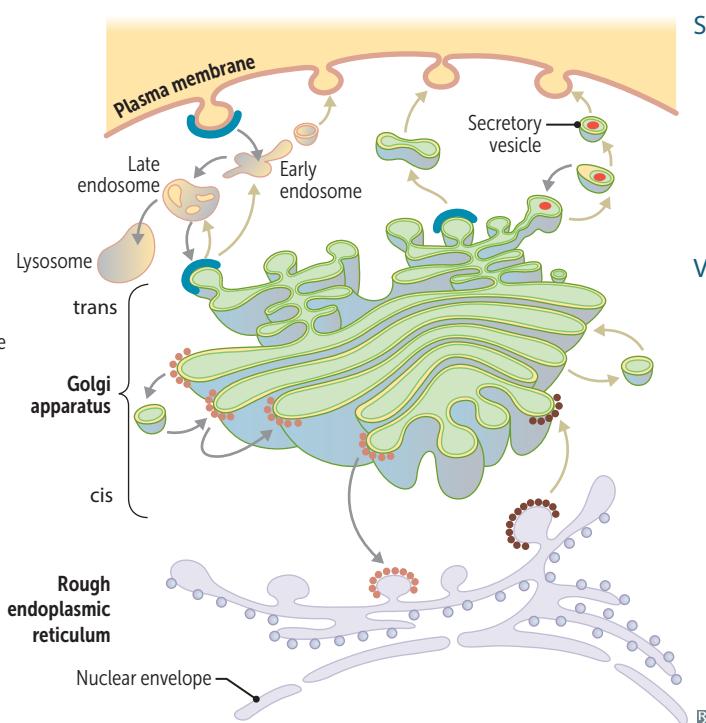
Liver hepatocytes and steroid hormone-producing cells of the adrenal cortex and gonads are rich in SER.

**Cell trafficking**

Golgi is distribution center for proteins and lipids from ER to vesicles and plasma membrane.  
Posttranslational events in O-oligosaccharides include modifying N-oligosaccharides on asparagine, adding O-oligosaccharides on serine and threonine, and adding mannose-6-phosphate to proteins for lysosomal and other proteins.  
Endosomes are sorting centers for material from outside the cell or from the Golgi, sending it to lysosomes for destruction or back to the membrane/Golgi for further use.

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

- Key:
- Clathrin
  - COP I
  - COP II
  - Retrograde
  - Anterograde

**Signal recognition particle (SRP)**

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

**Vesicular trafficking proteins**

COP I: Golgi → Golgi (retrograde); cis-Golgi → ER.

COP II: ER → cis-Golgi (anterograde).

**“Two (COP II) steps forward (anterograde); one (COP I) step back (retrograde.”**

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

**Peroxisome**

Membrane-enclosed organelle involved in:

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

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

**Refsum disease**—autosomal recessive disorder of  $\alpha$ -oxidation  $\rightarrow$  buildup of phytanic acid due to inability to degrade it. Scaly skin, ataxia, cataracts/night blindness, shortening of 4th toe, epiphyseal dysplasia. Treatment: diet, plasmapheresis.

**Adrenoleukodystrophy**—X-linked recessive disorder of  $\beta$ -oxidation due to mutation in *ABCD1* gene  $\rightarrow$  VLCFA buildup in **adrenal** glands, white (**leuko**) matter of brain, testes. Progressive disease that can lead to adrenal gland crisis, progressive loss of neurologic function, death.

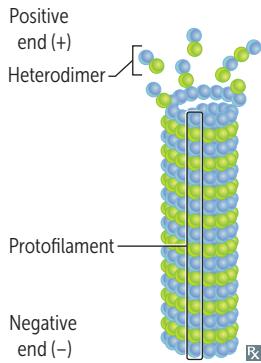
**Proteasome**

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
<b>Microfilaments</b>	Muscle contraction, cytokinesis	Actin, microvilli.
<b>Intermediate filaments</b>	Maintain cell structure	Vimentin, desmin, cytokeratin, lamins, glial fibrillary acidic protein (GFAP), neurofilaments.
<b>Microtubules</b>	Movement, cell division	Cilia, flagella, mitotic spindle, axonal trafficking, centrioles.

**Microtubule**

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

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

- Retrograde to microtubule  $(+ \rightarrow -)$ —**dynein**.
- Anterograde to microtubule  $(- \rightarrow +)$ —**kinesin**.

*Clostridium tetani* toxin, herpes simplex virus, poliovirus, and rabies virus use dynein for retrograde transport to the neuronal cell body.

Drugs that act on microtubules (**microtubules get constructed very terribly**):

- **Mebendazole** (antihelminthic)
- **Griseofulvin** (antifungal)
- **Colchicine** (antigout)
- **Vinca alkaloids** (anticancer)
- **Taxanes** (anticancer)

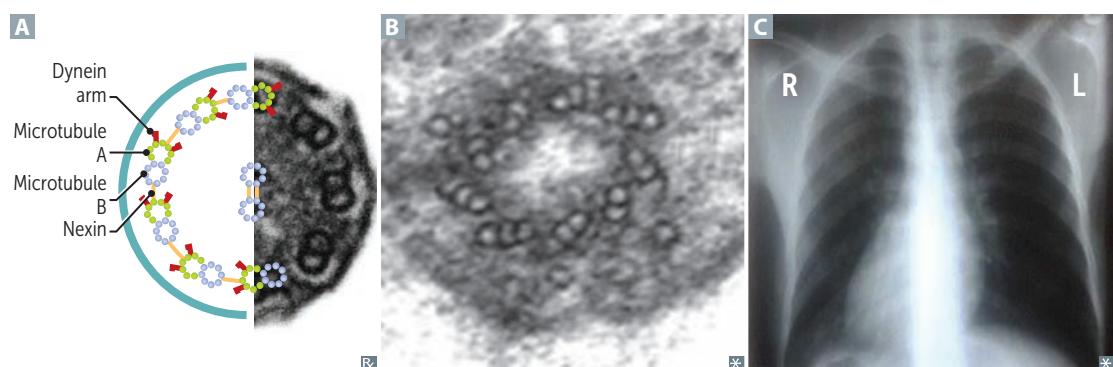
Negative end **near nucleus**.

Positive end points to **periphery**.

**Ready? Attack!**

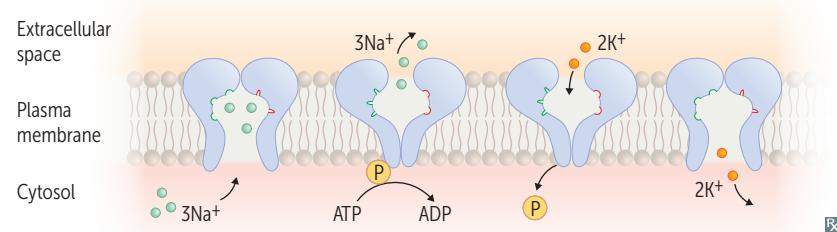
**Cilia structure**

9 doublet + 2 singlet arrangement of microtubules **A**.  
 Basal body (base of cilium below cell membrane) consists of 9 microtubule triplets **B** with no central microtubules.  
 Axonemal dynein—ATPase that links peripheral 9 doublets and causes bending of cilium by differential sliding of doublets.  
 Gap junctions enable coordinated ciliary movement.

**Sodium-potassium pump**

$\text{Na}^+$ - $\text{K}^+$  ATPase is located in the plasma membrane with ATP site on cytosolic side. For each ATP consumed, **2  $\text{K}^+$**  go **in** to the cell (pump dephosphorylated) and **3  $\text{Na}^+$**  go **out** of the cell (pump phosphorylated).

**Kartagener syndrome**—autosomal recessive dynein arm defect → immotile cilia → dysfunctional ciliated epithelia. Findings: developmental abnormalities due to impaired migration and orientation (eg, situs inversus **C**, hearing loss due to dysfunctional eustachian tube cilia); recurrent infections (eg, sinusitis, ear infections, bronchiectasis due to impaired ciliary clearance of debris/pathogens); infertility ( $\uparrow$  risk of ectopic pregnancy due to dysfunctional fallopian tube cilia, immotile spermatozoa). Lab findings:  $\downarrow$  nasal nitric oxide (used as screening test).



**Collagen**

Most abundant protein in the human body.  
Extensively modified by posttranslational modification.  
Organizes and strengthens extracellular matrix.

Type I - **Skeleton**  
Type II - **Cartilage**  
Type III - **Arteries**  
Type IV - **Basement membrane**  
**SCAB**

**Type I**

Most common (90%)—Bone (made by osteoblasts), Skin, Tendon, dentin, fascia, cornea, **late** wound repair.

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

**Type II**

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

Type **II**: cartilage.

**Type III**

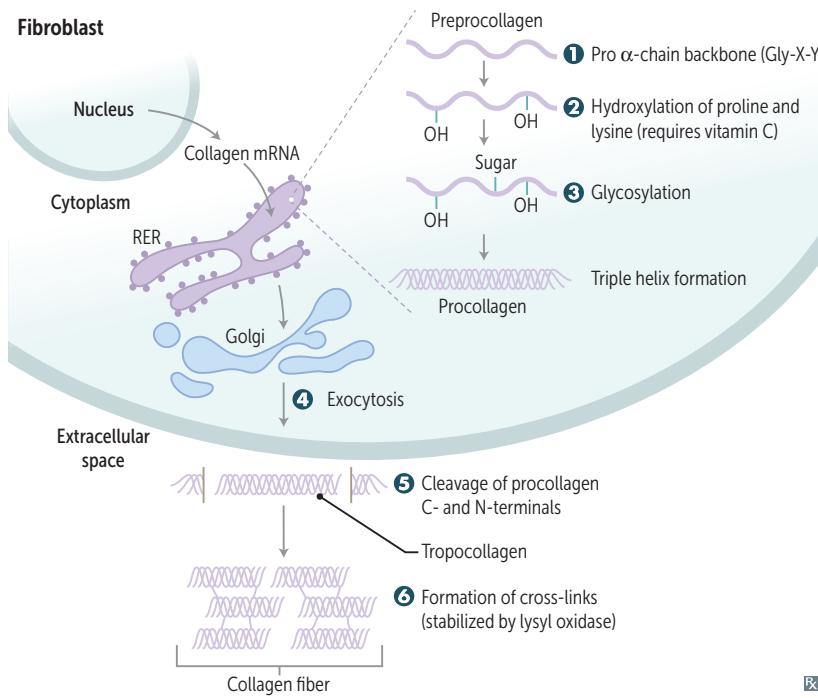
Reticulin—skin, **blood vessels**, uterus, fetal tissue, **early** wound repair.

Type **III**: deficient in **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  $\alpha$  chains (procollagen)—usually Gly-X-Y (X and Y are proline or lysine). Collagen is  $\frac{1}{3}$  glycine; glycine content of collagen is less variable than that of lysine and proline. Hydroxyproline is used for lab quantification of collagen.

**2 Hydroxylation**—hydroxylation (“hydroxylation”) of specific proline and lysine residues. Requires vitamin **C**; deficiency → scurvy.

**3 Glycosylation**—glycosylation of pro- $\alpha$ -chain hydroxylysine residues and formation of procollagen via hydrogen and disulfide bonds (triple helix of 3 collagen  $\alpha$  chains). Problems forming triple helix → osteogenesis imperfecta.

**4 Exocytosis**—exocytosis of procollagen into extracellular space.

**5 Proteolytic processing**—cleavage of disulfide-rich terminal regions of procollagen → insoluble tropocollagen.

**6 Cross-linking**—reinforcement of many staggered tropocollagen molecules by covalent lysine-hydroxylysine cross-linkage (by copper-containing lysyl oxidase) to make collagen fibrils. Cross-linking of collagen increases with age. Problems with cross-linking → Menkes disease.

### Osteogenesis imperfecta



Upper extremity

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 (altered triple helix formation). Manifestations include:

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

May be confused with child abuse.

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

**B**ones = multiple fractures

**I**(eye) = blue sclerae

**T**eeth = dental imperfections

**E**ar = hearing loss



### Ehlers-Danlos syndrome

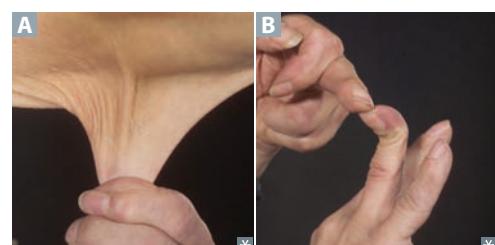
Faulty collagen synthesis causing hyperextensible skin A, hypermobile joints B, and tendency to bleed (easy bruising).

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

Hypermobility type (joint instability): most common type.

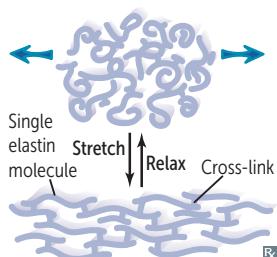
Classical type (joint and skin symptoms): caused by a mutation in type V collagen (eg, COL5A1, COL5A2).

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



### Menkes disease

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

**Elastin**

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

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

Tropoelastin with fibrillin scaffolding.

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

Broken down by elastase, which is normally inhibited by  $\alpha_1$ -antitrypsin.

$\alpha_1$ -Antitrypsin deficiency results in unopposed elastase activity, which can cause COPD.

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



**Marfan syndrome**—autosomal dominant (with variable expression) connective tissue disorder affecting skeleton, heart, and eyes. *FBN1* gene mutation on chromosome 15 (fifteen) results in defective fibrillin-1, a glycoprotein that forms a sheath around elastin and sequesters TGF- $\beta$ . Findings: tall with long extremities; chest wall deformity (pectus carinatum [pigeon chest] or pectus excavatum A); hypermobile joints; long, tapering fingers and toes (arachnodactyly); cystic medial necrosis of aorta; aortic root aneurysm rupture or dissection (most common cause of death); mitral valve prolapse; ↑ risk of spontaneous pneumothorax.

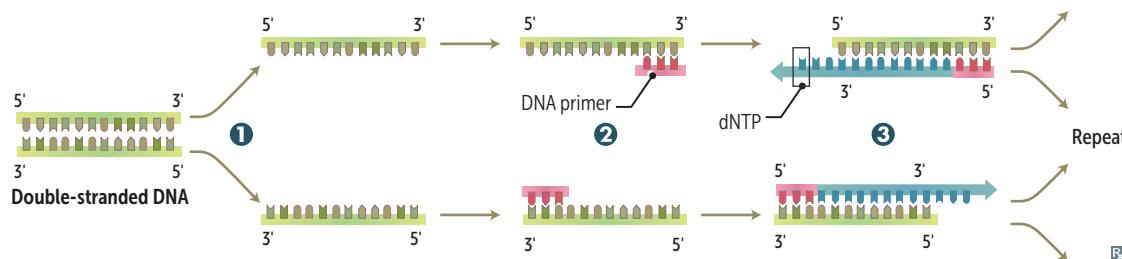
**Homocystinuria**—presentation similar to Marfan syndrome with pectus deformity, tall stature, ↑ arm:height ratio, ↓ upper:lower body segment ratio, arachnodactyly, joint hyperlaxity, skin hyperelasticity, scoliosis.

	Marfan syndrome	Homocystinuria
INHERITANCE	Autosomal dominant	Autosomal recessive
INTELLECT	Normal	Decreased
VASCULAR COMPLICATIONS	Aortic root dilatation	Thrombosis
LENS DISLOCATION	Upward (Marfan fans out)	Downward

## BIOCHEMISTRY—LABORATORY TECHNIQUES

### Polymerase chain reaction

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



**① Denaturation**—DNA is heated to ~95°C to separate the strands.

**② Annealing**—Sample is cooled to ~55°C. DNA primers, a heat-stable DNA polymerase (*Taq*), and deoxynucleotide triphosphates (dNTPs) are added. DNA primers anneal to the specific sequence to be amplified on each strand.

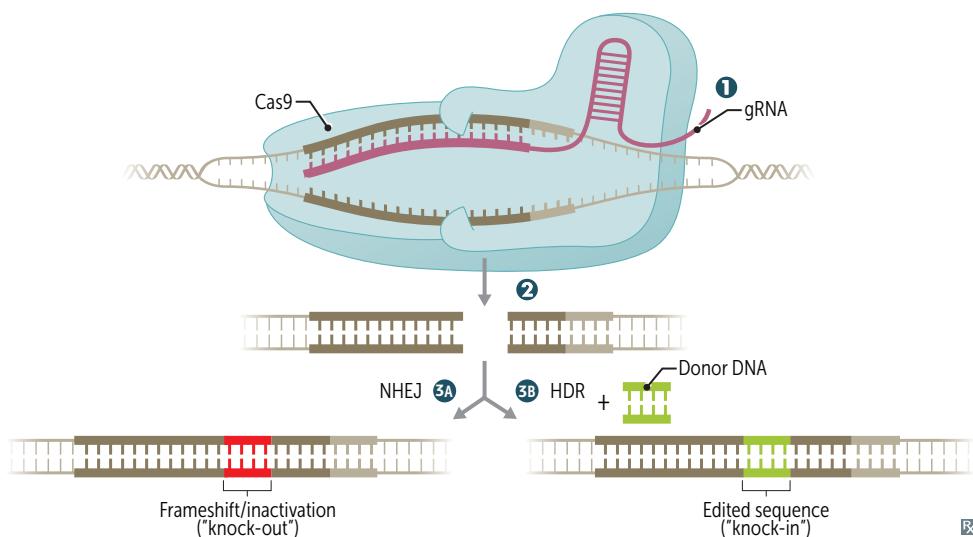
**③ Elongation**—Temperature is increased to ~72°C. DNA polymerase attaches dNTPs to the strand to replicate the sequence after each primer.

Heating and cooling cycles continue until the amount of DNA is sufficient.

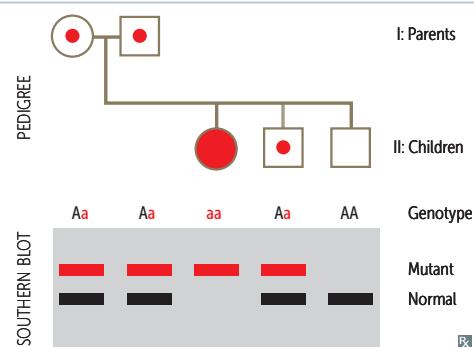
**CRISPR/Cas9**

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

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

**Blotting procedures****Southern blot**

1. 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.

**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**.

**Southwestern blot**

Identifies **DNA-binding proteins** (eg, c-Jun, c-Fos [leucine zipper motif]) using labeled double-stranded DNA probes.

**SNoW DRoP:**

**Southern** = **DNA**

**Northern** = **RNA**

**Western** = **Protein**

Northern blots detect splicing errors.

**Flow cytometry**

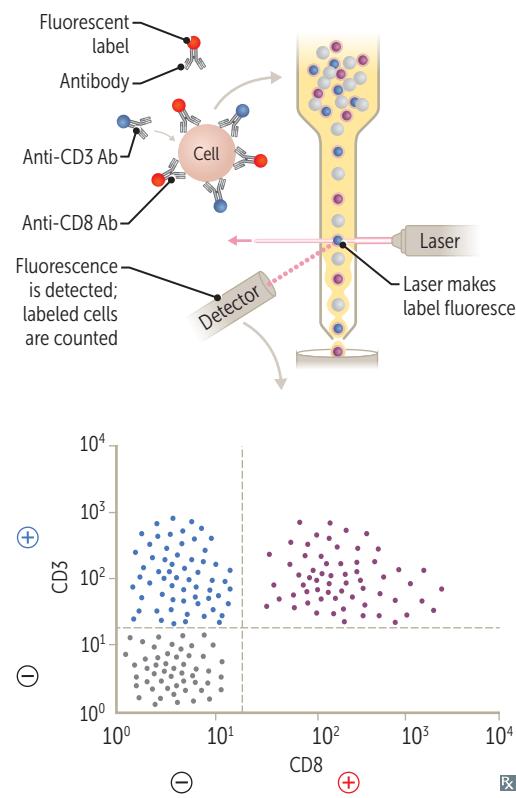
Laboratory technique to assess size, granularity, and protein expression (immunophenotype) of individual cells in a sample.

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

Commonly used in workup of hematologic abnormalities (eg, leukemia, paroxysmal nocturnal hemoglobinuria, fetal RBCs in pregnant person's blood) and immunodeficiencies (eg, CD4 $^{+}$  cell count in HIV).

**Microarrays**

Array consisting of thousands of DNA oligonucleotides arranged in a grid on a glass or silicon chip. The DNA or RNA samples being compared are attached to different fluorophores and hybridized to the array. The ratio of fluorescence signal at a particular oligonucleotide reflects the relative amount of the hybridizing nucleic acid in the two samples.

Used to compare the relative expression of genes in two samples. Can detect single nucleotide polymorphisms (SNPs) and copy number variants (CNVs) for genotyping, clinical genetic testing, forensic analysis, and cancer mutation and genetic linkage analysis.

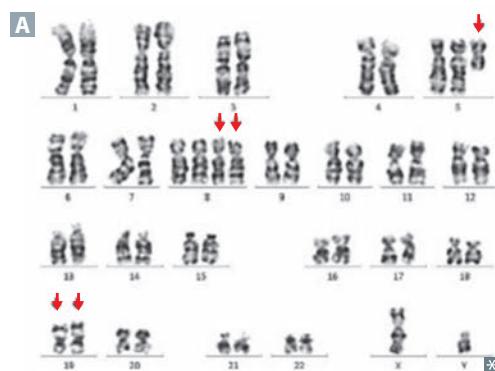
**Enzyme-linked immunosorbent assay**

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

**Karyotyping**

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

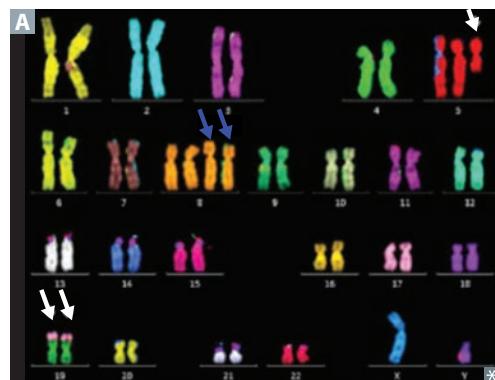
Can be performed on a sample of blood, bone marrow, amniotic fluid, or placental tissue. Used to diagnose chromosomal imbalances (eg, autosomal trisomies, sex chromosome disorders).

**Fluorescence in situ hybridization**

Fluorescent DNA or RNA probe binds to specific gene site of interest on chromosomes (arrows in A point to abnormalities in a cancer cell; each fluorescent color represents a chromosome-specific probe).

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

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

**Molecular cloning**

Production of a recombinant DNA molecule in a bacterial host.

Steps:

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

**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.

Random insertion—constitutive expression.

Targeted insertion—conditional expression.

**RNA interference****MicroRNA**

Process whereby small non-coding RNA molecules target mRNAs to inhibit gene expression.

Naturally produced by cell as hairpin structures. Loose nucleotide pairing allows broad targeting of related mRNAs. When miRNA binds to mRNA, it blocks translation of mRNA and sometimes facilitates its degradation.

Abnormal expression of miRNAs contributes to certain malignancies (eg, by silencing an mRNA from a tumor suppressor gene).

**Small interfering RNA**

Usually derived from exogenous dsRNA source (eg, virus). Once inside a cell, siRNA requires complete nucleotide pairing, leading to highly specific mRNA targeting. Results in mRNA cleavage prior to translation.

Can be produced by in vitro transcription for gene “knockdown” experiments.

## ► BIOCHEMISTRY—GENETICS

**Genetic terms**

TERM	DEFINITION	EXAMPLE
<b>Codominance</b>	Both alleles contribute to the phenotype of the heterozygote.	Blood groups A, B, AB; $\alpha_1$ -antitrypsin deficiency; HLA groups.
<b>Variable expressivity</b>	Patients with the same genotype have varying phenotypes.	2 patients with neurofibromatosis type 1 (NF1) may have varying disease severity.
<b>Incomplete penetrance</b>	Not all individuals with a mutant genotype show the mutant phenotype. % penetrance $\times$ probability of inheriting genotype = risk of expressing phenotype.	BRCA1 gene mutations do not always result in breast or ovarian cancer.
<b>Pleiotropy</b>	One gene contributes to multiple phenotypic effects.	Untreated phenylketonuria (PKU) manifests with light skin, intellectual disability, and musty body odor.
<b>Anticipation</b>	Increased severity or earlier onset of disease in succeeding generations.	Trinucleotide repeat diseases (eg, Huntington disease).
<b>Loss of heterozygosity</b>	If a patient inherits or develops a mutation in a tumor suppressor gene, the wild type 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.

**Genetic terms (continued)**

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

**Hardy-Weinberg population genetics**

A (p)		a (q)
A (p)	AA (p <sup>2</sup> )	Aa (pq)
a (q)	Aa (pq)	aa (q <sup>2</sup> )

If **p** and **q** represent the frequencies of alleles A and a, respectively, in a population, then

$$\mathbf{p} + \mathbf{q} = 1:$$

- **p**<sup>2</sup> = frequency of homozygosity for allele A
- **q**<sup>2</sup> = frequency of homozygosity for allele a
- 2**pq** = frequency of heterozygosity (carrier frequency, if an autosomal recessive disease)

Therefore, the sum of the frequencies of these genotypes is **p**<sup>2</sup> + 2**pq** + **q**<sup>2</sup> = 1.

The frequency of an X-linked recessive disease in males = q and in females = **q**<sup>2</sup>.

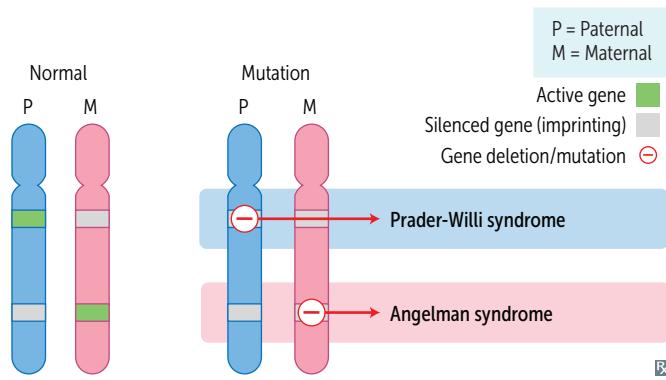
Hardy-Weinberg law assumptions include:

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

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

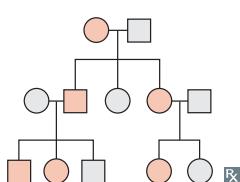
**Disorders of imprinting** **Imprinting**—one gene copy is silenced by methylation, and only the other copy is expressed  
 → parent-of-origin effects.

	Prader-Willi syndrome	Angelman syndrome
WHICH GENE IS SILENT?	Maternally derived genes are silenced Disease occurs when the <b>paternal</b> allele is deleted or mutated	Paternally derived <b>UBE3A</b> is silenced Disease occurs when the <b>maternal</b> allele is deleted or mutated
SIGNS AND SYMPTOMS	Hyperphagia, obesity, intellectual disability, hypogonadism, hypotonia	Seizures, Ataxia, severe Intellectual disability, inappropriate Laughter Set <b>SAIL</b> for Angel Island
CHROMOSOMES INVOLVED	Chromosome 15 of paternal origin	<b>UBE3A</b> on maternal copy of chromosome 15
NOTES	25% of cases are due to maternal uniparental disomy	5% of cases are due to paternal uniparental disomy
	<b>POP:</b> Prader-Willi, Obesity/overeating, Paternal allele deleted	<b>MAMAS:</b> Maternal allele deleted, Angelman syndrome, Mood, Ataxia, Seizures



### Modes of inheritance

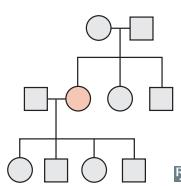
#### Autosomal dominant



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

A	a
a	Aa
a	Aa

#### Autosomal recessive

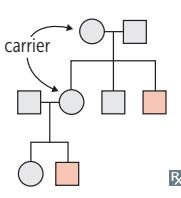


With 2 carrier (heterozygous) parents, on average:  
 $\frac{1}{4}$  of children will be affected (homozygous),  
 $\frac{1}{2}$  of children will be carriers, and  $\frac{1}{4}$  of  
children will be neither affected nor carriers.

A	a
A	AA
a	Aa

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.

#### X-linked recessive

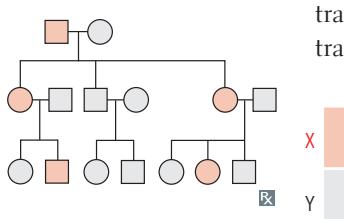


Sons of heterozygous mothers have a 50% chance of being affected. No male-to-male transmission. Skips generations.

X	X	X	X
X	XX	XX	X
Y	XY	XY	Y

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

#### X-linked dominant

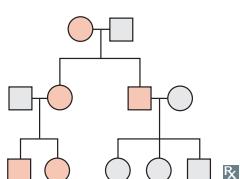


Transmitted through both parents. Mothers transmit to 50% of daughters and sons; fathers transmit to all daughters but no sons.

X	X	X	X
X	XX	XX	X
Y	XY	XY	Y

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

#### Mitochondrial inheritance



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

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

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

#### Mitochondrial myopathies

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

**Leber hereditary optic neuropathy** (LHON)—cell death in optic nerve neurons → subacute bilateral vision loss in teens/young adults, 90% males. Usually permanent. Also leads to neurologic dysfunction, cardiac conduction defects.

### Autosomal dominant diseases

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

### Autosomal recessive diseases

Oculocutaneous albinism, phenylketonuria, cystic fibrosis, sickle cell disease, Wilson disease, sphingolipidoses (except Fabry disease), hemochromatosis, glycogen storage diseases, thalassemia, mucopolysaccharidoses (except Hunter syndrome), Friedreich ataxia, Kartagener syndrome, ARPKD. Oh please! Can students who score high grades tell me features of the kidney disorder **Autosomal Recessive Polycystic Kidney Disease?**

### Cystic fibrosis

#### GENETICS

Autosomal recessive; defect in CFTR gene on chromosome 7; commonly a deletion of Phe508. Most common lethal genetic disease in patients with European ancestry.

#### PATHOPHYSIOLOGY

CFTR encodes an ATP-gated Cl<sup>-</sup> channel that secretes Cl<sup>-</sup> in lungs and GI tract, and reabsorbs Cl<sup>-</sup> in sweat glands. Phe508 deletion → misfolded protein → improper protein trafficking and protein retention in RER → protein absent from cell membrane → ↓ Cl<sup>-</sup> (and H<sub>2</sub>O) secretion; ↑ intracellular Cl<sup>-</sup> results in compensatory ↑ Na<sup>+</sup> reabsorption via epithelial Na<sup>+</sup> channels (ENaC) → ↑ H<sub>2</sub>O reabsorption → abnormally thick mucus secreted into lungs and GI tract. ↑ Na<sup>+</sup> reabsorption also causes more negative transepithelial potential difference.

#### DIAGNOSIS

↑ Cl<sup>-</sup> concentration in pilocarpine-induced sweat test is diagnostic. Can present with contraction alkalosis and hypokalemia (ECF effects analogous to a patient taking a loop diuretic) because of ECF H<sub>2</sub>O/Na<sup>+</sup> losses via sweating and concomitant renal K<sup>+</sup>/H<sup>+</sup> wasting. ↑ immunoreactive trypsinogen (newborn screening) due to clogging of pancreatic duct.

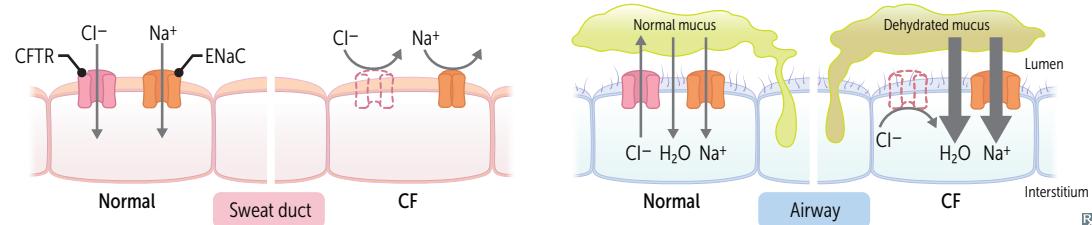
#### COMPLICATIONS

Recurrent pulmonary infections (eg, *S aureus* [infancy and early childhood], *P aeruginosa* [adulthood], allergic bronchopulmonary aspergillosis [ABPA]), chronic bronchitis and bronchiectasis → reticulonodular pattern on CXR, opacification of sinuses. Nasal polyps, nail clubbing. Pancreatic insufficiency, malabsorption with steatorrhea, and fat-soluble vitamin deficiencies (A, D, E, K) progressing to endocrine dysfunction (CF-related diabetes), biliary cirrhosis, liver disease. Meconium ileus in newborns.

Infertility in males (absence of vas deferens, spermatogenesis may be unaffected) and subfertility in females (amenorrhea, abnormally thick cervical mucus).

#### TREATMENT

Multifactorial: chest physiotherapy, albuterol, aerosolized dornase alfa (DNase), and inhaled hypertonic saline facilitate mucus clearance. Azithromycin used as anti-inflammatory agent. Ibuprofen slows disease progression. Pancreatic enzyme replacement therapy (pancrelipase) for pancreatic insufficiency. Combination of lumacaftor or tezacaftor (each corrects misfolded proteins and improves their transport to cell surface) with ivacaftor. (opens Cl<sup>-</sup> channels → improved chloride transport).



### X-linked recessive diseases

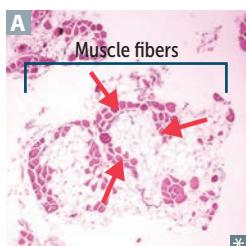
Bruton agammaglobulinemia, Duchenne and Becker muscular dystrophies, Fabry disease, G6PD deficiency, hemophilia A and B, Hunter syndrome, Lesch-Nyhan syndrome, ocular albinism, ornithine transcarbamylase deficiency, Wiskott-Aldrich syndrome.

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

**X-inactivation (lyonization)**—during development, one of the X chromosomes in each XX cell is randomly deactivated and condensed into a Barr body (methylated heterochromatin). If skewed inactivation occurs, XX individuals may express X-linked recessive diseases (eg, G6PD); penetrance and severity of X-linked dominant diseases in XX individuals may also be impacted.

### Muscular dystrophies

#### Duchenne



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

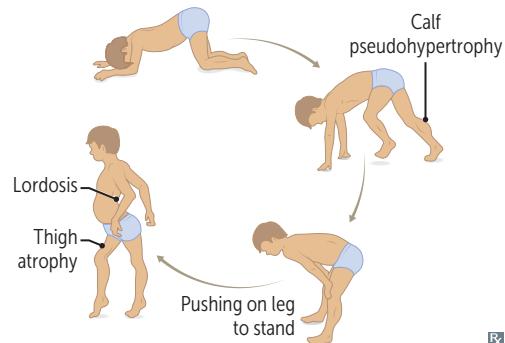
Onset before 5 years of age. Dilated cardiomyopathy is common cause of death.

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

**Duchenne** = deleted **dystrophin**.

Dystrophin gene (*DMD*) is the largest protein-coding human gene → ↑ 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 → myonecrosis.

↑ CK and aldolase; genetic testing confirms diagnosis.



#### Becker

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

#### Myotonic dystrophy

Autosomal dominant. Onset 20–30 years. **CTG** trinucleotide repeat expansion in the *DMPK* gene → abnormal expression of myotonin protein kinase → myotonia (eg, difficulty releasing hand from handshake), muscle wasting, cataracts, testicular atrophy, frontal balding, arrhythmia.

Deletions can cause both Duchenne and Becker muscular dystrophies.  $\frac{1}{2}$  of cases have large deletions spanning one or more exons.

Cataracts, Toupee (early balding in males), Gonadal atrophy.

**Rett syndrome**

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

**Fragile X syndrome**

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

Trinucleotide repeat expansion  $[(\text{CGG})_n]$  occurs during oogenesis.  
Premutation (50–200 repeats) → tremor, ataxia, 1° ovarian insufficiency.  
Full mutation ( $>200$  repeats) → postpubertal macroorchidism (enlarged testes), long face with large jaw, large everted ears, autism, mitral valve prolapse, hypermobile joints.  
Self-mutilation is common and can be confused with Lesch-Nyhan syndrome.

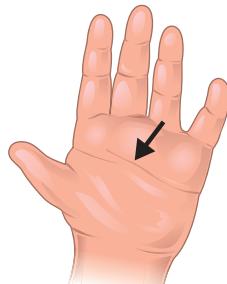
**Trinucleotide repeat expansion diseases**

May show genetic anticipation (disease severity ↑ and age of onset ↓ in successive generations).

DISEASE	TRINUCLEOTIDE REPEAT	MODE OF INHERITANCE	MNEMONIC
Huntington disease	(CAG) <sub>n</sub>	AD	Caudate has ↓ ACh and GABA
Myotonic dystrophy	(CTG) <sub>n</sub>	AD	Cataracts, Toupee (early balding in males), Gonadal atrophy in males, reduced fertility in females
Fragile X syndrome	(CGG) <sub>n</sub>	XD	Chin (protruding), Giant Gonads
Friedreich ataxia	(GAA) <sub>n</sub>	AR	Ataxic GAAit

**Autosomal trisomies**

Autosomal monosomies are incompatible with life due to a high chance of expression of recessive traits for that chromosome.

**Down syndrome  
(trisomy 21)**

Single palmar crease

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

95% of cases due to meiotic nondisjunction, most commonly during meiosis I (↑ with advanced maternal age: from 1:1500 in females < 20 to 1:25 in females > 45). 4% of cases due to unbalanced Robertsonian translocation, most typically between chromosomes 14 and 21. Only 1% of cases are due to postfertilization mitotic error.

Incidence 1:700.

Drinking age (21).

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

First-trimester ultrasound commonly shows ↑ nuchal translucency and hypoplastic nasal bone. Markers for Down syndrome are **hi** up: ↑ hCG, ↑ inhibin.

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

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

**Edwards syndrome  
(trisomy 18)**

Clenched fists with overlapping fingers

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

Incidence 1:8000.

Election age (18).

2nd most common autosomal trisomy resulting in live birth (most common is Down syndrome). In Edwards syndrome, every prenatal screening marker decreases.

**Patau syndrome  
(trisomy 13)**

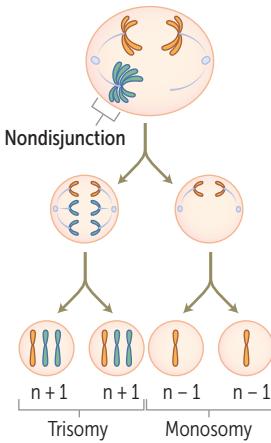
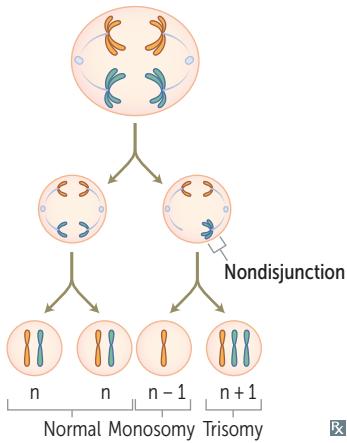
Cutis aplasia

Findings: severe intellectual disability, rocker-bottom feet, microphthalmia, microcephaly, cleft lip/palate, holoprosencephaly, polydactyly, cutis aplasia, congenital heart (pump) disease, polycystic kidney disease, omphalocele. Death usually occurs by age 1.

Incidence 1:15,000.

Puberty at age 13.

Defect in fusion of prechordal mesoderm → midline defects.

**Nondisjunction in meiosis I****Meiosis I****Nondisjunction in meiosis II****Gametes****1st trimester screening**

Trisomy	$\beta$ -hCG	PAPP-A
21	↑	↓
18	↓	↓
13	↓	↓

**2nd trimester screening**

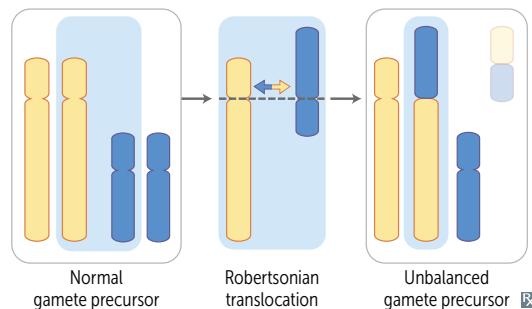
Trisomy	$\beta$ -hCG	Inhibin A	Estriol	AFP
21	↑	↑	↓	↓
18	↓	— or ↓	↓	↓
13	—	—	—	—

### 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, tuberous sclerosis ( <i>TSC1</i> )
11	Wilms tumor, $\beta$ -globin gene defects (eg, sickle cell disease, $\beta$ -thalassemia), MEN1
13	Patau syndrome, Wilson disease, retinoblastoma ( <i>RBL</i> ), <i>BRCA2</i>
15	Prader-Willi syndrome, Angelman syndrome, Marfan syndrome
16	ADPKD ( <i>PKD1</i> ), $\alpha$ -globin gene defects (eg, $\alpha$ -thalassemia), tuberous sclerosis ( <i>TSC2</i> )
17	Neurofibromatosis type 1, <i>BRCA1</i> , <i>TP53</i> (Li-Fraumeni syndrome)
18	Edwards syndrome
21	Down syndrome
22	Neurofibromatosis type 2, DiGeorge syndrome (22q11)
X	Fragile X syndrome, X-linked agammaglobulinemia, Klinefelter syndrome (XXY)

### Robertsonian translocation

Chromosomal translocation that commonly involves chromosome pairs **21**, **22**, **13**, **14**, and **15**. One of the most common types of translocation. Occurs when the long arms of 2 acrocentric chromosomes (chromosomes with centromeres near their ends) fuse at the centromere and the 2 short arms are lost. Balanced translocations (no gain or loss of significant genetic material) normally do not cause abnormal phenotype. Unbalanced translocations (missing or extra genes) can result in miscarriage, stillbirth, and chromosomal imbalance (eg, Down syndrome, Patau syndrome).



### Cri-du-chat syndrome

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

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

### Williams syndrome

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

## ► BIOCHEMISTRY—NUTRITION

**Essential fatty acids**

Polyunsaturated fatty acids that cannot be synthesized in the body and must be provided in the diet (eg, nuts and seeds, plant oils, seafood). Linoleic acid (omega-6) is metabolized to arachidonic acid, which serves as the precursor to leukotrienes and prostaglandins. Linolenic acid (omega-3) and its metabolites have cardioprotective and antihyperlipidemic effects.

**Vitamins: fat soluble**

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

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

**Vitamins: water soluble**

B<sub>1</sub> (thiamine: TPP)  
B<sub>2</sub> (riboflavin: FAD, FMN)  
B<sub>3</sub> (niacin: NAD<sup>+</sup>)  
B<sub>5</sub> (pantothenic acid: CoA)  
B<sub>6</sub> (pyridoxine: PLP)  
B<sub>7</sub> (biotin)  
B<sub>9</sub> (folate)  
B<sub>12</sub> (cobalamin)  
C (ascorbic acid)

Wash out easily from body except B<sub>12</sub> and B<sub>9</sub>.  
B<sub>12</sub> stored in liver for ~ 3–4 years. B<sub>9</sub> 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 coenzymes (eg, FAD, NAD<sup>+</sup>).

**Vitamin A**

## FUNCTION

Includes retinal, retinol, retinoic acid.

Antioxidant; constituent of visual pigments (**retinal**); essential for normal differentiation of epithelial cells into specialized tissue (pancreatic cells, mucus-secreting cells); prevents squamous metaplasia.

**Retinol** is vitamin **A**, so think **retin-A** (used topically for wrinkles and **Acne**).

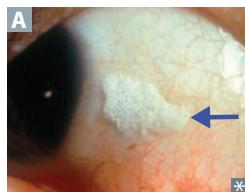
Found in liver and leafy vegetables.

Supplementation in vitamin A-deficient measles patients may improve outcomes.

Use oral isotretinoin to treat severe cystic acne.

Use *all-trans* retinoic acid to treat acute promyelocytic leukemia.

## DEFICIENCY



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

## EXCESS

Acute toxicity—nausea, vomiting, ↑ ICP (eg, vertigo, blurred vision).  
Chronic toxicity—alopecia, dry skin (eg, scaliness), hepatic toxicity and enlargement, arthralgias, and idiopathic intracranial hypertension.

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

**Isotretinoin is teratogenic.**

**Vitamin B<sub>1</sub>**

Also called thiamine.

## FUNCTION

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

- Branched-chain ketoacid dehydrogenase
- $\alpha$ -Ketoglutarate dehydrogenase (TCA cycle)
- Pyruvate dehydrogenase (links glycolysis to TCA cycle)
- Transketolase (HMP shunt)

## DEFICIENCY

Impaired glucose breakdown → ATP depletion worsened by glucose infusion; highly aerobic tissues (eg, brain, heart) are affected first. In patients with chronic alcohol overuse or malnutrition, give thiamine before dextrose to ↓ risk of precipitating Wernicke encephalopathy.

Diagnosis made by ↑ in RBC transketolase activity following vitamin B<sub>1</sub> administration.

DISORDER	CHARACTERISTICS
<b>Wernicke encephalopathy</b>	Acute, reversible, life-threatening neurologic condition. Symptoms: <b>Confusion</b> , <b>Ophthalmoplegia</b> / <b>Nystagmus</b> , <b>Ataxia</b> ( <b>CorONA</b> beer).
<b>Korsakoff syndrome</b>	Amnestic disorder due to chronic alcohol overuse; presents with confabulation, personality changes, memory loss (permanent).
<b>Wernicke-Korsakoff syndrome</b>	Damage to medial dorsal nucleus of thalamus, mammillary bodies. Presentation is combination of Wernicke encephalopathy and Korsakoff syndrome.
<b>Dry beriberi</b>	Polyneuropathy, symmetric muscle wasting.
<b>Wet beriberi</b>	High-output cardiac failure (dilated cardiomyopathy), edema.

Spell beriberi as **Ber1Ber1** to remember vitamin **B<sub>1</sub>**.

**Vitamin B<sub>2</sub>**

Also called riboflavin.

FUNCTION	Component of flavins FAD and FMN, used as cofactors in redox reactions, eg, the succinate dehydrogenase reaction in the TCA cycle.	FAD and FMN are derived from riboFlavin ( $B_2 \approx 2$ ATP).
DEFICIENCY	Cheilosis (inflammation of lips, scaling and fissures at the corners of the mouth), “magenta” tongue, corneal vascularization.	The 2 C’s of $B_2$ .

**Vitamin B<sub>3</sub>**

Also called niacin, nicotinic acid.

FUNCTION	Constituent of NAD <sup>+</sup> , NADP <sup>+</sup> (used in redox reactions and as cofactor by dehydrogenases). Derived from tryptophan. Synthesis requires vitamins B <sub>2</sub> and B <sub>6</sub> . Used to treat dyslipidemia ( $\downarrow$ VLDL, $\uparrow$ HDL).	NAD derived from Niacin ( $B_3 \approx 3$ ATP).
DEFICIENCY	Glossitis. Severe deficiency of B <sub>3</sub> leads to pellagra, which can also be caused by Hartnup disease, malignant carcinoid syndrome ( $\uparrow$ tryptophan metabolism $\rightarrow$ $\uparrow$ serotonin synthesis), and isoniazid ( $\downarrow$ vitamin B <sub>6</sub> ). Symptoms of B <sub>3</sub> deficiency (pellagra) (the 3 D’s): diarrhea, dementia (also hallucinations), dermatitis (C3/C4 dermatome circumferential “broad collar” rash [Casal necklace], hyperpigmentation of sun-exposed limbs <b>A</b> ).	<b>Hartnup disease</b> —autosomal recessive. Deficiency of neutral amino acid (eg, tryptophan) transporters in proximal renal tubular cells and on enterocytes $\rightarrow$ neutral aminoaciduria and $\downarrow$ absorption from the gut $\rightarrow$ $\downarrow$ tryptophan for conversion to niacin $\rightarrow$ pellagra-like symptoms. Treat with high-protein diet and nicotinic acid. Deficiency of vitamin B <sub>3</sub> $\rightarrow$ pellagra. Less B <sub>3</sub> .
EXCESS	Facial flushing (induced by prostaglandin, not histamine; can avoid by taking aspirin with niacin), hyperglycemia, hyperuricemia.	Excess of vitamin B <sub>3</sub> $\rightarrow$ podagra (gout). Overdose (excess) B <sub>3</sub> .

**Vitamin B<sub>5</sub>**Also called pantothenic acid. B<sub>5</sub> is “pento”thenic acid.

FUNCTION	Component of coenzyme A (CoA, a cofactor for acyl transfers) and fatty acid synthase.
DEFICIENCY	Dermatitis, enteritis, alopecia, adrenal insufficiency may lead to burning sensation of feet (“burning feet syndrome”; distal paresthesias, dysesthesia).

**Vitamin B<sub>6</sub>**

Also called pyridoxine.

FUNCTION	Converted to pyridoxal phosphate (PLP), a cofactor used in transamination (eg, ALT and AST), decarboxylation reactions, glycogen phosphorylase. Synthesis of glutathione, cystathione, heme, niacin, histamine, and neurotransmitters including serotonin, epinephrine, norepinephrine (NE), dopamine, and GABA.
DEFICIENCY	Convulsions, hyperirritability, peripheral neuropathy (deficiency inducible by isoniazid and oral contraceptives), sideroblastic anemia (due to impaired hemoglobin synthesis and iron excess).

**Vitamin B<sub>7</sub>**

Also called biotin.

## FUNCTION

Cofactor for carboxylation enzymes (which add a 1-carbon group):

- Pyruvate carboxylase (gluconeogenesis): pyruvate (3C) → oxaloacetate (4C)
- Acetyl-CoA carboxylase (fatty acid synthesis): acetyl-CoA (2C) → malonyl-CoA (3C)
- Propionyl-CoA carboxylase (fatty acid oxidation): propionyl-CoA (3C) → methylmalonyl-CoA (4C)

## DEFICIENCY

Relatively rare. Dermatitis, enteritis, alopecia. Caused by long-term antibiotic use or excessive ingestion of raw egg whites.

**"Avidin** in egg whites **avidly** binds biotin."

**Vitamin B<sub>9</sub>**

Also called folate.

## FUNCTION

Converted to tetrahydrofolic acid (THF), a coenzyme for 1-carbon transfer/methylation reactions.

Important for the synthesis of nitrogenous bases in DNA and RNA.

Found in leafy green vegetables. Also produced by gut flora. Absorbed in jejunum. **Folate from foliage**.

Small reserve pool stored primarily in the liver.

## DEFICIENCY

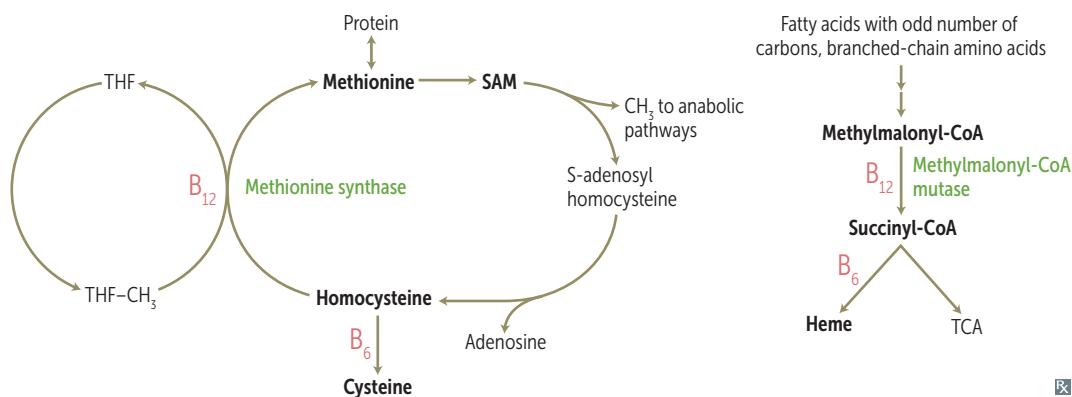
Macrocytic, megaloblastic anemia; hypersegmented polymorphonuclear cells (PMNs); glossitis; no neurologic symptoms (as opposed to vitamin B<sub>12</sub> deficiency).  
Labs: ↑ homocysteine, normal methylmalonic acid levels. Seen in chronic alcohol overuse and in pregnancy.

Deficiency can be caused by several drugs (eg, phenytoin, sulfonamides, methotrexate).

Supplemental folic acid at least 1 month prior to conception and during early pregnancy to ↓ risk of neural tube defects. Give vitamin B<sub>9</sub> for the **9** months of pregnancy.

**Vitamin B<sub>12</sub>**

<b>FUNCTION</b>	Also called cobalamin.	Found in animal products.
<b>DEFICIENCY</b>	Cofactor for methionine synthase (transfers CH <sub>3</sub> groups as methylcobalamin) and methylmalonyl-CoA mutase. Important for DNA synthesis.	Synthesized only by microorganisms. Very large reserve pool (several years) stored primarily in the liver. Deficiency caused by malabsorption (eg, sprue, enteritis, <i>Diphyllobothrium latum</i> , achlorhydria, bacterial overgrowth, alcohol overuse), lack of intrinsic factor (eg, pernicious anemia, gastric bypass surgery), absence of terminal ileum (surgical resection, eg, for Crohn disease), certain drugs (eg, metformin), or insufficient intake (eg, veganism). B <sub>9</sub> supplementation can mask the hematologic symptoms of B <sub>12</sub> deficiency, but not the neurologic symptoms.
	Macrocytic, megaloblastic anemia; hypersegmented PMNs; paresthesias and subacute combined degeneration (degeneration of dorsal columns, lateral corticospinal tracts, and spinocerebellar tracts) due to abnormal myelin. Associated with ↑ serum homocysteine and methylmalonic acid levels, along with 2° folate deficiency. Prolonged deficiency → irreversible nerve damage.	

**Vitamin C**

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

**Vitamin D**

D<sub>3</sub> (cholecalciferol) from exposure of skin (stratum basale) to sun, ingestion of fish, milk, plants.  
 D<sub>2</sub> (ergocalciferol) from ingestion of plants, fungi, yeasts.  
 Both converted to 25-OH D<sub>3</sub> (storage form) in liver and to the active form 1,25-(OH)<sub>2</sub> D<sub>3</sub> (calcitriol) in kidney.

**FUNCTION**

- ↑ intestinal absorption of Ca<sup>2+</sup> and PO<sub>4</sub><sup>3-</sup>.
- ↑ bone mineralization at low levels.
- ↑ bone resorption at higher levels.

**REGULATION**

- ↑ PTH, ↓ Ca<sup>2+</sup>, ↓ PO<sub>4</sub><sup>3-</sup> → ↑ 1,25-(OH)<sub>2</sub>D<sub>3</sub> production.
- 1,25-(OH)<sub>2</sub>D<sub>3</sub> feedback inhibits its own production.
- ↑ PTH → ↑ Ca<sup>2+</sup> reabsorption and ↓ PO<sub>4</sub><sup>3-</sup> reabsorption in the kidney.

**DEFICIENCY**

Rickets in children (deformity, such as genu varum “bowlegs” **A**), osteomalacia in adults (bone pain and muscle weakness), hypocalcemic tetany.  
 Caused by malabsorption, ↓ sun exposure, poor diet, chronic kidney disease (CKD), advanced liver disease.  
 Give oral vitamin D to breastfed infants.  
 Darker skin and prematurity predispose to deficiency.

**EXCESS**

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

**Vitamin E**

Includes tocopherol, tocotrienol.

**FUNCTION**

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

**DEFICIENCY**

Hemolytic anemia, acanthocytosis, muscle weakness, demyelination of posterior columns (↓ proprioception and vibration sensation) and spinocerebellar tract (ataxia).

Neurologic presentation may appear similar to vitamin B<sub>12</sub> deficiency, but without megaloblastic anemia, hypersegmented neutrophils, or ↑ serum methylmalonic acid levels.

**EXCESS**

Risk of enterocolitis in infants.

High-dose supplementation may alter metabolism of vitamin K → enhanced anticoagulant effects of warfarin.

**Vitamin K**

<b>FUNCTION</b>	Includes phytomenadione, phylloquinone, phytonadione, menaquinone.	
<b>DEFICIENCY</b>	Activated by epoxide reductase to the reduced form, which is a cofactor for the $\gamma$ -carboxylation of glutamic acid residues on various proteins required for blood clotting. Synthesized by intestinal flora.	<b>K</b> is for <b>Koagulation</b> . Necessary for the maturation of clotting factors II, VII, IX, X, and proteins C and S. Warfarin inhibits vitamin K-dependent synthesis of these factors and proteins.
	Neonatal hemorrhage with $\uparrow$ PT and $\uparrow$ 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; “breast-fed infants <b>D</b> on’t <b>K</b> now about vitamins <b>D</b> and <b>K</b> ”. Neonates are given vitamin K injection at birth to prevent hemorrhagic disease of the newborn.

**Zinc**

<b>FUNCTION</b>	Mineral essential for the activity of 100+ enzymes. Important in the formation of zinc fingers (transcription factor motif).	
<b>DEFICIENCY</b>	Delayed wound healing, suppressed immunity, male hypogonadism, $\downarrow$ adult hair (axillary, facial, pubic), dysgeusia, anosmia. Associated with acrodermatitis enteropathica ( <b>A</b> , defect in intestinal zinc absorption). May predispose to alcoholic cirrhosis.	
		

**Protein-energy malnutrition****Kwashiorkor**

Protein malnutrition resulting in skin lesions, edema due to  $\downarrow$  plasma oncotic pressure (due to low serum albumin), liver malfunction (fatty change due to  $\downarrow$  apolipoprotein synthesis and deposition). Clinical picture is small child with swollen abdomen **A**.

Kwashiorkor results from protein-deficient **MEALS**:

**M**alnutrition

**E**dema

**A**nemia

**L**iver (fatty)

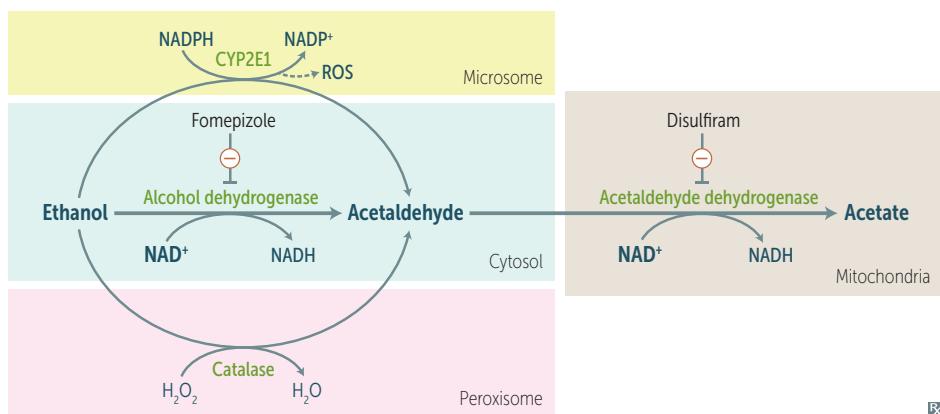
**S**kin lesions (eg, hyperkeratosis, dyspigmentation)

**Marasmus**

Malnutrition not causing edema. Diet is deficient in calories but no nutrients are entirely absent.

Marasmus results in **muscle wasting** **B**.

### Ethanol metabolism



↑ NADH/NAD<sup>+</sup> ratio inhibits TCA cycle → ↑ acetyl-CoA used in ketogenesis (→ ketoacidosis), lipogenesis (→ hepatosteatosis).

Females are more susceptible than males to effects of alcohol due to ↓ activity of gastric alcohol dehydrogenase, ↓ body size, ↓ percentage of water in body weight.

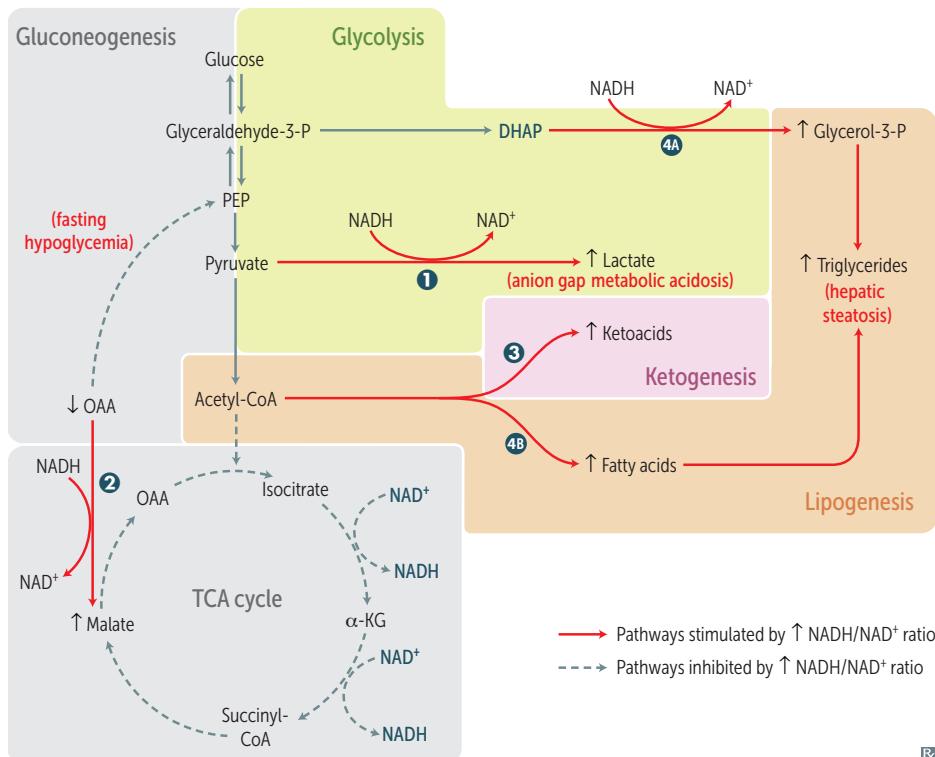
NAD<sup>+</sup> is the limiting reagent. Alcohol dehydrogenase operates via zero-order kinetics.

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

- ① Lactic acidosis—↑ pyruvate conversion to lactate
- ② Fasting hypoglycemia—↓ gluconeogenesis due to ↑ conversion of OAA to malate
- ③ Ketoacidosis—diversion of acetyl-CoA into ketogenesis rather than TCA cycle
- ④ Hepatosteatosis—↑ conversion of DHAP to glycerol-3-P  
④A; acetyl-CoA diverges into fatty acid synthesis ④B, which combines with glycerol-3-P to synthesize triglycerides

**Fomepizole**—blocks alcohol dehydrogenase; preferred antidote for overdoses of **methanol** or **ethylene glycol**. Alcohol dehydrogenase has higher affinity for ethanol than for methanol or ethylene glycol → ethanol can be used as competitive inhibitor of alcohol dehydrogenase to treat methanol or ethylene glycol poisoning.

**Disulfiram**—blocks acetaldehyde dehydrogenase → ↑ acetaldehyde → ↑ hangover symptoms → **discouraging drinking**.



## ► BIOCHEMISTRY—METABOLISM

**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.

<b>Kinase</b>	Catalyzes transfer of a phosphate group from a high-energy molecule (usually ATP) to a substrate (eg, phosphofructokinase).
<b>Phosphorylase</b>	Adds inorganic phosphate onto substrate without using ATP (eg, glycogen phosphorylase).
<b>Phosphatase</b>	Removes phosphate group from substrate (eg, fructose-1,6-bisphosphatase 1).
<b>Dehydrogenase</b>	Catalyzes oxidation-reduction reactions (eg, pyruvate dehydrogenase).
<b>Hydroxylase</b>	Adds hydroxyl group ( $-OH$ ) onto substrate (eg, tyrosine hydroxylase).
<b>Carboxylase</b>	Transfers $CO_2$ groups with the help of biotin (eg, pyruvate carboxylase).
<b>Mutase</b>	Relocates a functional group within a molecule (eg, vitamin $B_{12}$ -dependent methylmalonyl-CoA mutase).
<b>Synthase/synthetase</b>	Joins two molecules together using a source of energy (eg, ATP, acetyl-CoA, nucleotide sugar).

**Rate-determining enzymes of metabolic processes**

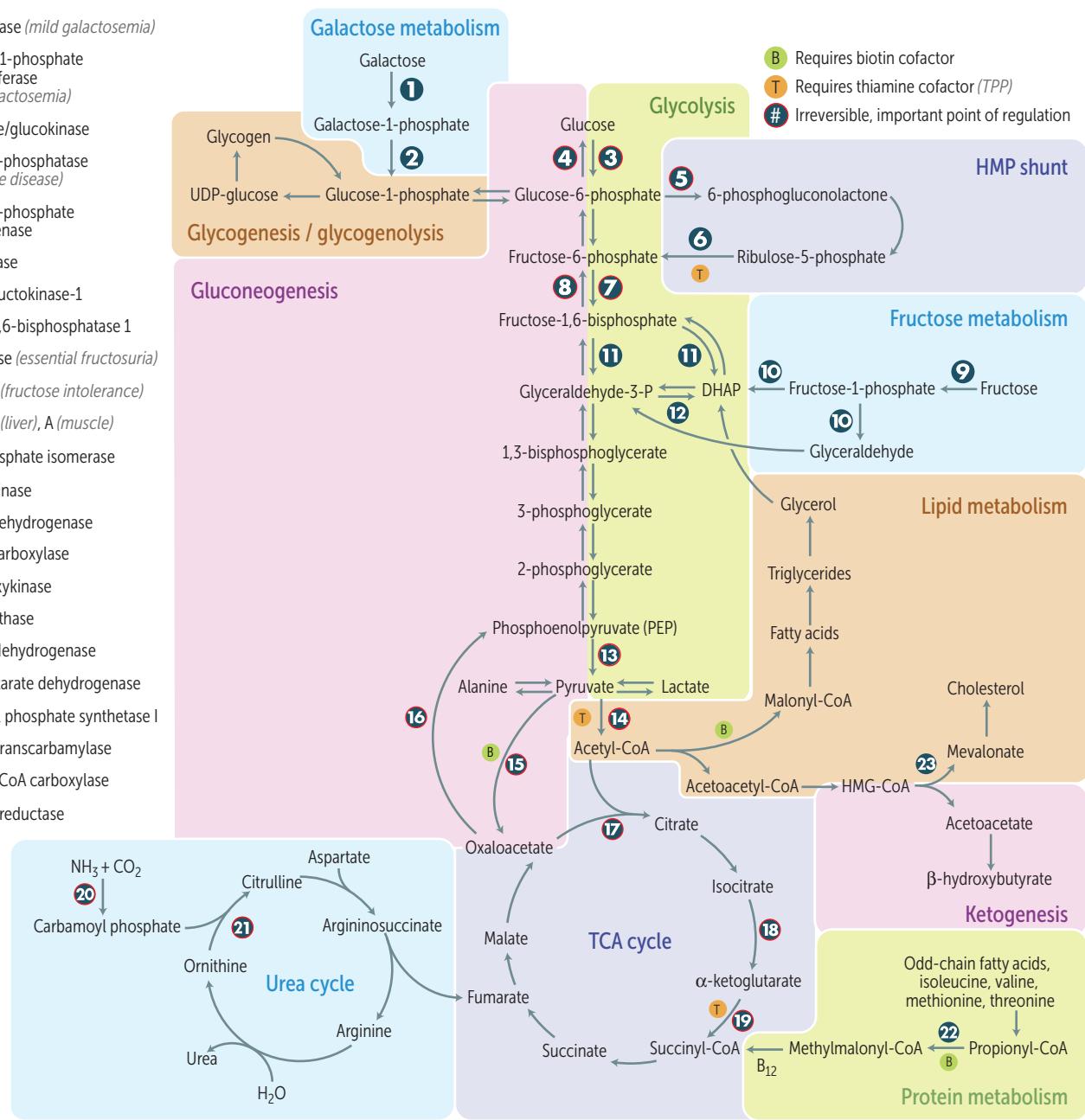
PROCESS	ENZYME	REGULATORS
<b>Glycolysis</b>	Phosphofructokinase-1 (PFK-1)	AMP $\oplus$ , fructose-2,6-bisphosphate $\oplus$ ATP $\ominus$ , citrate $\ominus$
<b>Gluconeogenesis</b>	Fructose-1,6-bisphosphatase 1	AMP $\ominus$ , fructose-2,6-bisphosphate $\ominus$
<b>TCA cycle</b>	Isocitrate dehydrogenase	ADP $\oplus$ ATP $\ominus$ , NADH $\ominus$
<b>Glycogenesis</b>	Glycogen synthase	Glucose-6-phosphate $\oplus$ , insulin $\oplus$ , cortisol $\oplus$ Epinephrine $\ominus$ , glucagon $\ominus$
<b>Glycogenolysis</b>	Glycogen phosphorylase	Epinephrine $\oplus$ , glucagon $\oplus$ , AMP $\oplus$ Glucose-6-phosphate $\ominus$ , insulin $\ominus$ , ATP $\ominus$
<b>HMP shunt</b>	Glucose-6-phosphate dehydrogenase (G6PD)	NADP $^+$ $\oplus$ NADPH $\ominus$
<b>De novo pyrimidine synthesis</b>	Carbamoyl phosphate synthetase II	ATP $\oplus$ , PRPP $\oplus$ UTP $\ominus$
<b>De novo purine synthesis</b>	Glutamine-phosphoribosylpyrophosphate (PRPP) amidotransferase	AMP $\ominus$ , inosine monophosphate (IMP) $\ominus$ , GMP $\ominus$
<b>Urea cycle</b>	Carbamoyl phosphate synthetase I	N-acetylglutamate $\oplus$
<b>Fatty acid synthesis</b>	Acetyl-CoA carboxylase (ACC)	Insulin $\oplus$ , citrate $\oplus$ Glucagon $\ominus$ , palmitoyl-CoA $\ominus$
<b>Fatty acid oxidation</b>	Carnitine acyltransferase I	Malonyl-CoA $\ominus$
<b>Ketogenesis</b>	HMG-CoA synthase	
<b>Cholesterol synthesis</b>	HMG-CoA reductase	Insulin $\oplus$ , thyroxine $\oplus$ , estrogen $\oplus$ Glucagon $\ominus$ , cholesterol $\ominus$

**Metabolism sites**

<b>Mitochondria</b>	Fatty acid oxidation ( $\beta$ -oxidation), acetyl-CoA production, TCA cycle, oxidative phosphorylation, ketogenesis.
<b>Cytoplasm</b>	Glycolysis, HMP shunt, and synthesis of cholesterol (SER), proteins (ribosomes, RER), fatty acids, and nucleotides.
<b>Both</b>	Heme synthesis, urea cycle, gluconeogenesis. <b>Hugs take two</b> (both).

**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 Phosphofructokinase-1
- ⑧ Fructose-1,6-bisphosphatase 1
- ⑨ Fructokinase (*essential fructosuria*)
- ⑩ Aldolase B (*fructose intolerance*)
- ⑪ Aldolase B (*liver*), A (*muscle*)
- ⑫ Triose phosphate isomerase
- ⑬ Pyruvate kinase
- ⑭ Pyruvate dehydrogenase
- ⑮ Pyruvate carboxylase
- ⑯ PEP carboxykinase
- ⑰ Citrate synthase
- ⑱ Isocitrate dehydrogenase
- ⑲  $\alpha$ -ketoglutarate dehydrogenase
- ⑳ Carbamoyl phosphate synthetase I
- ㉑ Ornithine transcarbamylase
- ㉒ Propionyl-CoA carboxylase
- ㉓ HMG-CoA reductase



**ATP production**

Aerobic metabolism of one glucose molecule produces 32 net ATP via malate-aspartate shuttle (heart and liver), 30 net ATP via glycerol-3-phosphate shuttle (muscle).  
Anaerobic glycolysis produces only 2 net ATP per glucose molecule.  
ATP hydrolysis can be coupled to energetically unfavorable reactions.

Arsenic causes glycolysis to produce zero net ATP.

**Activated carriers**

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

**Universal electron acceptors**

Nicotinamides (NAD<sup>+</sup>, NADP<sup>+</sup> from vitamin B<sub>3</sub>) and flavin nucleotides (FAD from vitamin B<sub>2</sub>). NAD<sup>+</sup> is generally used in **catabolic** processes to carry reducing equivalents away as NADH. NADPH is used in **anabolic** processes (eg, steroid and fatty acid synthesis) as a supply of reducing equivalents.

NADPH is a product of the HMP shunt. NADPH is used in:

- Anabolic processes
- Respiratory burst
- Cytochrome P-450 system
- Glutathione reductase

**Hexokinase vs glucokinase**

Phosphorylation of glucose to yield glucose-6-phosphate is catalyzed by glucokinase in the liver and hexokinase in other tissues. Hexokinase sequesters glucose in tissues, where it is used even when glucose concentrations are low. At high glucose concentrations, glucokinase helps to store glucose in liver. Glucokinase deficiency is a cause of maturity onset diabetes of the young (MODY) and gestational diabetes.

	Hexokinase	Glucokinase
Location	Most tissues, except liver and pancreatic β cells	Liver, β cells of pancreas
K <sub>m</sub>	Lower (↑ affinity)	Higher (↓ affinity)
V <sub>max</sub>	Lower (↓ capacity)	Higher (↑ capacity)
Induced by insulin	No	Yes
Feedback inhibition by	Glucose-6-phosphate	Fructose-6-phosphate

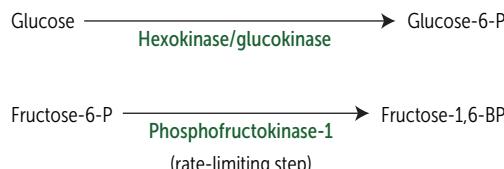
### Glycolysis regulation, key enzymes

Net glycolysis (cytoplasm):



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

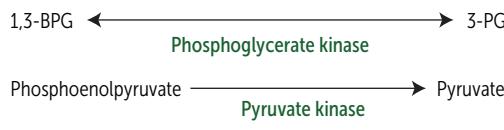
REQUIRE ATP



Glucose-6-P  $\ominus$  hexokinase.  
Fructose-6-P  $\ominus$  glucokinase.

AMP  $\oplus$ , fructose-2,6-bisphosphate  $\oplus$ .  
ATP  $\ominus$ , citrate  $\ominus$ .

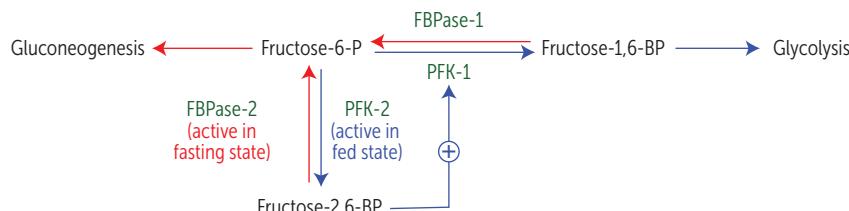
PRODUCE ATP



Fructose-1,6-bisphosphate  $\oplus$ .  
ATP  $\ominus$ , alanine  $\ominus$ , glucagon  $\ominus$ .

### Regulation by fructose-2,6-bisphosphate

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



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

**FaBian the Peasant (FBP)** has to work hard when starving.

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

**Prince FredericK (PFK)** works only when fed.

### Pyruvate dehydrogenase complex

Mitochondrial enzyme complex linking glycolysis and TCA cycle. Differentially regulated in fed (active)/fasting (inactive) states. Reaction: pyruvate + NAD<sup>+</sup> + CoA  $\rightarrow$  acetyl-CoA + CO<sub>2</sub> + NADH.

Contains 3 enzymes requiring 5 cofactors:

1. Thiamine pyrophosphate (B<sub>1</sub>)
2. Lipoic acid
3. CoA (B<sub>5</sub>, pantothenic acid)
4. FAD (B<sub>2</sub>, riboflavin)
5. NAD<sup>+</sup> (B<sub>3</sub>, niacin)

Activated by:  $\uparrow$  NAD<sup>+</sup>/NADH ratio,  $\uparrow$  ADP,  $\uparrow$  Ca<sup>2+</sup>.

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

**The lovely coenzymes for nerds.**

Arsenic inhibits lipoic acid. Arsenic poisoning clinical findings: imagine a vampire (pigmentary skin changes, skin cancer), vomiting and having diarrhea, running away from a cutie (QT prolongation) with garlic breath.

### Pyruvate dehydrogenase complex deficiency

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

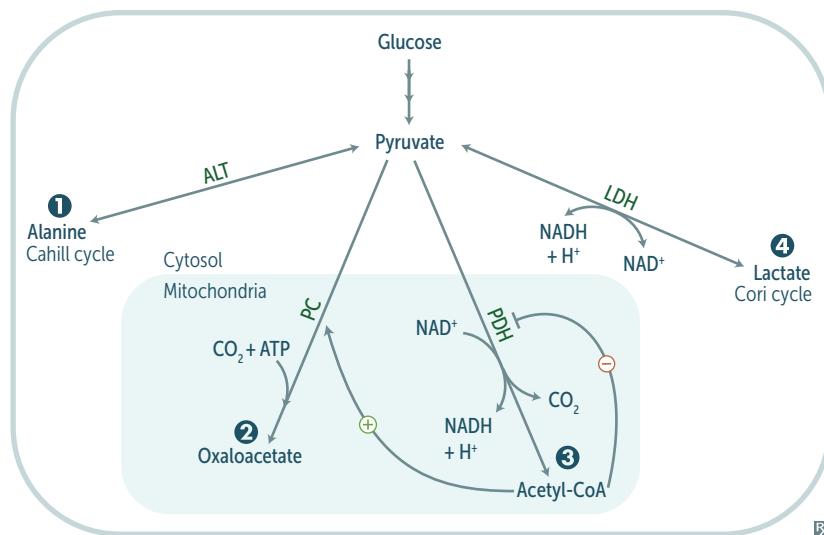
#### FINDINGS

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

#### TREATMENT

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

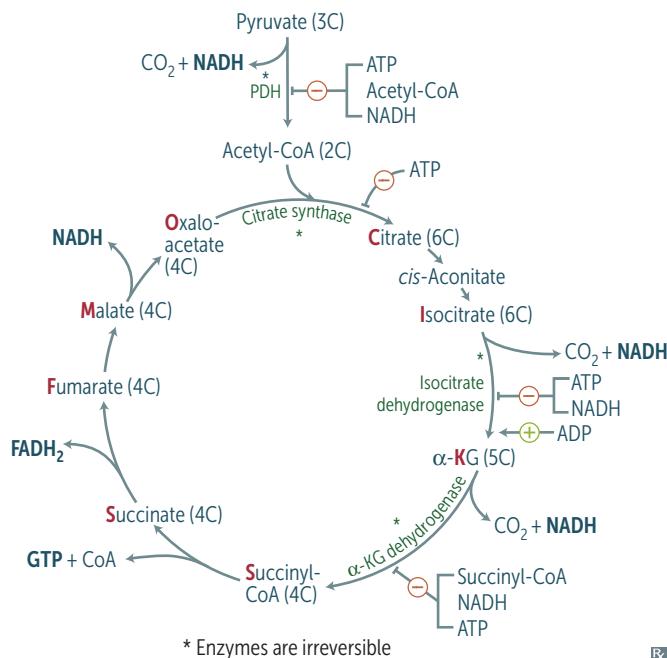
### Pyruvate metabolism



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

- ① Alanine aminotransferase ( $B_6$ ): alanine carries amino groups to the liver from muscle
- ② Pyruvate carboxylase ( $B_7$ ): oxaloacetate can replenish TCA cycle or be used in gluconeogenesis
- ③ Pyruvate dehydrogenase ( $B_1, B_2, B_3, B_5$ , lipoic acid): transition from glycolysis to the TCA cycle
- ④ Lactic acid dehydrogenase ( $B_3$ ): end of anaerobic glycolysis (major pathway in RBCs, WBCs, kidney medulla, lens, testes, and cornea)

### TCA cycle



Also called Krebs cycle. Pyruvate → acetyl-CoA produces 1 NADH, 1 CO<sub>2</sub>.

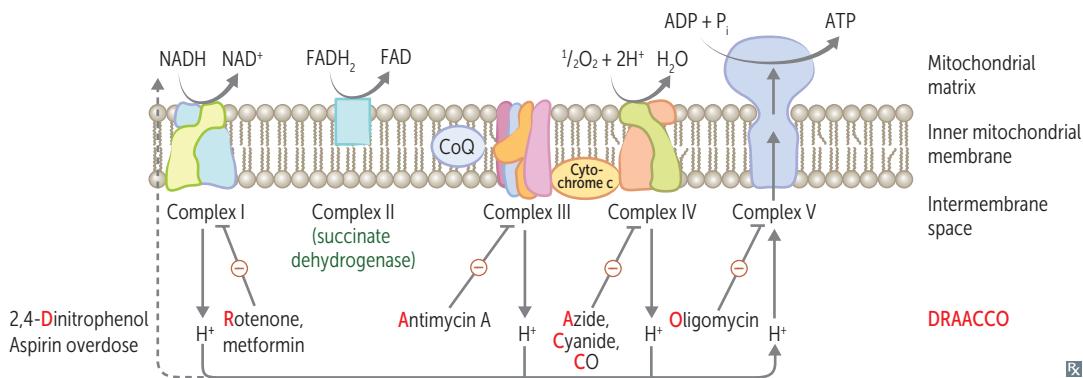
The TCA cycle produces 3 NADH, 1 FADH<sub>2</sub>, 2 CO<sub>2</sub>, 1 GTP per acetyl-CoA = 10 ATP/acetyl-CoA (2× everything per glucose). TCA cycle reactions occur in the mitochondria.

$\alpha$ -ketoglutarate dehydrogenase complex requires the same cofactors as the pyruvate dehydrogenase complex (vitamins  $B_1, B_2, B_3, B_5$ , lipoic acid).

Citrate is Krebs' starting substrate for making oxaloacetate.

## Electron transport chain and oxidative phosphorylation

NADH electrons from glycolysis enter mitochondria via the malate-aspartate or glycerol-3-phosphate shuttle. FADH<sub>2</sub> electrons are transferred to complex II (at a lower energy level than NADH). The passage of electrons results in the formation of a proton gradient that, coupled to oxidative phosphorylation, drives the production of ATP.



### ATP PRODUCED VIA ATP SYNTHASE

$$1 \text{ NADH} \rightarrow 2.5 \text{ ATP}; 1 \text{ FADH}_2 \rightarrow 1.5 \text{ ATP}$$

### OXIDATIVE PHOSPHORYLATION POISONS

<b>Electron transport inhibitors</b>	Directly inhibit electron transport, causing a ↓ proton gradient and block of ATP synthesis.	Rotenone: complex <b>one</b> inhibitor. “An- <b>3</b> -mycin” (antimycin) A: complex <b>3</b> inhibitor. <b>Cyanide</b> , carbon monoxide, azide (the <b>-ides</b> , 4 letters) inhibit complex <b>IV</b> .
<b>ATP synthase inhibitors</b>	Directly inhibit mitochondrial ATP synthase, causing an ↑ proton gradient. No ATP is produced because electron transport stops.	Oligomycin.
<b>Uncoupling agents</b>	↑ permeability of membrane, causing a ↓ proton gradient and ↑ O <sub>2</sub> consumption. ATP synthesis stops, but electron transport continues. Produces heat.	2,4-Dinitrophenol (used illicitly for weight loss), aspirin (fevers often occur after overdose), thermogenin in brown fat (has more mitochondria than white fat).

## Gluconeogenesis, irreversible enzymes

<b>Pyruvate carboxylase</b>	In mitochondria. Pyruvate → oxaloacetate.	Pathway produces <b>fresh</b> glucose.
<b>Phosphoenolpyruvate carboxykinase</b>	In cytosol. Oxaloacetate → phosphoenolpyruvate (PEP).	Requires biotin, ATP. Activated by acetyl-CoA.
<b>Fructose-1,6-bisphosphatase 1</b>	In cytosol. Fructose-1,6-bisphosphate → fructose-6-phosphate.	Requires GTP.
<b>Glucose-6-phosphatase</b>	In ER. Glucose-6-phosphate → glucose.	Citrate ⊕, AMP ⊖, fructose 2,6-bisphosphate ⊖.
	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).	
	<b>Odd-chain fatty acids</b> yield 1 propionyl-CoA during metabolism, which can enter the TCA cycle (as succinyl-CoA), undergo gluconeogenesis, and serve as a <b>glucose</b> source (It's <b>odd</b> for <b>fatty acids</b> to make <b>glucose</b> ). Even-chain fatty acids cannot produce new glucose, since they yield only acetyl-CoA equivalents.	

## Pentose phosphate pathway

Also called HMP shunt. Provides a source of NADPH from abundantly available glucose-6-P (NADPH is required for reductive reactions, eg, glutathione reduction inside RBCs, fatty acid and cholesterol biosynthesis). Additionally, this pathway yields ribose for nucleotide synthesis. Two distinct phases (oxidative and nonoxidative), both of which occur in the cytoplasm. No ATP is used or produced.

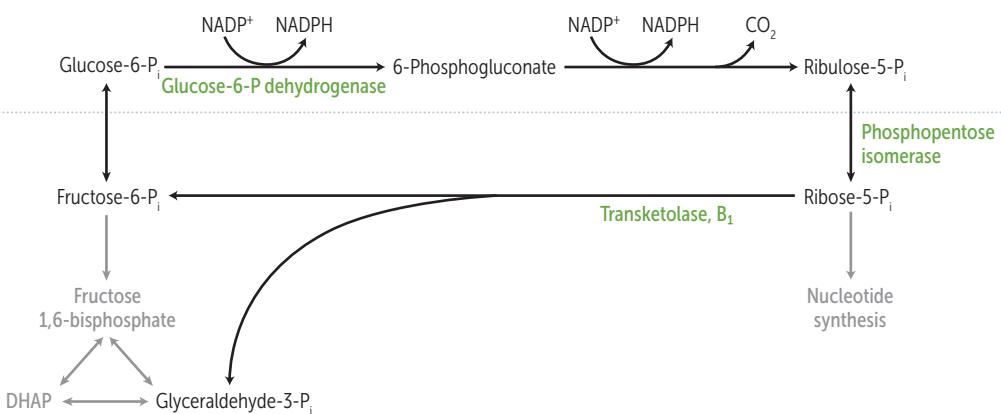
Sites: lactating mammary glands, liver, adrenal cortex (sites of fatty acid or steroid synthesis), RBCs.

### REACTIONS

#### Oxidative (irreversible)



#### Nonoxidative (reversible)



Rx

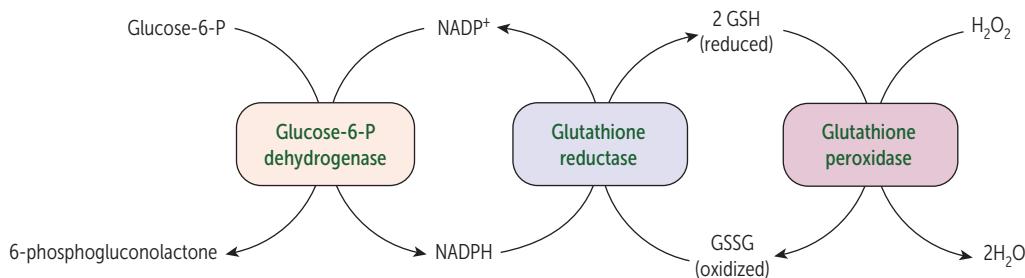
## Glucose-6-phosphate dehydrogenase deficiency

NADPH is necessary to keep glutathione reduced, which in turn detoxifies free radicals and peroxides. ↓ NADPH in RBCs leads to hemolytic anemia due to poor RBC defense against oxidizing agents (eg, fava beans, sulfonamides, nitrofurantoin, primaquine/ chloroquine, antituberculosis drugs). Infection (most common cause) can also precipitate hemolysis; inflammatory response produces free radicals that diffuse into RBCs, causing oxidative damage.

X-linked recessive disorder; most common human enzyme deficiency; more prevalent among descendants of populations in malaria-endemic regions (eg, sub-Saharan Africa, Southeast Asia).

**Heinz bodies**—denatured globin chains precipitate within RBCs due to oxidative stress.

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



### Disorders of fructose metabolism

#### Essential fructosuria

Involves a defect in **fructokinase**. Autosomal recessive. A benign, asymptomatic condition (fructokinase deficiency is **kinder**), since fructose is not trapped in cells. Hexokinase becomes 1° pathway for converting fructose to fructose-6-phosphate.

Symptoms: fructose appears in blood and urine.

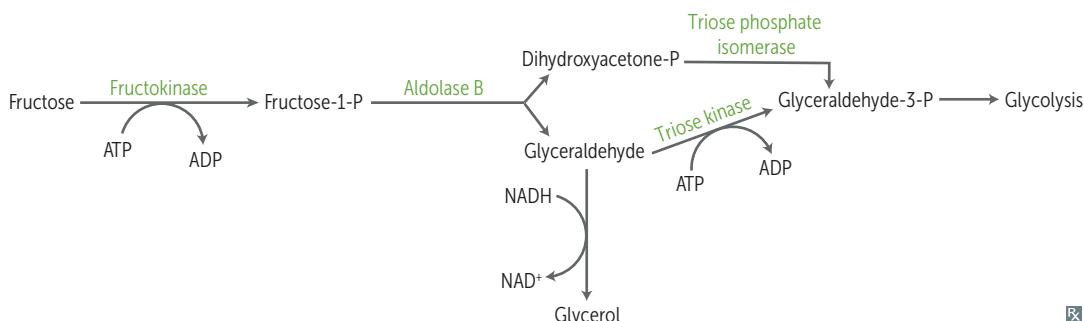
Disorders of fructose metabolism cause milder symptoms than analogous disorders of galactose metabolism.

#### Hereditary fructose intolerance

Hereditary deficiency of **aldolase B**. Autosomal recessive. Fructose-1-phosphate accumulates, causing a ↓ in available phosphate, which results in inhibition of glycogenolysis and gluconeogenesis. Symptoms present following consumption of fruit, juice, or honey. Urine dipstick will be ⊖ (tests for glucose only); reducing sugar can be detected in the urine (nonspecific test for inborn errors of carbohydrate metabolism).

Symptoms: hypoglycemia, jaundice, cirrhosis, vomiting.

Treatment: ↓ intake of fructose, sucrose (glucose + fructose), and sorbitol (metabolized to fructose).



Rx

### Disorders of galactose metabolism

#### Galactokinase deficiency

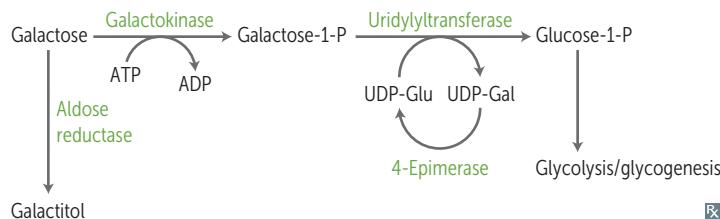
Hereditary deficiency of **galactokinase**. Galactitol accumulates if galactose is present in diet. Relatively mild condition. Autosomal recessive.

Symptoms: galactose appears in blood (galactosemia) and urine (galactosuria); infantile cataracts. May present as failure to track objects or to develop a social smile. Galactokinase deficiency is **kinder** (benign condition).

#### Classic galactosemia

Absence of **galactose-1-phosphate uridylyltransferase**. Autosomal recessive. Damage is caused by accumulation of toxic substances (including galactitol, which accumulates in the lens of the eye). Symptoms develop when infant begins feeding (lactose present in breast milk and routine formula) and include failure to thrive, jaundice, hepatomegaly, infantile cataracts, intellectual disability. Can predispose to *E. coli* sepsis in neonates.

Treatment: exclude galactose and lactose (galactose + glucose) from diet.



Fructose is to **Aldolase B** as Galactose is to **UridylTransferase (FAB GUT)**.  
The more serious defects lead to  $\text{PO}_4^{3-}$  depletion.

Rx

**Sorbitol**

An alternative method of trapping glucose in the cell is to convert it to its alcohol counterpart, sorbitol, via aldose reductase. Some tissues then convert sorbitol to fructose using sorbitol dehydrogenase; tissues with an insufficient amount/activity of this enzyme are at risk of intracellular sorbitol accumulation, causing osmotic damage (eg, cataracts, retinopathy, and peripheral neuropathy seen with chronic hyperglycemia in diabetes). High blood levels of galactose also result in conversion to the osmotically active galactitol via aldose reductase.

Liver, ovaries, and seminal vesicles have both enzymes (they **lose** sorbitol).



Lens has primarily Aldose reductase. Retina, Kidneys, and Schwann cells have only aldose reductase (**LARKS**).

**Lactase deficiency**

Insufficient lactase enzyme → dietary lactose intolerance. Lactase functions on the intestinal brush border to digest lactose (in milk and milk products) into glucose and galactose.  
 Primary: age-dependent decline after childhood (absence of lactase-persistent allele), common in people of Asian, African, or Native American descent.  
 Secondary: loss of intestinal brush border due to gastroenteritis (eg, rotavirus), autoimmune disease.  
 Congenital lactase deficiency: rare, due to defective gene.  
 Stool demonstrates ↓ pH and breath shows ↑ hydrogen content with lactose hydrogen breath test (H<sup>+</sup> is produced when colonic bacteria ferment undigested lactose). Intestinal biopsy reveals normal mucosa in patients with hereditary lactose intolerance.

**FINDINGS**

Bloating, cramps, flatulence, osmotic diarrhea.

**TREATMENT**

Avoid dairy products or add lactase pills to diet; lactose-free milk.

**Amino acids**

Only L-amino acids are found in proteins.

**Essential**

**PVT TIM HALL:** Phenylalanine, Valine, Tryptophan, Threonine, Isoleucine, Methionine, Histidine, Leucine, Lysine.

Glucogenic: Methionine, histidine, valine. We **met his valentine**, who is so **sweet** (glucogenic).

Glucogenic/ketogenic: Isoleucine, phenylalanine, threonine, tryptophan.

Ketogenic: leucine, lysine. The only purely ketogenic amino acids.

**Acidic**

Aspartic acid, glutamic acid.

Negatively charged at body pH.

**Basic**

Arginine, histidine, lysine.

Arginine is most basic. Histidine has no charge at body pH.

Arginine and histidine are required during periods of growth.

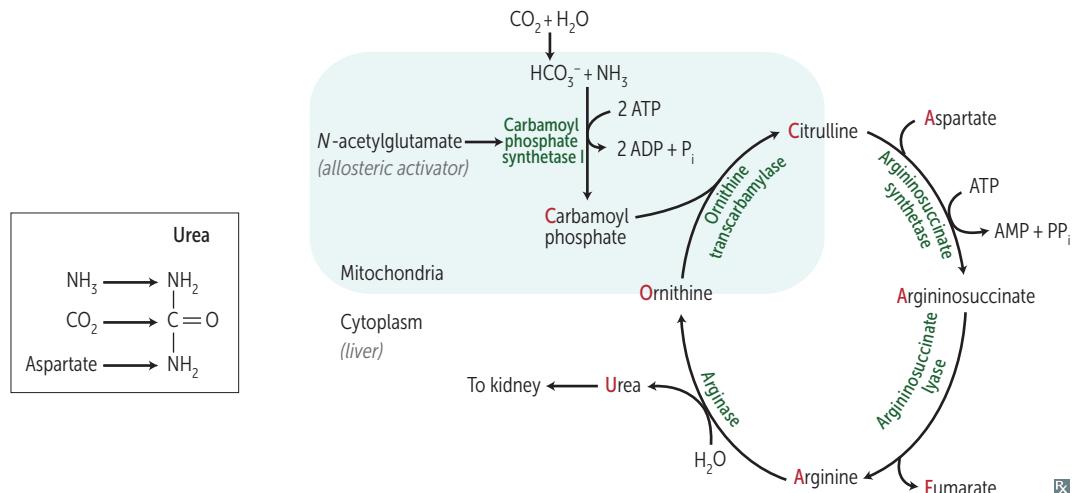
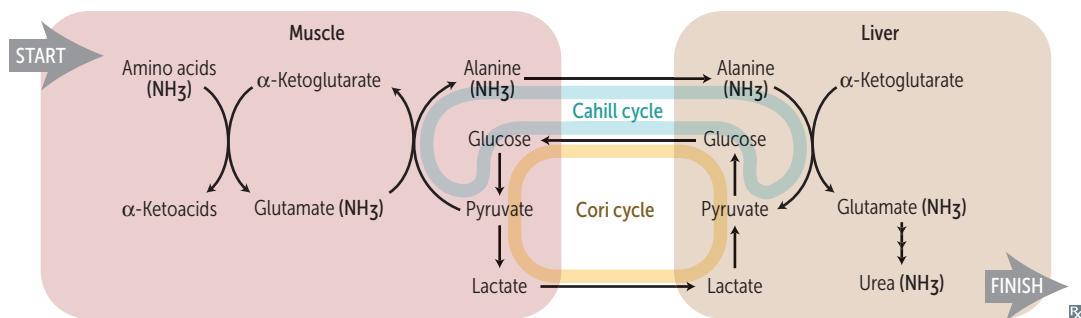
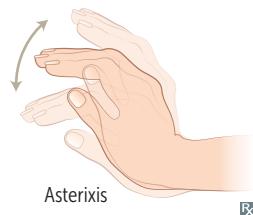
Arginine and lysine are ↑ in histones which bind negatively charged DNA.

**His lys** (lies) are basic.

**Urea cycle**

Amino acid catabolism generates common metabolites (eg, pyruvate, acetyl-CoA), which serve as metabolic fuels. Excess nitrogen is converted to urea and excreted by the kidneys.

Ordinarily, Careless Crappers Are Also Frivolous About Urination.

**Transport of ammonia by alanine****Hyperammonemia**

Can be acquired (eg, liver disease) or hereditary (eg, urea cycle enzyme deficiencies).

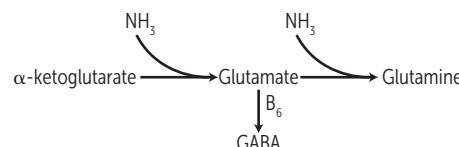
Presents with flapping tremor (asterixis), slurring of speech, somnolence, vomiting, cerebral edema, blurring of vision.

$\uparrow \text{NH}_3$  changes relative amounts of  $\alpha$ -ketoglutarate, glutamate, GABA, and glutamine to favor  $\uparrow$  glutamine. CNS toxicity may involve  $\downarrow$  GABA,  $\downarrow$   $\alpha$ -ketoglutarate, TCA cycle inhibition, and cerebral edema due to glutamine-induced osmotic shifts.

Treatment: limit protein in diet.

May be given to  $\downarrow$  ammonia levels:

- Lactulose to acidify GI tract and trap  $\text{NH}_4^+$  for excretion.
- Antibiotics (eg, rifaximin, neomycin) to  $\downarrow$  ammoniagenic bacteria.
- Benzoate, phenylacetate, or phenylbutyrate react with glycine or glutamine, forming products that are excreted renally.

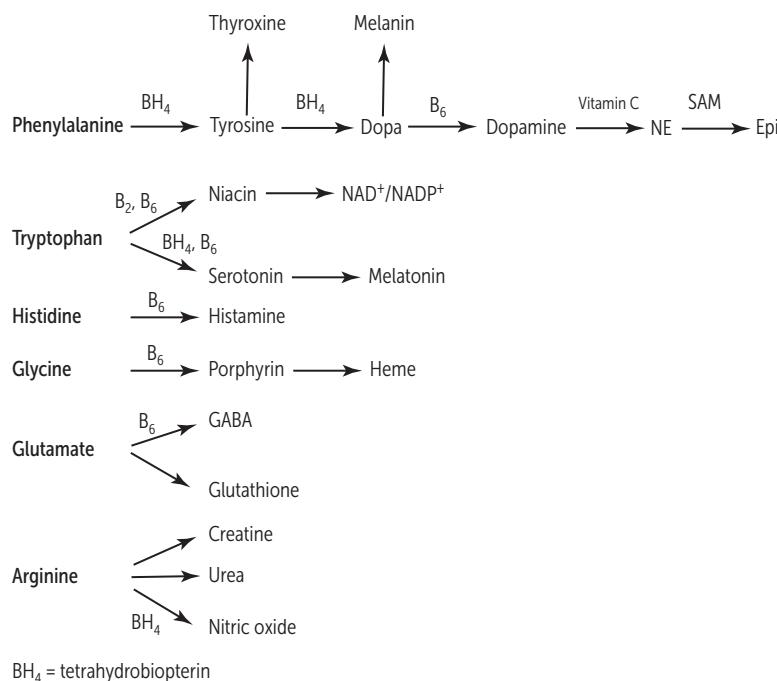


### Ornithine transcarbamylase deficiency

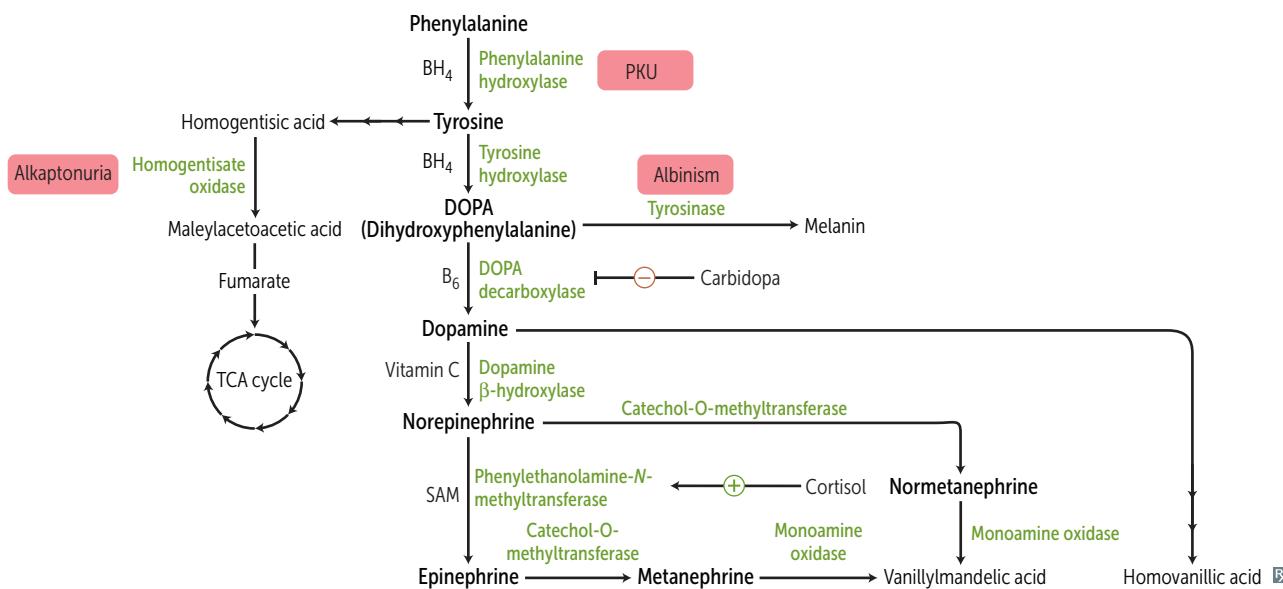
Most common urea cycle disorder. X-linked recessive (vs other urea cycle enzyme deficiencies, which are autosomal recessive). Interferes with the body's ability to eliminate ammonia. Often evident in the first few days of life, but may present later. Excess carbamoyl phosphate is converted to orotic 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**

Caused by ↓ phenylalanine hydroxylase or ↓ tetrahydrobiopterin (BH<sub>4</sub>) cofactor (malignant PKU). Tyrosine becomes essential. ↑ phenylalanine → ↑ phenyl ketones in urine.

Findings: intellectual disability, microcephaly, seizures, hypopigmented skin, eczema, musty body odor.

Treatment: ↓ phenylalanine and ↑ tyrosine in diet, tetrahydrobiopterin supplementation.

**Maternal PKU**—due to elevated maternal phenylalanine levels. Can be prevented by dietary intake. Findings in infant: microcephaly, intellectual disability, growth restriction, congenital heart defects.

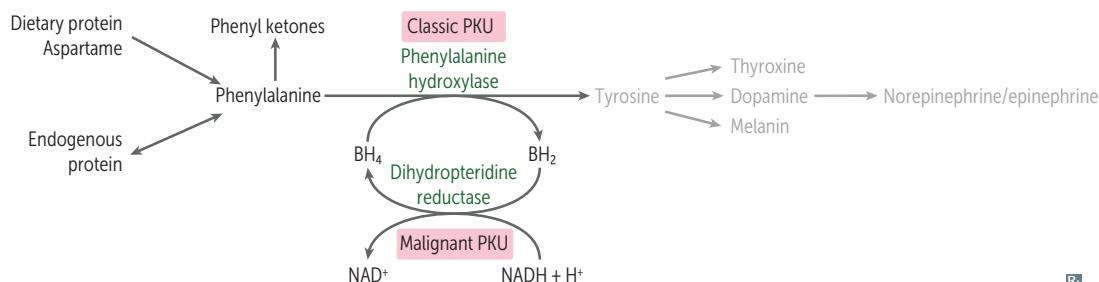
Autosomal recessive. Incidence ≈ 1:10,000.

Screening occurs 2–3 days after birth (normal at birth because of maternal enzyme during fetal life).

Phenyl ketones—phenylacetate, phenyllactate, and phenylpyruvate.

Disorder of **aromatic** amino acid metabolism → musty body **odor**.

PKU patients must avoid the artificial sweetener aspartame, which contains phenylalanine.



Rx

**Maple syrup urine disease**

Blocked degradation of **branched** amino acids (**I**soleucine, **l**eucine, **v**aline) due to ↓ branched-chain α-ketoacid dehydrogenase (B<sub>1</sub>). Causes ↑ α-ketoacids in the blood, especially those of leucine.

Treatment: restriction of isoleucine, leucine, valine in diet, and thiamine supplementation.

Autosomal recessive.

Presentation: vomiting, poor feeding, urine smells like maple syrup/burnt sugar. Causes progressive neurological decline.

I love Vermont **maple syrup** from maple trees (with **B<sub>1</sub>ranches**).

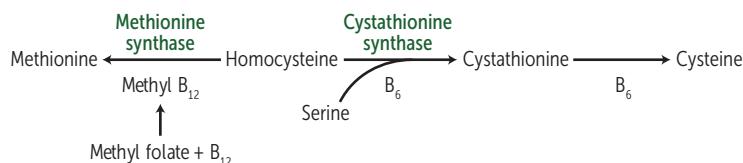
**Alkaptonuria**

Congenital deficiency of homogentisate oxidase in the degradative pathway of tyrosine to fumarate → pigment-forming homogentisic acid builds up in tissue **A**. Autosomal recessive. Usually benign. Findings: bluish-black connective tissue, ear cartilage, and sclerae (ochronosis); urine turns black on prolonged exposure to air. May have debilitating arthralgias (homogentisic acid toxic to cartilage).

**Homocystinuria**

Causes (all autosomal recessive):

- Cystathione synthase deficiency (treatment: ↓ methionine, ↑ cysteine, ↑ B<sub>6</sub>, B<sub>12</sub>, and folate in diet)
- ↓ affinity of cystathione synthase for pyridoxal phosphate (treatment: ↑↑ B<sub>6</sub> and ↑ cysteine in diet)
- Methionine synthase (homocysteine methyltransferase) deficiency (treatment: ↑ methionine in diet)
- Methylene tetrahydrofolate reductase (MTHFR) deficiency (treatment: ↑ folate in diet)

**Cystinuria**

Hereditary defect of renal PCT and intestinal amino acid transporter that prevents reabsorption of **Cystine**, **Ornithine**, **Lysine**, and **Arginine** (**COLA**).

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

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; diet low in methionine.

All forms result in excess homocysteine.

**HOMOCYsturia:** ↑↑ Homocysteine in urine, **Osteoporosis**, **Marfanoid habitus**, **Ocular changes** (downward and inward lens subluxation), **Cardiovascular effects** (thrombosis and atherosclerosis → stroke and MI), **KYphosis**, intellectual disability, hypopigmented skin. In homocystinuria, lens subluxes “down and in” (vs **Marfan**, “up and **fans out**”).

**Organic acidemias**

Most commonly present in infancy with poor feeding, vomiting, hypotonia, high anion gap metabolic acidosis, hepatomegaly, seizures. Organic acid accumulation:

- Inhibits gluconeogenesis → ↓ fasting blood glucose levels, ↑ ketoacidosis → high anion gap metabolic acidosis
- Inhibits urea cycle → hyperammonemia

**Propionic acidemia**

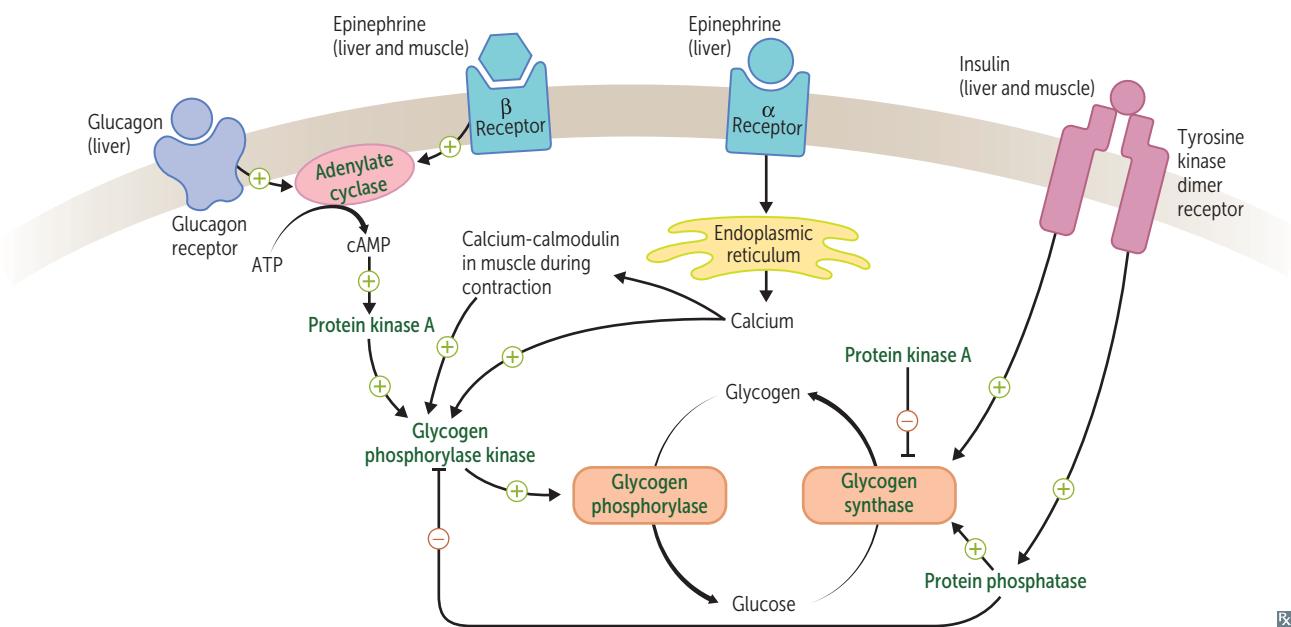
Deficiency of propionyl-CoA carboxylase → ↑ propionyl-CoA, ↓ methylmalonic acid.

Treatment: low-protein diet limited in substances that metabolize into propionyl-CoA: **Valine**, **Odd-chain fatty acids**, **Methionine**, **Isoleucine**, **Threonine** (**VOMIT**).

**Methylmalonic acidemia**

Deficiency of methylmalonyl-CoA mutase or vitamin B<sub>12</sub>.

### 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 → glucose-1-phosphate → glucose-6-phosphate, which is rapidly metabolized during exercise.

### Hepatocytes

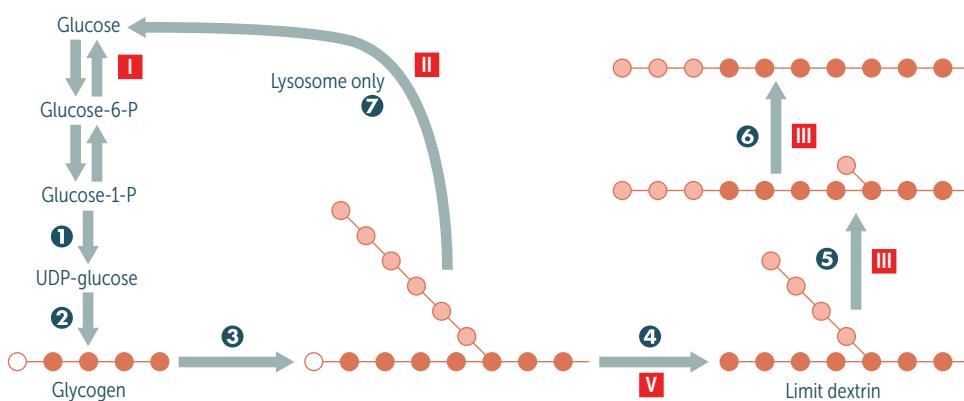
Glycogen is stored and undergoes glycogenolysis to maintain blood sugar at appropriate levels. Glycogen phosphorylase **④** liberates glucose-1-phosphate residues off branched glycogen until 4 glucose units remain on a branch. Then 4-α-D-glucanotransferase (debranching enzyme **⑤**) moves 3 of the 4 glucose units 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 two to four residues remaining on a branch after glycogen phosphorylase has already shortened it.

### Glycogen storage disease type

- I Von Gierke disease
- II Pompe disease
- III Cori disease
- V McArdle disease

### Glycogen enzymes

- ① UDP-glucose pyrophosphorylase
- ② Glycogen synthase
- ③ Branching enzyme
- ④ Glycogen phosphorylase
- ⑤ Debranching enzyme (4-α-D-glucanotransferase)
- ⑥ Debranching enzyme (α-1,6-glucosidase)
- ⑦ α-1,4-glucosidase



Note: A small amount of glycogen is degraded in lysosomes by ⑦ α-1,4-glucosidase (acid maltase).

**Glycogen storage diseases**

At least 15 types have been identified, all resulting in abnormal glycogen metabolism and an accumulation of glycogen within cells. Periodic acid–Schiff stain identifies glycogen and is useful in identifying these diseases.

Vice president can't accept money.  
Types I–V are autosomal recessive.  
**Andersen:** Branching.  
**Cori:** Debranching. (**ABCD**)

DISEASE	FINDINGS	DEFICIENT ENZYME	COMMENTS
<b>Von Gierke disease (type I)</b>	Severe fasting hypoglycemia, ↑↑ Glycogen in liver and kidneys, ↑ blood lactate, ↑ triglycerides, ↑ uric acid (Gout), and hepatomegaly, renomegaly. Liver does not regulate blood glucose.	Glucose-6-phosphatase.	Treatment: frequent oral glucose/cornstarch; avoidance of fructose and galactose. Impaired gluconeogenesis and glycogenolysis.
<b>Pompe disease (type II)</b>	Cardiomyopathy, hypotonia, exercise intolerance, and systemic findings lead to early death.	Lysosomal acid $\alpha$ -1,4-glucosidase (acid maltase) with $\alpha$ -1,6-glucosidase activity.	<b>Pompe</b> trashes the pump (1st and 4th letter; heart, liver, and muscle).
<b>Cori disease (type III)</b>	Similar to von Gierke disease, but milder symptoms and normal blood lactate levels. Can lead to cardiomyopathy. Limit dextrin-like structures accumulate in cytosol.	Debranching enzymes ( $\alpha$ -1,6-glucosidase and 4- $\alpha$ -D-glucanotransferase).	Gluconeogenesis is intact.
<b>Andersen disease (type IV)</b>	Most commonly presents with hepatosplenomegaly and failure to thrive in early infancy. Other findings include infantile cirrhosis, muscular weakness, hypotonia, cardiomyopathy early childhood death.	Branching enzyme. Neuromuscular form can present at any age.	Hypoglycemia occurs late in the disease.
<b>McArdle disease (type V)</b>	↑ glycogen in muscle, but muscle cannot break it down → painful muscle cramps, myoglobinuria (red urine) with strenuous exercise, and arrhythmia from electrolyte abnormalities. Second-wind phenomenon noted during exercise due to ↑ muscular blood flow.	Skeletal muscle glycogen phosphorylase (myophosphorylase). Characterized by a flat venous lactate curve with normal rise in ammonia levels during exercise.	Blood glucose levels typically unaffected. <b>McArdle</b> = muscle.

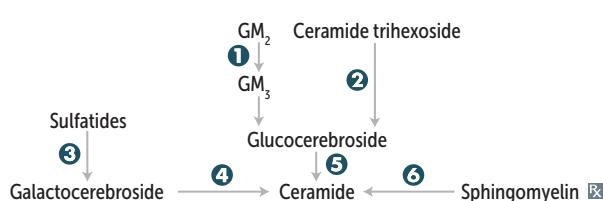
### Lysosomal storage diseases

Lysosomal enzyme deficiency → accumulation of abnormal metabolic products. ↑ incidence of Tay-Sachs, Niemann-Pick, and some forms of Gaucher disease in Ashkenazi Jews.

DISEASE	FINDINGS	DEFICIENT ENZYME	ACCUMULATED SUBSTRATE	INHERITANCE
<b>Sphingolipidoses</b>				
<b>Tay-Sachs disease</b>	Progressive neurodegeneration, developmental delay, hyperreflexia, hyperacusis, “cherry-red” spot on macula <b>A</b> (lipid accumulation in ganglion cell layer), lysosomes with onion skin, no hepatosplenomegaly (vs Niemann-Pick).	① Hexosaminidase A	GM <sub>2</sub> ganglioside. (“TAY-Sax”).	AR
<b>Fabry disease</b>	Early: triad of episodic peripheral neuropathy, angiokeratomas <b>B</b> , hypohidrosis. Late: progressive renal failure, cardiovascular disease.	② α-galactosidase A.	Ceramide trihexoside (globotriaosylceramide).	XR
<b>Metachromatic leukodystrophy</b>	Central and peripheral demyelination with ataxia, dementia.	③ Arylsulfatase A.	Cerebroside sulfate.	AR
<b>Krabbe disease</b>	Peripheral neuropathy, destruction of oligodendrocytes, developmental delay, optic atrophy, globoid cells.	④ Galactocerebrosidase (galactosylceramidase).	Galactocerebroside, psychosine.	AR
<b>Gaucher disease</b>	Most common. Hepatosplenomegaly, pancytopenia, osteoporosis, avascular necrosis of femur, bone crises, Gaucher cells <b>C</b> (lipid-laden macrophages resembling crumpled tissue paper).	⑤ Glucocerebrosidase (β-glucuronidase); treat with recombinant glucocerebrosidase.	Glucocerebroside.	AR
<b>Niemann-Pick disease</b>	Progressive neurodegeneration, hepatosplenomegaly, foam cells (lipid-laden macrophages) <b>D</b> , “cherry-red” spot on macula <b>A</b> .	⑥ Sphingomyelinase.	Sphingomyelin.	AR

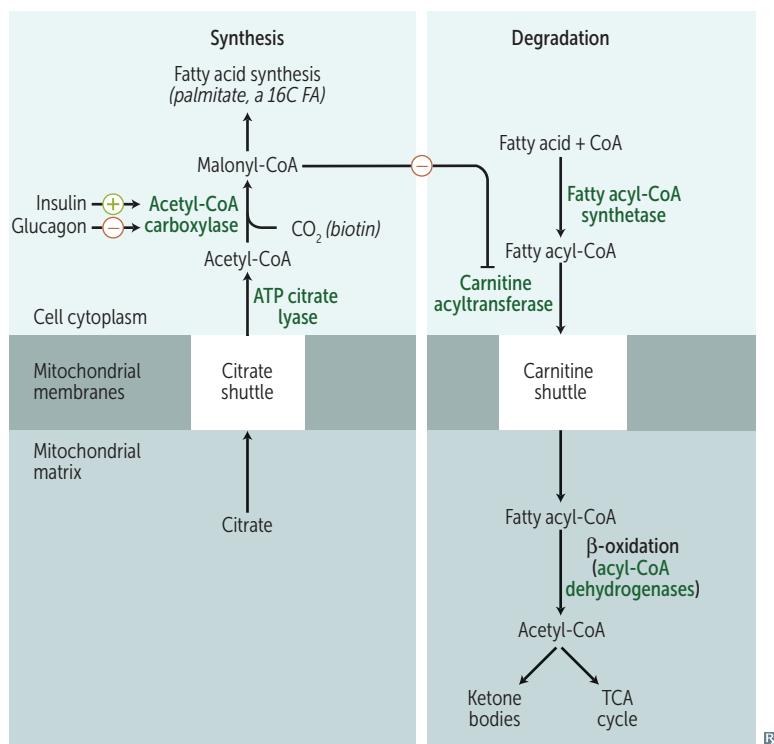
### Mucopolysaccharidoses

<b>Hurler syndrome</b>	Developmental delay, skeletal abnormalities, airway obstruction, corneal clouding, hepatosplenomegaly.	α-L-iduronidase.	Heparan sulfate, dermatan sulfate.	AR
<b>Hunter syndrome</b>	Mild Hurler + aggressive behavior, no corneal clouding.	Iduronate-2 (two)-sulfatase.	Heparan sulfate, dermatan sulfate.	XR



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

### Fatty acid metabolism



Fatty acid synthesis requires transport of citrate from mitochondria to cytosol. Predominantly occurs in liver, lactating mammary glands, and adipose tissue.

Long-chain fatty acid (LCFA) degradation requires carnitine-dependent transport into the mitochondrial matrix.

“Sytrate” = synthesis.

Carnitine = carnage of fatty acids.

**Systemic 1° carnitine deficiency**—no cellular uptake of carnitine → no transport of LCFAs into mitochondria → toxic accumulation of LCFAs in the cytosol. Causes weakness, hypotonia, hypoketotic hypoglycemia, dilated cardiomyopathy.

### Medium-chain acyl-CoA dehydrogenase deficiency

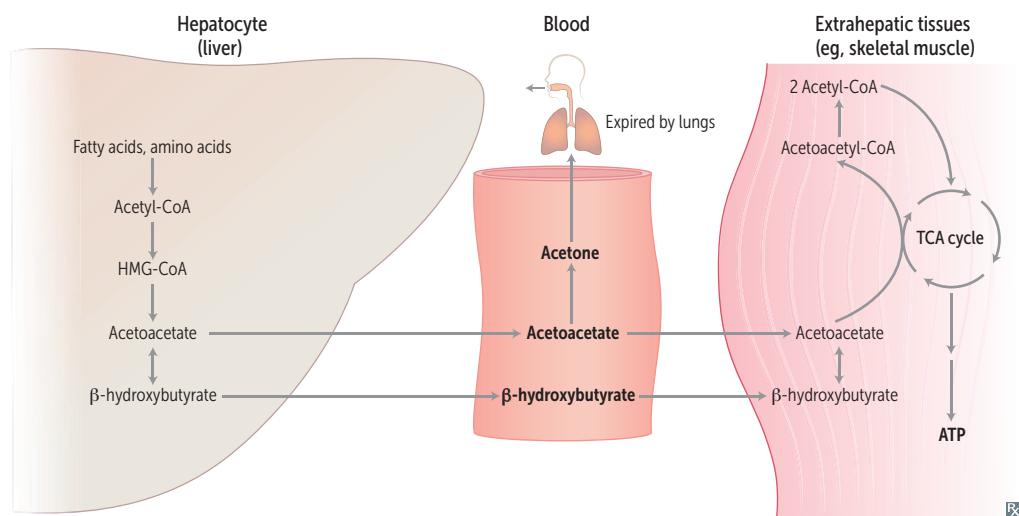
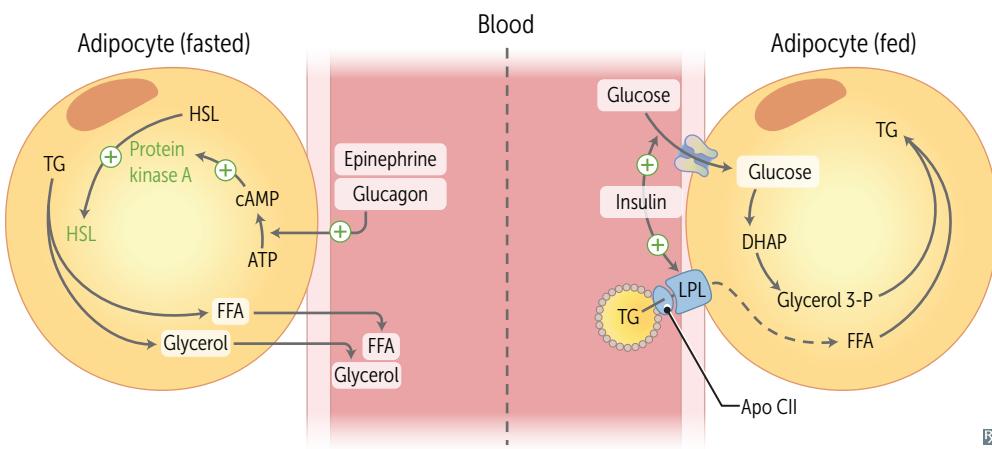
deficiency—↓ ability to break down fatty acids into acetyl-CoA → accumulation of fatty acyl carnitines in the blood with hypoketotic hypoglycemia. Causes vomiting, lethargy, seizures, coma, liver dysfunction, hyperammonemia. Can lead to sudden death in infants or children. Treat by avoiding fasting.

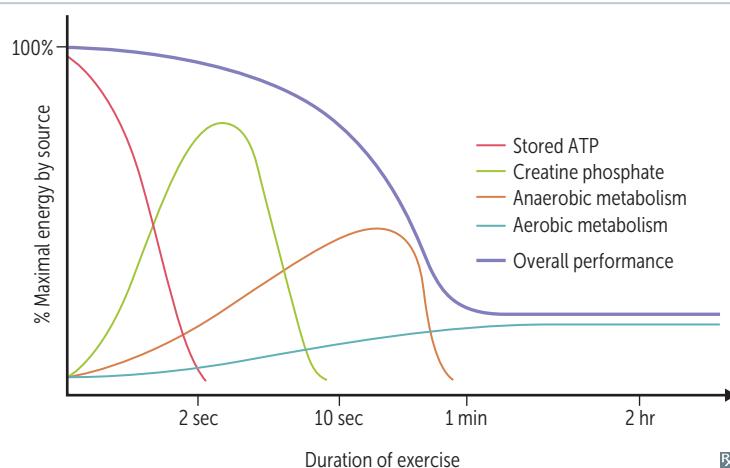
**Ketone bodies**

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

In prolonged starvation and diabetic ketoacidosis, oxaloacetate is depleted for gluconeogenesis. With chronic alcohol overuse, excess NADH shunts oxaloacetate to malate. All of these processes lead to a buildup of acetyl-CoA, which is shunted into ketone body synthesis.

**Ketone bodies:** acetone, acetoacetate,  $\beta$ -hydroxybutyrate.  
 Breath smells like acetone (fruity odor).  
 Urine test for ketones can detect acetoacetate, but not  $\beta$ -hydroxybutyrate.  
 RBCs cannot utilize ketones; they strictly use glucose.  
 HMG-CoA lyase for ketone production.  
 HMG-CoA reductase for cholesterol synthesis.

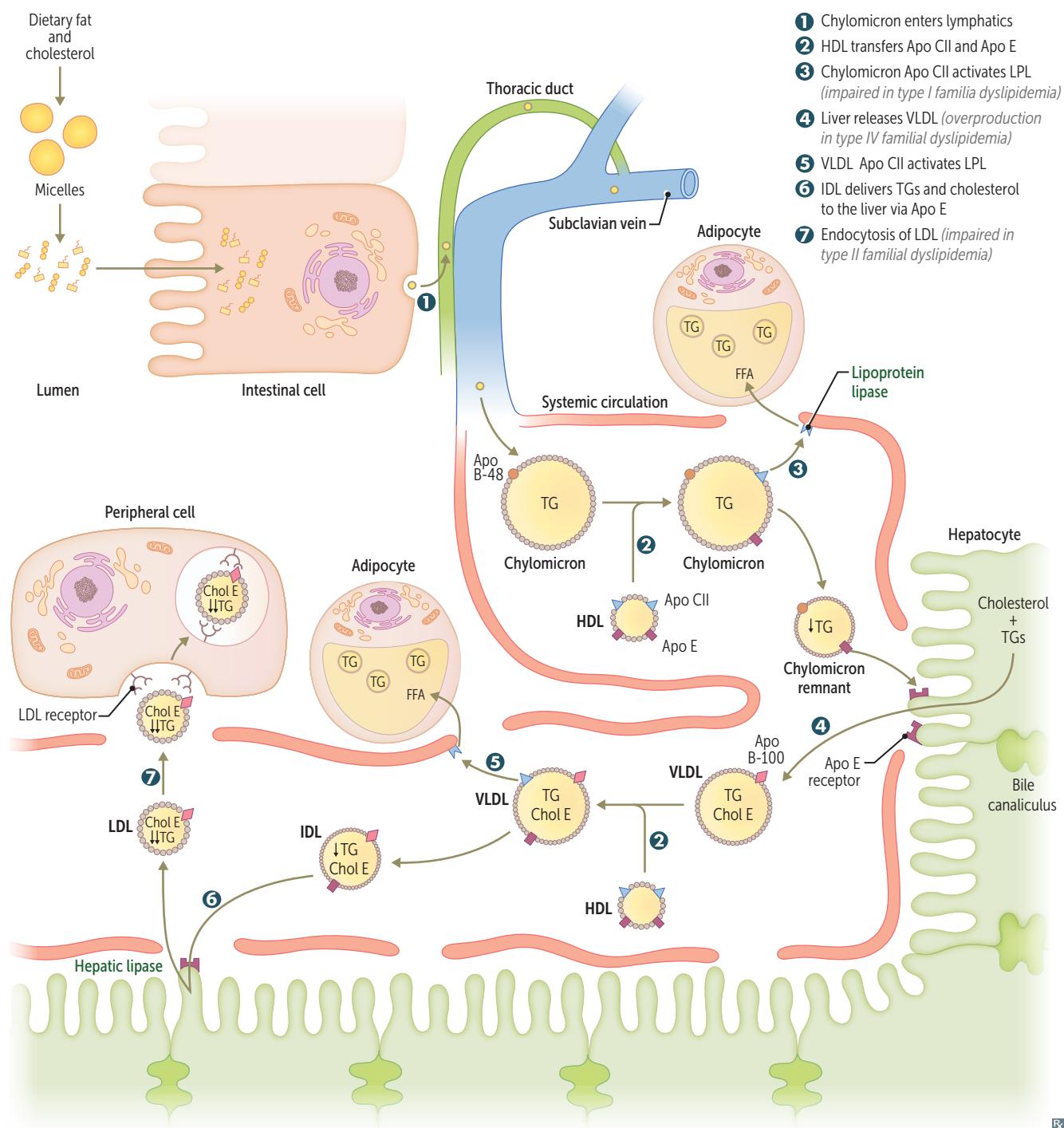
**Fasted vs fed state**

**Metabolic fuel use**

$\lg \text{carb/protein} = 4 \text{ kcal}$   
 $\lg \text{alcohol} = 7 \text{ kcal}$   
 $\lg \text{fatty acid} = 9 \text{ kcal}$   
 (# letters = # kcal)

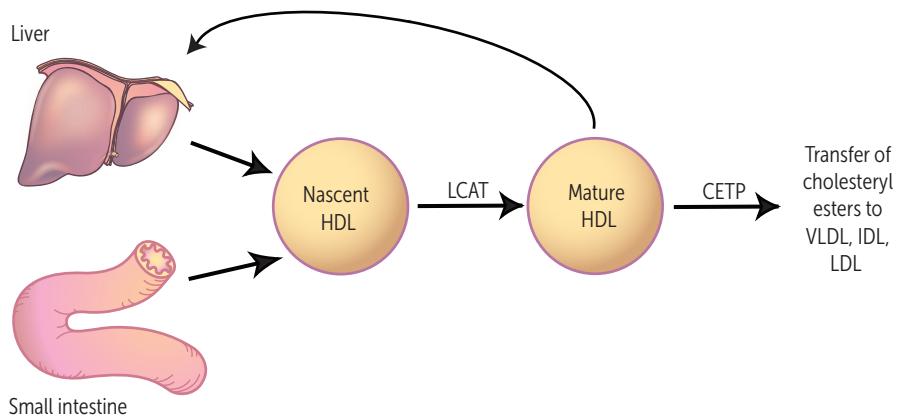
**Fasting and starvation** Priorities are to supply sufficient glucose to the brain and RBCs and to preserve protein.

<b>Fed state (after a meal)</b>	Glycolysis and aerobic respiration.	Insulin stimulates storage of lipids, proteins, and glycogen.
<b>Fasting (between meals)</b>	Hepatic glycogenolysis (major); hepatic gluconeogenesis, adipose release of FFA (minor).	Glucagon and epinephrine stimulate use of fuel reserves.
<b>Starvation days 1–3</b>	Blood glucose levels maintained by: <ul style="list-style-type: none"> <li>■ Hepatic glycogenolysis</li> <li>■ Adipose release of FFA</li> <li>■ Muscle and liver, which shift fuel use from glucose to FFA</li> <li>■ Hepatic gluconeogenesis from peripheral tissue lactate and alanine, and from adipose tissue glycerol and propionyl-CoA (from odd-chain FFA—the only triacylglycerol components that contribute to gluconeogenesis)</li> </ul>	Glycogen reserves depleted after day 1. RBCs lack mitochondria and therefore cannot use ketones.
<b>Starvation after day 3</b>	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.	<p>The graph plots 'Stored energy (kg)' on the y-axis (0 to 12) against 'Weeks of starvation' on the x-axis (0 to 8). Three curves are shown:</p> <ul style="list-style-type: none"> <li><b>Carbohydrate</b>: Red curve, starts at ~12 kg and drops to 0 by week 1.</li> <li><b>Fat</b>: Purple curve, starts at ~12 kg and decreases steadily, reaching ~1 kg by week 8.</li> <li><b>Protein</b>: Brown curve, starts at ~12 kg and decreases more slowly than fat, reaching ~1 kg by week 8.</li> </ul>

**Lipid transport**

**Key enzymes in lipid transport**

<b>Cholesteryl ester transfer protein</b>	Mediates transfer of cholesteryl esters to other lipoprotein particles.
<b>Hepatic lipase</b>	Degrades TGs remaining in IDL and chylomicron remnants.
<b>Hormone-sensitive lipase</b>	Degradates TGs stored in adipocytes. Promotes gluconeogenesis by releasing glycerol.
<b>Lecithin-cholesterol acyltransferase</b>	Catalyzes esterification of $\frac{1}{2}$ of plasma cholesterol (ie, required for HDL maturation).
<b>Lipoprotein lipase</b>	Degradates TGs in circulating chylomicrons.
<b>Pancreatic lipase</b>	Degradates dietary TGs in small intestine.
<b>PCSK9</b>	Degradates LDL receptor $\rightarrow$ ↑ serum LDL. Inhibition $\rightarrow$ ↑ LDL receptor recycling $\rightarrow$ ↓ serum LDL.

**Major apolipoproteins**

Apolipoprotein	Function	Chylomicron	Chylomicron remnant	VLDL	IDL	LDL	HDL
E	Mediates remnant uptake (everything <b>except</b> LDL)	✓	✓	✓	✓	✓	✓
A-I	Found only on <b>alpha</b> -lipoproteins (HDL), activates LCAT						✓
C-II	Lipoprotein lipase <b>cofactor</b> that <b>catalyzes cleavage</b> .	✓		✓	✓		✓
B-48	Mediates chylomicron secretion into lymphatics Only on particles originating from the intestines	✓	✓				
B-100	Binds LDL receptor Only on particles originating from the liver			✓	✓	✓	

**Lipoprotein functions**

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

Cholesterol is needed to maintain cell membrane integrity and synthesize bile acids, steroids, and vitamin D.

**Chylomicron**

Delivers dietary TGs to peripheral tissues. Delivers cholesterol to liver in the form of chylomicron remnants, which are mostly depleted of their TGs. Secreted by intestinal epithelial cells.

**VLDL**

Delivers hepatic TGs to peripheral tissue. Secreted by liver.

**IDL**

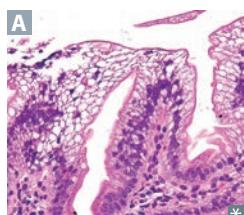
Delivers TGs and cholesterol to liver. Formed from degradation of VLDL.

**LDL**

Delivers hepatic cholesterol to peripheral tissues. Formed by hepatic lipase modification of IDL in the liver and peripheral tissue. Taken up by target cells via receptor-mediated endocytosis. **LDL is Lethal.**

**HDL**

Mediates reverse cholesterol transport from peripheral tissues to liver. Acts as a repository for apolipoproteins C and E (which are needed for chylomicron and VLDL metabolism). Secreted from both liver and intestine. Alcohol ↑ synthesis. **HDL is Healthy.**

**Abetalipoproteinemia**

Autosomal recessive. Mutation in gene that encodes microsomal transfer protein (MTP).

Chylomicrons, VLDL, LDL absent. Deficiency in ApoB-48, ApoB-100. Affected infants present with severe fat malabsorption, steatorrhea, failure to thrive. Later manifestations include retinitis pigmentosa, spinocerebellar degeneration due to vitamin E deficiency, progressive ataxia, acanthocytosis. Intestinal biopsy shows lipid-laden enterocytes **A**.

Treatment: restriction of long-chain fatty acids, large doses of oral vitamin E.

**Familial dyslipidemias**

TYPE	INHERITANCE	PATHOGENESIS	↑ BLOOD LEVEL	CLINICAL
I—Hyper-chylomicronemia	AR	Lipoprotein lipase or ApoC-2 deficiency	Chylomicrons, TG, cholesterol	Pancreatitis, hepatosplenomegaly, and eruptive/pruritic xanthomas (no ↑ risk for atherosclerosis). Creamy layer in supernatant.
II—Hyper-cholesterolemia	AD	Absent or defective LDL receptors, or defective ApoB-100	IIa: LDL, cholesterol IIb: LDL, cholesterol, VLDL	Heterozygotes (1:500) have cholesterol $\approx$ 300 mg/dL; homozygotes (very rare) have cholesterol $\geq$ 700 mg/dL. Accelerated atherosclerosis (may have MI before age 20), tendon (Achilles) xanthomas, and corneal arcus.
III—Dysbeta-lipoproteinemia	AR	ApoE (defective in type thr <sup>EE</sup> )	Chylomicrons, VLDL	Premature atherosclerosis, tuberoeruptive and <b>palmar</b> xanthomas. <b>ApE's palms.</b>
IV—Hyper-triglyceridemia	AD	Hepatic overproduction of VLDL	VLDL, TG	Hypertriglyceridemia ( $>$ 1000 mg/dL) can cause acute pancreatitis. Related to insulin resistance.

# HIGH-YIELD PRINCIPLES IN

# Immunology

*“I hate to disappoint you, but my rubber lips are immune to your charms.”*  
—Batman & Robin

*“Imagine the action of a vaccine not just in terms of how it affects a single body, but also in terms of how it affects the collective body of a community.”*

—Eula Biss

*“Some people are immune to good advice.”*  
—Saul Goodman, *Breaking Bad*

Learning the components of the immune system and their roles in host defense at the cellular level is essential for both the understanding of disease pathophysiology and clinical practice. Know the immune mechanisms of responses to vaccines. Both congenital and acquired immunodeficiencies are very testable. Cell surface markers are high yield for understanding immune cell interactions and for laboratory diagnosis. Know the roles and functions of major cytokines and chemokines.

- ▶ Lymphoid Structures 96
- ▶ Cellular Components 99
- ▶ Immune Responses 104
- ▶ Immunosuppressants 120

## ► IMMUNOLOGY—LYMPHOID STRUCTURES

**Immune system organs**

1° organs:

- Bone marrow—immune cell production, **B** cell maturation
- Thymus—**T** cell maturation

2° organs:

- Spleen, lymph nodes, tonsils, Peyer patches
- Allow immune cells to interact with antigen

**Lymph node**

A 2° lymphoid organ that has many afferents, 1 or more efferents. Encapsulated, with trabeculae

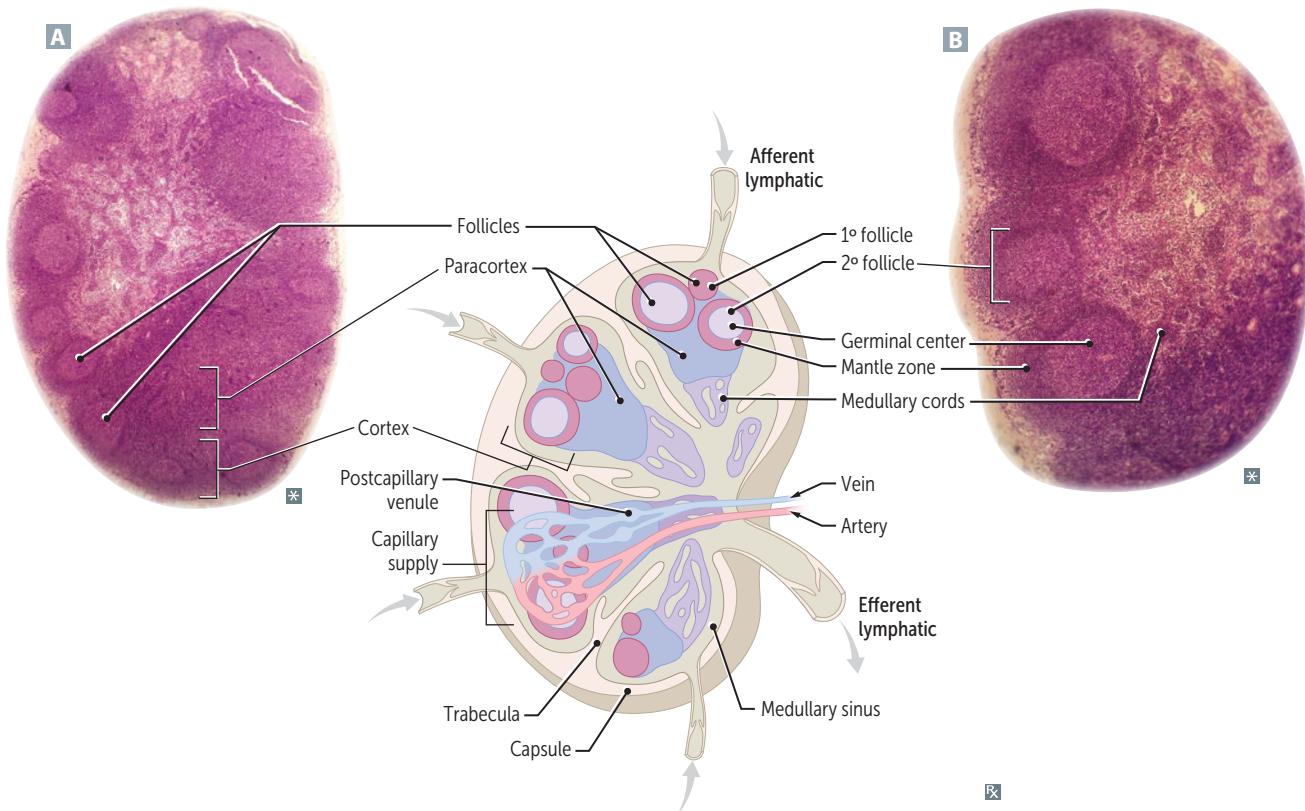
**A** **B**. Functions are nonspecific filtration by macrophages, circulation of B and T cells, and immune response activation.

**Follicle**

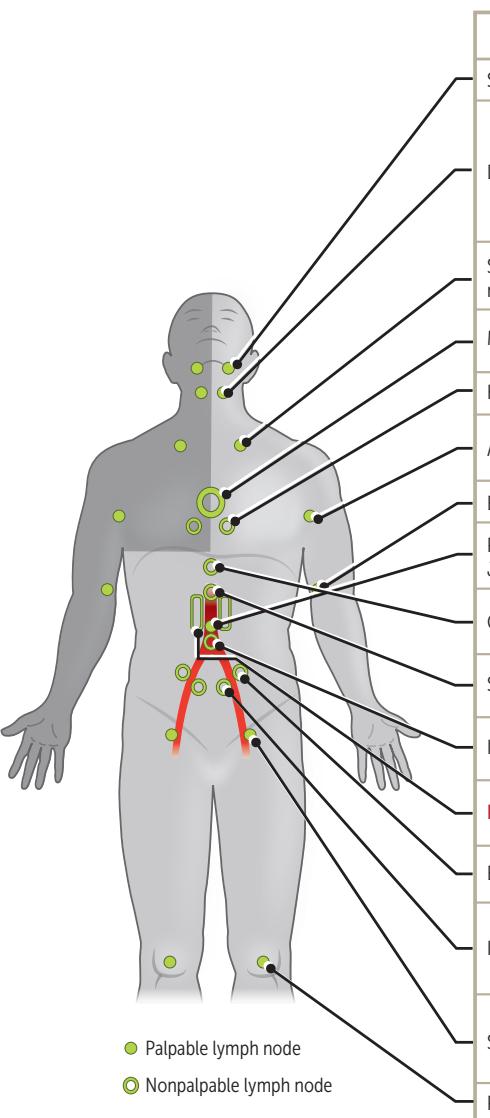
Site of B-cell localization and proliferation. In outer cortex. 1° follicles are dense and quiescent. 2° follicles have pale central germinal centers and are active.

**Medulla**

Consists of medullary cords (closely packed lymphocytes and plasma cells) and medullary sinuses. Medullary sinuses communicate with efferent lymphatics and contain reticular cells and macrophages.

**Paracortex**Contains T cells. Region of cortex between follicles and medulla. Contains high endothelial venules through which T and B cells enter from blood. Not well developed in patients with DiGeorge syndrome.  
Paracortex enlarges in an extreme cellular immune response (eg, EBV and other viral infections → paracortical hyperplasia → lymphadenopathy).

### Lymphatic drainage associations

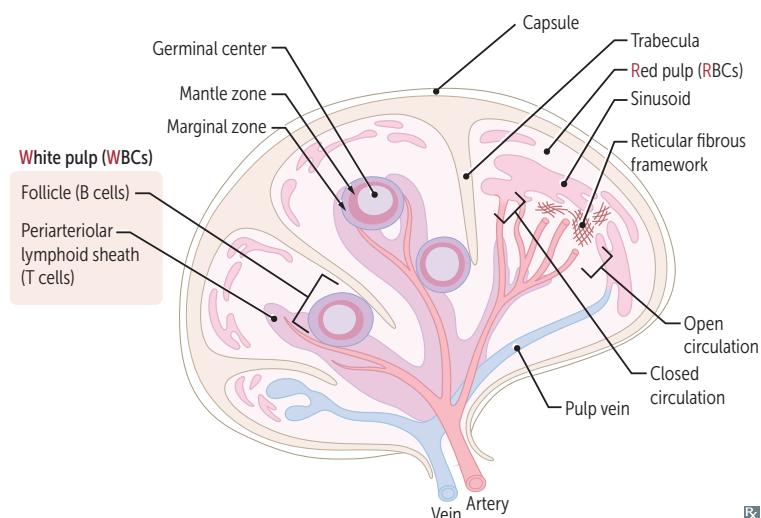


Lymph node cluster	Area of body drained	Associated pathology
Submandibular	Oral cavity	Malignancy of oral cavity
Deep cervical	Head, neck, oropharynx	Upper respiratory tract infection Infectious mononucleosis Kawasaki disease Malignancy of head, neck, oropharynx
Supraclavicular (Virchow node)	Abdomen, pelvis	Malignancy of abdomen, pelvis
Mediastinal	Trachea, esophagus	Pulmonary TB (unilateral hilar) Sarcoidosis (bilateral hilar) Lung cancer Granulomatous disease
Hilar	Lungs	
Axillary	Upper limb, breast, skin above umbilicus	Mastitis Metastasis (especially breast cancer)
Epitrochlear	Hand, forearm	Secondary syphilis
Periumbilical (Sister Mary Joseph node)	Abdomen, pelvis	Gastric cancer
Celiac	Liver, stomach, spleen, pancreas, upper duodenum	
Superior mesenteric	Lower duodenum, jejunum, ileum, colon to splenic flexure	Mesenteric lymphadenitis Inflammatory bowel disease Celiac disease
Inferior mesenteric	Colon from splenic flexure to upper rectum	
Para-aortic	Pair of testes, ovaries, kidneys, fallopian tubes (uterus)	Metastasis
External iliac	Cervix, superior bladder, body of uterus	
Internal iliac	Lower rectum to anal canal (above pectinate line), bladder, vagina (middle third), cervix, prostate	
Superficial inguinal	Anal canal (below pectinate line), skin below umbilicus (except popliteal area), scrotum, vulva	Sexually transmitted infections Medial foot/leg cellulitis (superficial inguinal)
Popliteal ("pop-lateral")	Dorsolateral foot, posterior calf	Lateral foot/leg cellulitis

■ Right lymphatic duct drains right side of body above diaphragm into junction of the right subclavian and internal jugular vein

■ Thoracic duct drains below the diaphragm and left thorax and upper limb into junction of left subclavian and internal jugular veins (rupture of thoracic duct can cause chylothorax) 

## Spleen



Located in LUQ of abdomen, anterolateral to left kidney, protected by 9th-11th ribs.  
Splenic dysfunction (eg, postsplenectomy, sickle cell disease autosplenectomy) → ↓ IgM  
→ ↓ complement activation → ↓ C3b opsonization → ↑ susceptibility to encapsulated organisms.

Postsplenectomy findings:

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

Vaccinate patients undergoing splenectomy or with splenic dysfunction against encapsulated organisms (pneumococci, Hib, meningococci).

### Periarteriolar lymphatic sheath

Contains T cells. Located within white pulp.

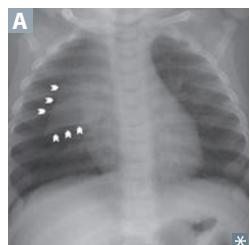
### Follicle

Contains B cells. Located within white pulp.

### Marginal zone

Contains macrophages and specialized B cells. Site where antigen-presenting cells (APCs) capture blood-borne antigens for recognition by lymphocytes. Located between red pulp and white pulp.

## Thymus



Located in the anterosuperior mediastinum. Site of T-cell differentiation and maturation. Encapsulated. Thymus epithelium is derived from third pharyngeal pouch (endoderm), whereas thymic lymphocytes are of mesodermal origin. Cortex is dense with immature T cells; medulla is pale with mature T cells and Hassall corpuscles containing epithelial reticular cells.

Normal neonatal thymus "sail-shaped" on CXR (asterisks in A), involutes by age 3 years.

**T** cells = Thymus

**B** cells = Bone marrow

Absent thymic shadow or hypoplastic thymus seen in some immunodeficiencies (eg, SCID, DiGeorge syndrome).

**Thymoma**—neoplasm of thymus. Associated with myasthenia gravis, superior vena cava syndrome, pure red cell aplasia, Good syndrome.

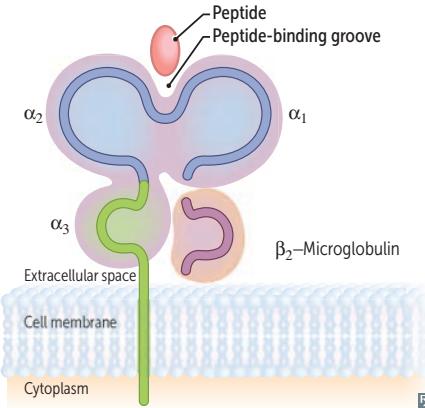
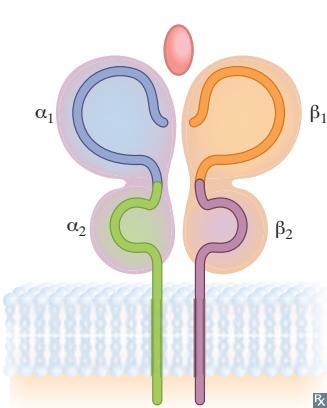
## ► IMMUNOLOGY—CELLULAR COMPONENTS

**Innate vs adaptive immunity**

	Innate immunity	Adaptive immunity
COMPONENTS	Neutrophils, macrophages, monocytes, dendritic cells, natural killer (NK) cells (lymphoid origin), complement, physical epithelial barriers, secreted enzymes	T cells, B cells, circulating antibodies
MECHANISM	Germline encoded	Variation through V(D)J recombination during lymphocyte development
RESPONSE TO PATHOGENS	Nonspecific Occurs rapidly (minutes to hours) No memory response	Highly specific, refined over time Develops over long periods; memory response is faster and more robust
SECRETED PROTEINS	Lysozyme, complement, C-reactive protein (CRP), defensins, cytokines	Immunoglobulins, cytokines
KEY FEATURES IN PATHOGEN RECOGNITION	Toll-like receptors (TLRs): pattern recognition receptors that recognize pathogen-associated molecular patterns (PAMPs) and lead to activation of NF-κB. Examples of PAMPs: LPS (gram $\ominus$ bacteria), flagellin (bacteria), nucleic acids (viruses)	Memory cells: activated B and T cells; subsequent exposure to a previously encountered antigen → stronger, quicker immune response

**Major****histocompatibility complex I and II**

MHC encoded by HLA genes. Present antigen fragments to T cells and bind T-cell receptors (TCRs).

	<b>MHC I</b>	<b>MHC II</b>
<b>LOCI</b>	HLA-A, HLA-B, HLA-C MHC I loci have <b>1</b> letter	HLA-DP, HLA-DQ, HLA-DR MHC II loci have <b>2</b> letters
<b>BINDING</b>	TCR and CD8	TCR and CD4
<b>STRUCTURE</b>	<b>1</b> long chain, <b>1</b> short chain	<b>2</b> equal-length chains ( <b>2</b> $\alpha$ , <b>2</b> $\beta$ )
<b>EXPRESSION</b>	All nucleated cells, APCs, platelets (except RBCs)	APCs
<b>FUNCTION</b>	Present endogenous antigens (eg, viral or cytosolic proteins) to CD8+ cytotoxic T cells	Present exogenous antigens (eg, bacterial proteins) to CD4+ helper T cells
<b>ANTIGEN LOADING</b>	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
<b>ASSOCIATED PROTEINS</b>	$\beta_2$ -microglobulin	Invariant chain
<b>STRUCTURE</b>		

**HLA subtypes associated with diseases**

HLA SUBTYPE	DISEASE	MNEMONIC
<b>B27</b>	Psoriatic arthritis, Ankylosing spondylitis, IBD-associated arthritis, Reactive arthritis	<b>PAIR.</b> Also called seronegative arthropathies
<b>B57</b>	Abacavir hypersensitivity	
<b>DQ2/DQ8</b>	Celiac disease	I ate ( <b>8</b> ) too ( <b>2</b> ) much gluten at <b>Dairy Queen</b>
<b>DR3</b>	DM type 1, <b>SLE</b> , Graves disease, Hashimoto thyroiditis, Addison disease	<b>2-3, S-L-E</b> DM type <b>1</b> : HLA- <b>3</b> and - <b>4</b> ( $1 + 3 = 4$ )
<b>DR4</b>	Rheumatoid arthritis, DM type <b>1</b> , Addison disease	There are <b>4</b> walls in <b>1</b> “rheum” (room)

**Functions of natural killer cells**

Lymphocyte member of innate immune system.  
Use perforin and granzymes to induce apoptosis of virally infected cells and tumor cells.  
Activity enhanced by IL-2, IL-12, IFN- $\alpha$ , and IFN- $\beta$ .  
Induced to kill when exposed to a nonspecific activation signal on target cell and/or to an absence of an inhibitory signal such as MHC I on target cell surface.  
Also kills via antibody-dependent cell-mediated cytotoxicity (CD16 binds Fc region of bound IgG, activating the NK cell).

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**Major functions of B and T cells****B cells**

Humoral immunity.  
Recognize and present antigen—undergo somatic hypermutation to optimize antigen specificity.  
Produce antibody—differentiate into plasma cells to secrete specific immunoglobulins.  
Maintain immunologic memory—memory B cells persist and accelerate future response to antigen.

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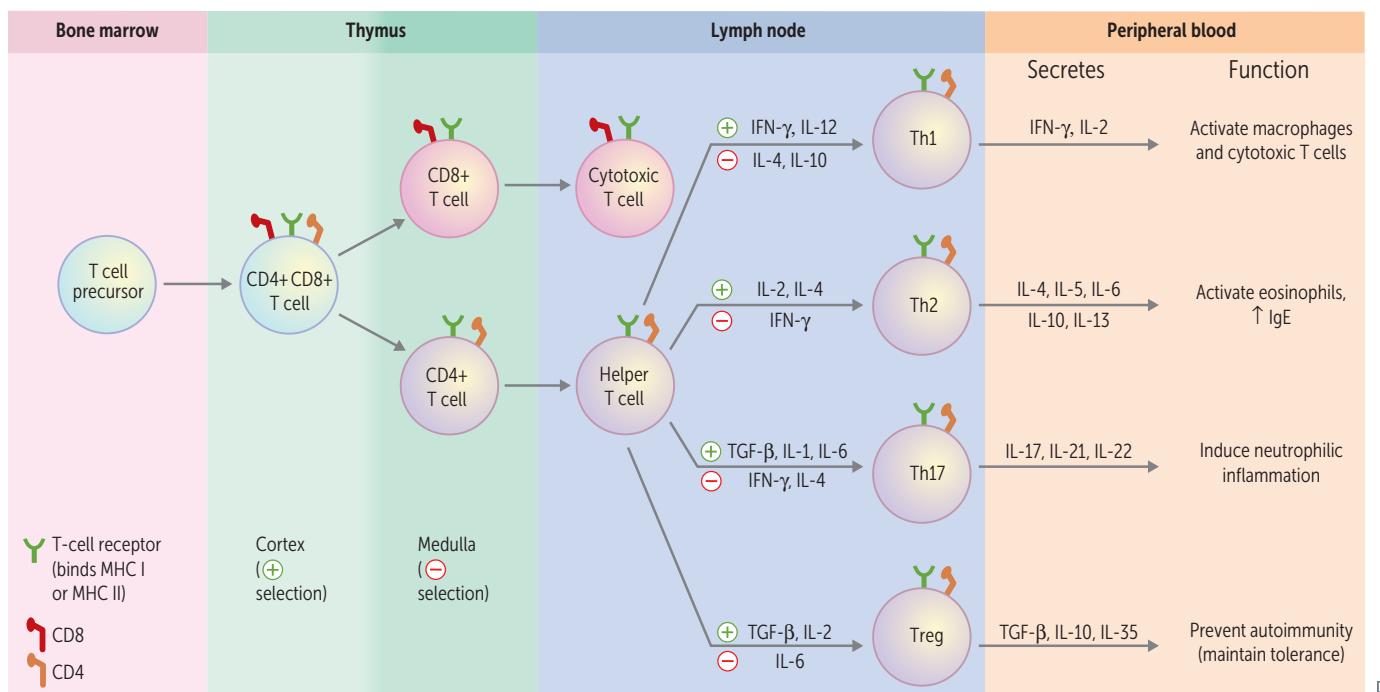
**T cells**

Cell-mediated immunity.  
CD4+ T cells help B cells make antibodies and produce cytokines to recruit phagocytes and activate other leukocytes.  
CD8+ T cells directly kill virus-infected and tumor cells via perforin and granzymes (similar to NK cells).  
Delayed cell-mediated hypersensitivity (type IV).  
Acute and chronic cellular organ rejection.

**Rule of 8:** MHC II  $\times$  CD4 = 8; MHC I  $\times$  CD8 = 8.

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### Differentiation of T cells



#### Positive selection

Thymic cortex. T cells expressing TCRs capable of binding self-MHC on cortical epithelial cells survive.

#### Negative selection

Thymic medulla. T cells expressing TCRs with high affinity for self antigens undergo apoptosis or become regulatory T cells. Tissue-restricted self-antigens are expressed in the thymus due to the action of autoimmune regulator (**AIRE**); deficiency leads to autoimmune polyendocrine syndrome-I (**Chronic mucocutaneous candidiasis, Hypoparathyroidism, Adrenal insufficiency, Recurrent Candida infections**). “Without **AIRE**, your body will **CHAR**”.

#### Macrophage-lymphocyte interaction

Th1 cells secrete IFN- $\gamma$ , which enhances the ability of monocytes and macrophages to kill microbes they ingest. This function is also enhanced by interaction of T cell CD40L with CD40 on macrophages. Macrophages also activate lymphocytes via antigen presentation.

#### Cytotoxic T cells

Kill virus-infected, neoplastic, and donor graft cells by inducing apoptosis. Release cytotoxic granules containing preformed proteins (eg, perforin, granzyme B). Cytotoxic T cells have CD8, which binds to MHC I on virus-infected cells.

#### Regulatory T cells

Help maintain specific immune tolerance by suppressing CD4 $^{+}$  and CD8 $^{+}$  T-cell effector functions. Identified by expression of CD3, CD4, CD25, and FOXP3. Activated regulatory T cells (Tregs) produce anti-inflammatory cytokines (eg, IL-10, TGF- $\beta$ ).

**IPEX (Immune dysregulation, Polyendocrinopathy, Enteropathy, X-linked) syndrome**—genetic deficiency of FOXP3 → autoimmunity. Characterized by enteropathy, endocrinopathy, nail dystrophy, dermatitis, and/or other autoimmune dermatologic conditions. Associated with diabetes in male infants.

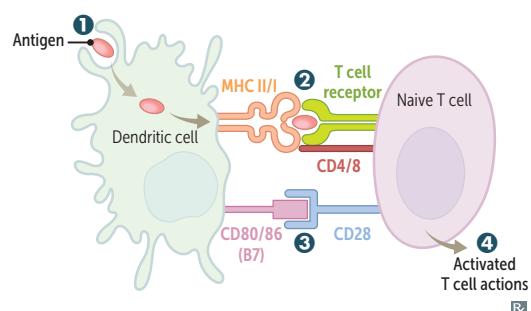
**T- and B-cell activation**

APCs: B cells, dendritic cells, Langerhans cells, macrophages.

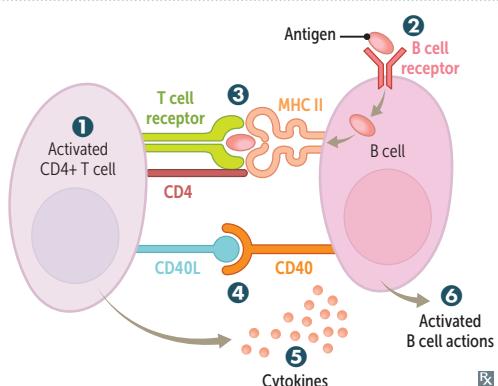
Two signals are required for T-cell activation, B-cell activation, and class switching.

**T-cell activation**

- ❶ Dendritic cell (specialized APC) ingests and processes antigen, then migrates to the draining lymph node.
- ❷ T-cell activation (signal 1): exogenous antigen is presented on MHC II and recognized by TCR on Th (CD4+) cell. Endogenous or cross-presented antigen is presented on MHC I to Tc (CD8+) cell.
- ❸ Proliferation and survival (signal 2): costimulatory signal via interaction of B7 protein (CD80/86) on dendritic cell and CD28 on naïve T cell.
- ❹ Activated Th cell produces cytokines. Tc cell able to recognize and kill virus-infected cell.

**B-cell activation and class switching**

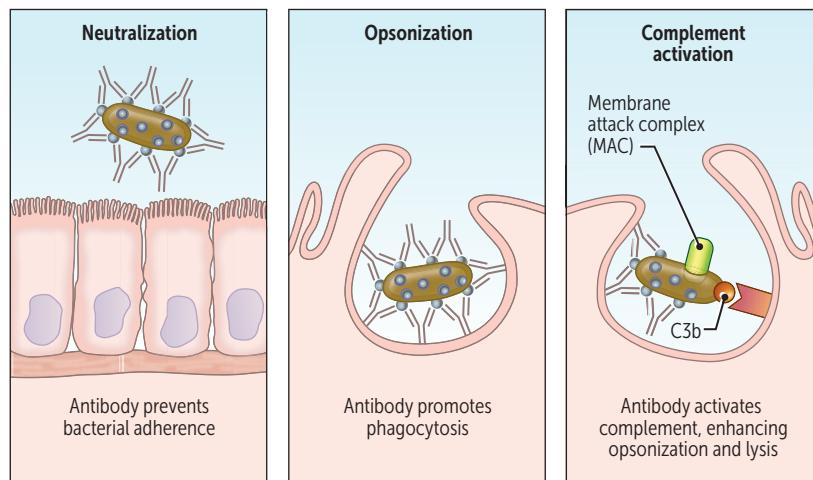
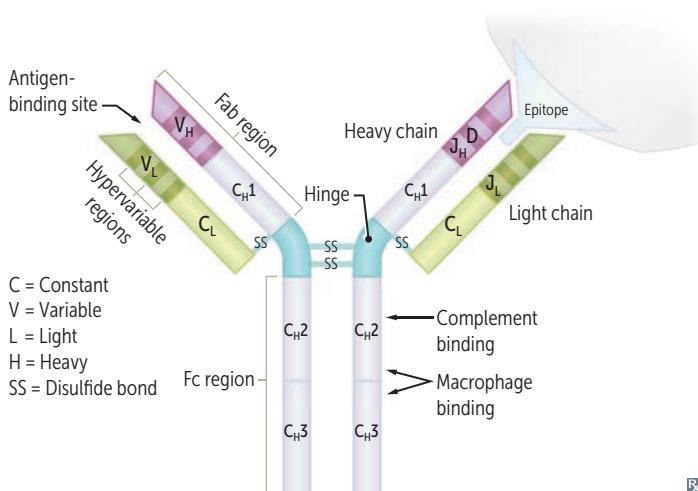
- ❶ Th-cell activation as above.
- ❷ B-cell receptor-mediated endocytosis.
- ❸ Exogenous antigen is presented on MHC II and recognized by TCR on Th cell.
- ❹ CD40 receptor on B cell binds CD40 ligand (CD40L) on Th cell.
- ❺ Th cells secrete cytokines that determine Ig class switching of B cells.
- ❻ B cells are activated and produce IgM. They undergo class switching and affinity maturation.



## ► IMMUNOLOGY—IMMUNE RESPONSES

**Antibody structure and function**

Fab fragment 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 idioype: unique antigen-binding pocket; only 1 antigenic specificity expressed per B cell

**Fc (5 C's):**

- Constant
- Carboxy terminal
- Complement binding
- Carbohydrate side chains
- Confers (determines) isotype (IgM, IgD, etc)

**Generation of antibody diversity (antigen independent)**

1. Random recombination of VJ (light-chain) or V(D)J (heavy-chain) genes
2. Random addition of nucleotides to DNA during recombination by terminal deoxynucleotidyl transferase (TdT)
3. Random combination of heavy chains with light chains

**Generation of antibody specificity (antigen dependent)**

4. Somatic hypermutation and affinity maturation (variable region)
5. Isotype switching (constant region)

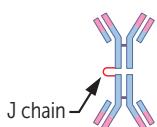
**Immunoglobulin isotypes**

All isotypes can exist as monomers. Mature, naïve B cells prior to activation express IgM and IgD on their surfaces. They may differentiate in germinal centers of lymph nodes by isotype switching (gene rearrangement; induced by cytokines and CD40L) into plasma cells that secrete IgA, IgE, or IgG.

Affinity refers to the individual antibody-antigen interaction, while avidity describes the cumulative binding strength of all antibody-antigen interactions in a multivalent molecule.

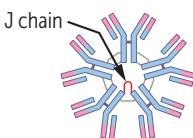
**IgG**

Main antibody in 2° response to an antigen. Most abundant isotype in serum. Fixes complement, opsonizes bacteria, neutralizes bacterial toxins and viruses. Only isotype that crosses the placenta (provides infants with passive immunity that starts to wane after birth). “IgG Greets the Growing fetus.” Associated with **warm** autoimmune hemolytic anemia (“**warm** weather is **Great!**”).

**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° (**IM**mediate) response to an antigen. Fixes complement. Antigen receptor on the surface of B cells. Monomer on B cell, pentamer with J chain when secreted. Pentamer enables avid binding to antigen while humoral response evolves. Associated with cold autoimmune hemolytic anemia.

**IgD**

Unclear function. Found on surface of many B cells and in serum.

**IgE**

Binds mast cells and basophils; cross-links when exposed to allergen, mediating immediate (type I) hypersensitivity through release of inflammatory mediators such as histamine. Contributes to immunity to parasites by activating **Eosinophils**.

**Antigen type and memory****Thymus-independent antigens**

Antigens lacking a peptide component (eg, lipopolysaccharides from gram ⊖ bacteria); cannot be presented by MHC to T cells. Weakly immunogenic; vaccines often require boosters and adjuvants (eg, capsular polysaccharide subunit of *Streptococcus pneumoniae* PPSV23 vaccine).

**Thymus-dependent antigens**

Antigens containing a protein component (eg, diphtheria toxoid). Class switching and immunologic memory occur as a result of direct contact of B cells with Th cells.

**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. The CH<sub>50</sub> test is used to screen for activation of the classical complement pathway.

## ACTIVATION PATHWAYS

**Classic**—IgG or IgM mediated.  
**Alternative**—microbe surface molecules.  
**Lectin**—mannose or other sugars on microbe surface.

GM makes **classic** cars.

## FUNCTIONS

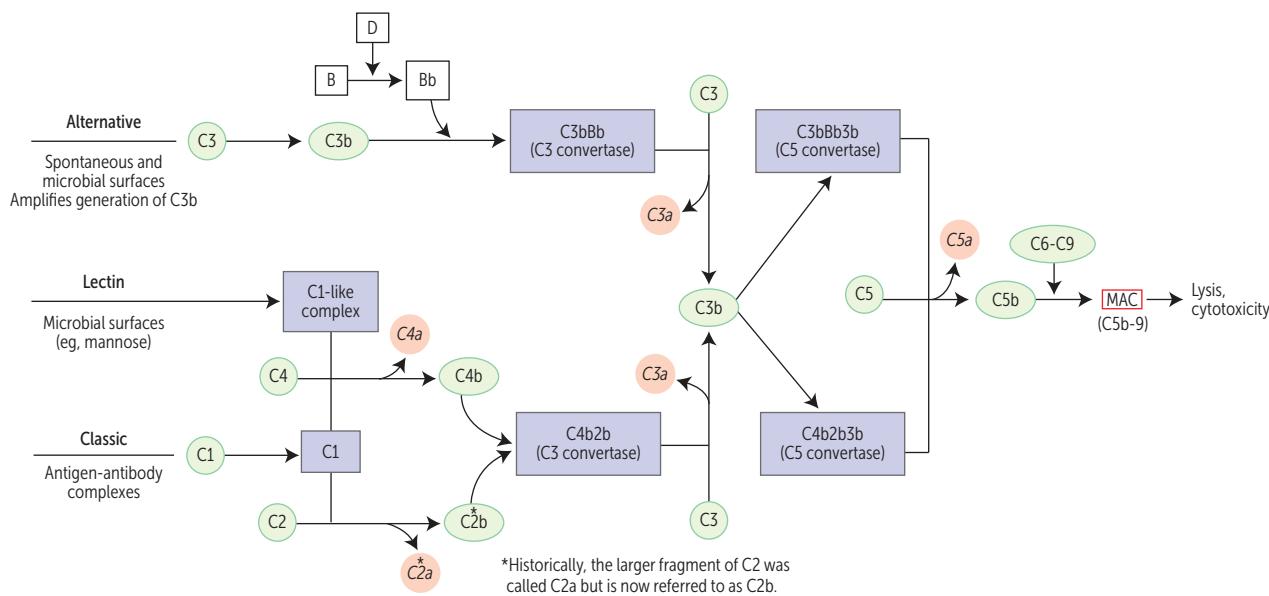
C3b—opsonization.  
C3a, C4a, C5a—anaphylaxis.  
C5a—neutrophil chemotaxis.  
**C5b-9** (MAC)—cytolysis.

C3b binds to lipopolysaccharides on **bacteria**.  
**MAC** complex is important for neutralizing **Neisseria** species. Deficiency results in recurrent infection.  
Get “**Neis**” (nice) Big **MAC**s from **5-9 pm**.

**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 Cl esterase inhibitor help prevent complement activation on self cells (eg, RBCs).



## Complement disorders

### Complement protein deficiencies

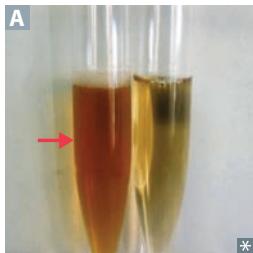
**Early complement deficiencies (C1-C4)** ↑ risk of severe, recurrent pyogenic sinus and respiratory tract infections. C3b used in clearance of antigen-antibody complexes → ↑ risk of **SLE** (think **SLEarly**).

**Terminal complement deficiencies (C5-C9)** ↑ susceptibility to recurrent *Neisseria* bacteremia.

### Complement regulatory protein deficiencies

**C1 esterase inhibitor deficiency** Causes hereditary angioedema due to unregulated activation of kallikrein → ↑ bradykinin. Characterized by ↓ C4 levels. ACE inhibitors are contraindicated (also ↑ bradykinin).

**Paroxysmal nocturnal hemoglobinuria** A defect in the *PIGA* gene prevents the formation of glycosylphosphatidylinositol (GPI) anchors for complement inhibitors, such as decay-accelerating factor (DAF/CD55) and membrane inhibitor of reactive lysis (MIRL/CD59). Causes complement-mediated intravascular hemolysis → ↓ haptoglobin, dark urine **A**. Can cause atypical venous thrombosis (eg, Budd-Chiari syndrome; portal vein, cerebral, or dermal thrombosis).



**Important cytokines**

SECRETED BY MACROPHAGES

**Interleukin-1**

Acute (IL-1, IL-6, TNF- $\alpha$ ), then recruit (IL-8, IL-12).

Causes fever, acute inflammation. Activates endothelium to express adhesion molecules. Induces chemokine secretion to recruit WBCs. Also called osteoclast-activating factor.

**"Hot T-bone stEAK":**

IL-1: fever (**hot**).  
 IL-2: stimulates **T** cells.  
 IL-3: stimulates **bone** marrow.  
 IL-4: stimulates Ig**E** production.  
 IL-5: stimulates Ig**A** production.  
 IL-6: stimulates a**K**ute-phase protein production.

**Interleukin-6**

Causes fever and stimulates production of acute-phase proteins.

**Tumor necrosis factor- $\alpha$** 

Activates endothelium. Causes WBC recruitment, vascular leak.

Causes cachexia in malignancy. Maintains granulomas in TB. IL-1, IL-6, TNF- $\alpha$  can mediate fever and sepsis.

**Interleukin-8**

Major chemotactic factor for neutrophils.

**"Clean up on aisle 8."** Neutrophils are recruited by **IL-8** to **clear** infections.

**Interleukin-12**

Induces differentiation of T cells into Th1 cells. Activates NK cells.

Facilitates granuloma formation in TB.

SECRETED BY T CELLS

**Interleukin-2**

Stimulates growth of helper, cytotoxic, and regulatory T cells, and NK cells.

**Interleukin-3**

Supports growth and differentiation of bone marrow stem cells. Functions like GM-CSF.

FROM Th1 CELLS

**Interferon- $\gamma$** 

Secreted by NK cells and T cells in response to antigen or IL-12 from macrophages; stimulates macrophages to kill phagocytosed pathogens. Inhibits differentiation of Th2 cells. Induces IgG isotype switching in B cells.

Also activates NK cells to kill virus-infected cells. Increases MHC expression and antigen presentation by all cells. Activates macrophages to induce granuloma formation.

FROM Th2 CELLS

**Interleukin-4**

Induces differentiation of T cells into Th (**helper**) 2 cells. Promotes growth of **B** cells. Enhances class switching to Ig**E** and Ig**G**.

Ain't too proud **2 BEG 4 help**.

**Interleukin-5**

Promotes growth and differentiation of **B** cells. Enhances class switching to Ig**A**. Stimulates growth and differentiation of Eosinophils.

I have **5 BAEs**.

**Interleukin-10**

Attenuates inflammatory response. Decreases expression of MHC class II and Th1 cytokines. Inhibits activated macrophages and dendritic cells. Also secreted by regulatory T cells.

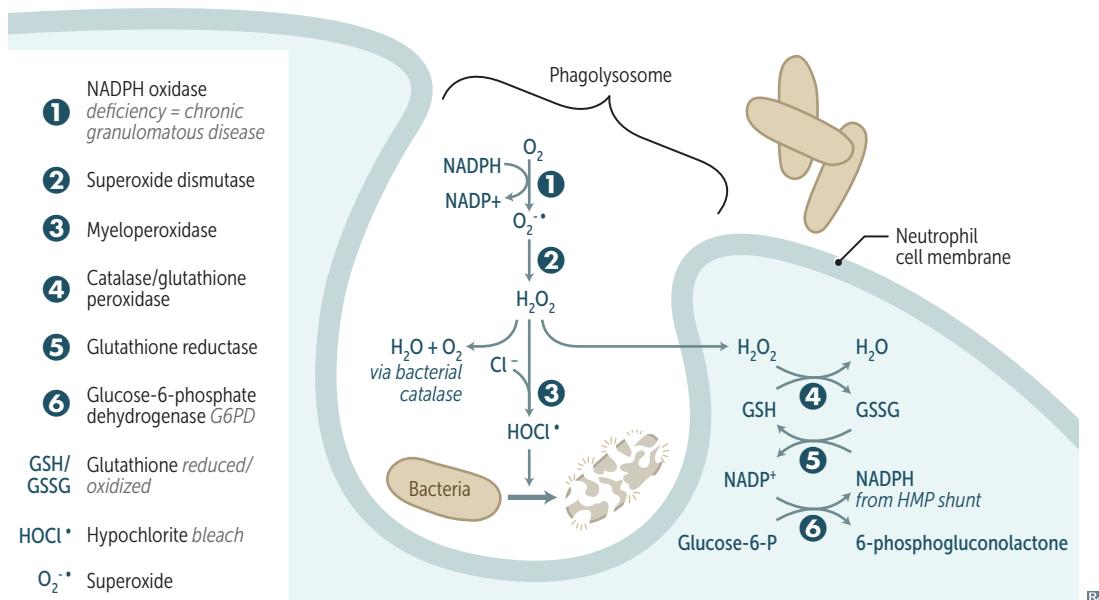
TGF- $\beta$  and IL-10 both attenuate the immune response.

**Interleukin-13**

Promotes IgE production by B cells. Induces alternative macrophage activation.

**Respiratory burst**

Also called oxidative burst. Involves the activation of the phagocyte NADPH oxidase complex (eg, in neutrophils, monocytes), which utilizes  $O_2$  as a substrate. Plays an important role in the immune response → rapid release of reactive oxygen species (ROS). NADPH plays a role in both the creation and neutralization of ROS. Myeloperoxidase contains a blue-green, heme-containing pigment that gives sputum its color.



Phagocytes of patients with CGD can utilize  $H_2O_2$  generated by invading organisms and convert it to ROS. Patients are at ↑ risk for infection by catalase + species (eg, *S aureus*, *Aspergillus*) capable of neutralizing their own  $H_2O_2$ , leaving phagocytes without ROS for fighting infections.

Pyocyanin of *P aeruginosa* generates ROS to kill competing pathogens. Oxidative burst also leads to  $K^+$  influx, which releases lysosomal enzymes. Lactoferrin is a protein found in secretory fluids and neutrophils that inhibits microbial growth via iron chelation.

**Interferons**

IFN- $\alpha$ , IFN- $\beta$ , IFN- $\gamma$

**MECHANISM**

A part of innate host defense, **interferons interfere** with both RNA and DNA viruses. Cells infected with a virus synthesize these glycoproteins, which act on local cells, priming them for viral defense by downregulating protein synthesis to resist potential viral replication and by upregulating MHC expression to facilitate recognition of infected cells. Also play a major role in activating antitumor immunity.

**CLINICAL USE**

Chronic HBV, Kaposi sarcoma, hairy cell leukemia, condyloma acuminatum, renal cell carcinoma, malignant melanoma, multiple sclerosis, chronic granulomatous disease.

**ADVERSE EFFECTS**

Flu-like symptoms, depression, neutropenia, myopathy, interferon-induced autoimmunity.

### Cell surface proteins

<b>T cells</b>	TCR (binds antigen-MHC complex) CD3 (associated with TCR for signal transduction) CD28 (binds B7 on APC)
<b>Helper T cells</b>	CD4, CD40L, CXCR4/CCR5 (co-receptors for HIV)
<b>Cytotoxic T cells</b>	CD8
<b>Regulatory T cells</b>	CD4, CD25
<b>B cells</b>	Ig (binds antigen) CD19, CD20, CD21 (receptor for Epstein-Barr virus), CD40 MHC II, B7
<b>Macrophages</b>	CD14 (receptor for PAMPs, eg, LPS), CD40 CCR5 MHC II, B7 (CD80/86) Fc and C3b receptors (enhanced phagocytosis)
<b>NK cells</b>	CD16 (binds Fc of IgG), CD56 (suggestive marker for NK)
<b>Hematopoietic stem cells</b>	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.

### Passive vs active immunity

	<b>Passive</b>	<b>Active</b>
MEANS OF ACQUISITION	Receiving preformed antibodies	Exposure to exogenous antigens
ONSET	Rapid	Slow
DURATION	Short span of antibodies (half-life = 3 weeks)	Long-lasting protection (memory)
EXAMPLES	IgA in breast milk, maternal IgG crossing placenta, antitoxin, humanized monoclonal antibody	Natural infection, vaccines, toxoid
NOTES	After exposure to tetanus toxin, HBV, varicella, rabies virus, botulinum toxin, or diphtheria toxin, unvaccinated patients are given preformed antibodies (passive)—“to Heal very rapidly before dying”	Combined passive and active immunizations can be given for hepatitis B or rabies exposure

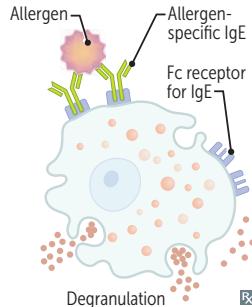
**Vaccination**

Induces an active immune response (humoral and/or cellular) to specific pathogens.

VACCINE TYPE	DESCRIPTION	PROS/CONS	EXAMPLES
<b>Live attenuated vaccine</b>	Microorganism rendered nonpathogenic but retains capacity for transient growth within inoculated host. Induces <b>cellular and humoral responses</b> . MMR and varicella vaccines can be given to people living with HIV without evidence of immunity if CD4 cell count $\geq 200$ cells/mm <sup>3</sup> .	Pros: induces strong, often lifelong immunity. Cons: may revert to virulent form. Contraindicated in pregnant and immunodeficient patients.	<b>A</b> drenovirus (nonattenuated, given to military recruits), <b>t</b> yphoid (Ty21a, oral), <b>p</b> olio (Sabin), <b>v</b> aricella (chickenpox), <b>s</b> mallpox, <b>BCG</b> , <b>y</b> ellow fever, <b>i</b> nfluenza (intranasal), <b>MMR</b> , <b>r</b> otavirus. <b>“Attention teachers! Please vaccinate <b>s</b>mall, <b>B</b>eautiful young <b>inf</b>ants with <b>MMR</b> regularly!”</b>
<b>Killed or inactivated vaccine</b>	Pathogen is inactivated by heat or chemicals. Maintaining epitope structure on surface antigens is important for immune response. Mainly induces a <b>humoral response</b> .	Pros: safer than live vaccines. Cons: weaker immune response; booster shots usually required.	Hepatitis <b>A</b> , <b>T</b> yphoid (Vi polysaccharide, intramuscular), <b>Rabies, <b>I</b>nfluenza, <b>P</b>olio (Sal<sup>K</sup>). <b>A TRIP could Kill you.</b></b>
<b>Subunit</b>	Includes only the antigens that best stimulate the immune system.	Pros: lower chance of adverse reactions. Cons: expensive, weaker immune response.	HBV (antigen = HBsAg), HPV (types 6, 11, 16, and 18), acellular pertussis (aP), <i>Neisseria meningitidis</i> (various strains), <i>Streptococcus pneumoniae</i> , <i>Haemophilus influenzae</i> type b.
<b>Toxoid</b>	Denatured bacterial toxin with an intact receptor binding site. Stimulates the immune system to make antibodies without potential for causing disease.	Pros: protects against the bacterial toxins. Cons: antitoxin levels decrease with time, may require a booster.	<i>Clostridium tetani</i> , <i>Corynebacterium diphtheriae</i> .

**Hypersensitivity types**

Four types (**ABCD**): **A**naphylactic and **A**topic (type I), **A**nti**B**ody-mediated (type II), **I**mune **C**omplex (type III), **D**elayed (cell-mediated, type IV). Types I, II, and III are all antibody-mediated.

**Type I hypersensitivity**

Anaphylactic and atopic—two phases:

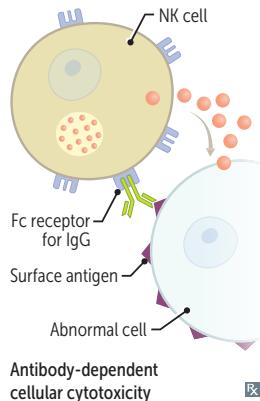
- Immediate (minutes): antigen crosslinks preformed IgE on presensitized mast cells → immediate degranulation → release of histamine (a vasoactive amine), tryptase (marker of mast cell activation), and leukotrienes.
- Late (hours): chemokines (attract inflammatory cells, eg, eosinophils) and other mediators from mast cells → inflammation and tissue damage.

**F**irst (type) and **F**ast (anaphylaxis).

Test: skin test or blood test (ELISA) for allergen-specific IgE.

Example:

- Anaphylaxis (eg, food, drug, or bee sting allergies)
- Allergic asthma

**Type II hypersensitivity**

Antibodies bind to cell-surface antigens → cellular destruction, inflammation, and cellular dysfunction.

Cellular destruction—cell is opsonized (coated) by antibodies, leading to either:

- Phagocytosis and/or activation of complement system.
- NK cell killing (antibody-dependent cellular cytotoxicity).

Inflammation—binding of antibodies to cell surfaces → activation of complement system and Fc receptor-mediated inflammation.

Cellular dysfunction—antibodies bind to cell surface receptors → abnormal blockade or activation of downstream process.

**D**irect Coombs test—detects antibodies attached **directly** to the RBC surface.

Indirect Coombs test—detects presence of unbound antibodies in the serum.

Examples:

- Autoimmune hemolytic anemia (including drug-induced form)
- Immune thrombocytopenia
- Transfusion reactions
- Hemolytic disease of the newborn

Examples:

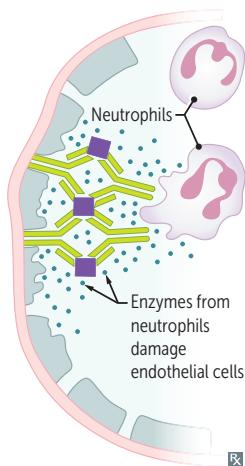
- Goodpasture syndrome
- Rheumatic fever
- Hyperacute transplant rejection

Examples:

- Myasthenia gravis
- Graves disease
- Pemphigus vulgaris

### Hypersensitivity types (continued)

#### Type III hypersensitivity



Immune complex—antigen-antibody (mostly IgG) complexes activate complement, which attracts neutrophils; neutrophils release lysosomal enzymes.

Can be associated with vasculitis and systemic manifestations.

In type **III** reaction, imagine an immune complex as **3** things stuck together: antigen-antibody-complement.

Examples:

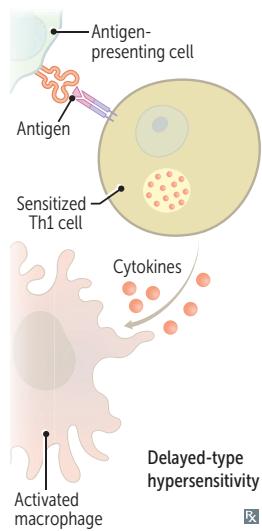
- SLE
- Rheumatoid arthritis
- Reactive arthritis
- Polyarteritis nodosa
- Poststreptococcal glomerulonephritis

Fever, urticaria, arthralgia, proteinuria, lymphadenopathy occur 1–2 weeks after antigen exposure. Serum sickness-like reactions are associated with some drugs (may act as haptens, eg, penicillin, monoclonal antibodies) and infections (eg, hepatitis B).

**Serum sickness**—the prototypic immune complex disease. Antibodies to foreign proteins are produced and 1–2 weeks later, antibody-antigen complexes form and deposit in tissues → complement activation → inflammation and tissue damage ( $\downarrow$  serum C3, C4).

**Arthus reaction**—a local subacute immune complex-mediated hypersensitivity reaction. Intradermal injection of antigen into a presensitized (has circulating IgG) individual leads to immune complex formation in the skin (eg, enhanced local reaction to a booster vaccination). Characterized by edema, fibrinoid necrosis, activation of complement.

#### Type IV hypersensitivity



Two mechanisms, each involving T cells:

1. Direct cell cytotoxicity: CD8+ cytotoxic T cells kill targeted cells.
2. Inflammatory reaction: effector CD4+ T cells recognize antigen and release inflammation-inducing cytokines (shown in illustration).

Response does not involve antibodies (vs types I, II, and III).

Examples:

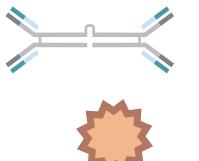
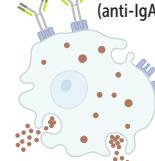
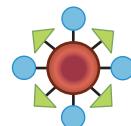
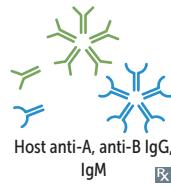
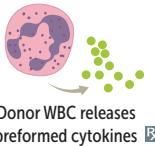
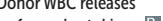
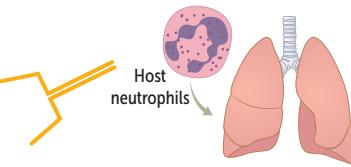
- Contact dermatitis (eg, poison ivy, nickel allergy)
- Graft-versus-host disease

Tests: PPD for TB infection; patch test for contact dermatitis; *Candida* skin test for T cell immune function.

**4T's:** **T** cells, **T**ransplant rejections, **T**B skin tests, **T**ouching (contact dermatitis).

**Fourth** (type) and **last** (delayed).

**Blood transfusion reactions**

TYPE	PATHOGENESIS	TIMING	CLINICAL PRESENTATION	DONOR BLOOD	HOST BLOOD
<b>Allergic/ anaphylactic reaction</b>	Type I hypersensitivity reaction against plasma proteins in transfused blood  IgA-deficient individuals should receive blood products without IgA	Within minutes to 2-3 hr (due to release of preformed inflammatory mediators in degranulating mast cells)	Allergies: urticaria, pruritus Anaphylaxis: wheezing, hypotension, respiratory arrest, shock	 Donor plasma proteins, including IgA	 Host mast cell 
<b>Acute hemolytic transfusion reaction</b>	Type II hypersensitivity reaction  Typically causes intravascular hemolysis (ABO blood group incompatibility)	During transfusion or within 24 hr (due to preformed antibodies)	Fever, hypotension, tachypnea, tachycardia, flank pain, hemoglobinuria (intravascular), jaundice (extravascular)	 Donor RBC with A and/or B group antigens	 Host anti-A, anti-B IgG, IgM 
<b>Febrile nonhemolytic transfusion reaction</b>	Cytokines created by donor WBCs accumulate during storage of blood products  Reactions prevented by leukoreduction of blood products	Within 1-6 hr (due to preformed cytokines)	Fever, headaches, chills, flushing More common in children	 Donor WBC releases preformed cytokines 	
<b>Transfusion- related acute lung injury</b>	Two-hit mechanism: <ul style="list-style-type: none"><li>▪ Neutrophils are sequestered and primed in pulmonary vasculature due to recipient risk factors</li><li>▪ Neutrophils are activated by a product (eg, antileukocyte antibodies) in the transfused blood and release inflammatory mediators → ↑ capillary permeability → pulmonary edema</li></ul>	Within minutes to 6 hr	Respiratory distress, noncardiogenic pulmonary edema	 Host neutrophils Donor antileukocyte IgG 	
<b>Delayed hemolytic transfusion reaction</b>	Anamnestic response to a foreign antigen on donor RBCs (Rh [D] or other minor blood group antigens) previously encountered by recipient  Typically causes extravascular hemolysis	Onset over 24 hr Usually presents within 1-2 wk (due to slow destruction by reticuloendothelial system)	Generally self limited and clinically silent Mild fever, hyperbilirubinemia	 Donor RBC with foreign antigens	 Host IgG 

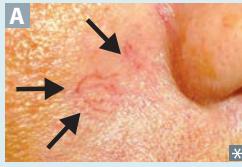
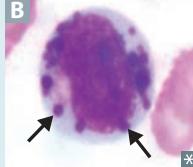
**Autoantibodies**

AUTOANTIBODY	ASSOCIATED DISORDER
Anti-postsynaptic ACh receptor	Myasthenia gravis
Anti-presynaptic voltage-gated calcium channel	Lambert-Eaton myasthenic syndrome
Anti- $\beta_2$ glycoprotein I	Antiphospholipid syndrome
Antinuclear (ANA)	Nonspecific screening antibody, often associated with SLE
Anticardiolipin, lupus anticoagulant	SLE, antiphospholipid syndrome
Anti-dsDNA, anti-Smith	SLE
Antihistone	Drug-induced lupus
Anti-U1 RNP (ribonucleoprotein)	Mixed connective tissue disease
Rheumatoid factor (IgM antibody against IgG Fc region), anti-CCP (more specific)	Rheumatoid arthritis
Anti-Ro/SSA, anti-La/SSB	Sjögren syndrome
Anti-Scl-70 (anti-DNA topoisomerase I)	Scleroderma (diffuse)
Anticentromere	Limited scleroderma (CREST syndrome)
Antisynthetase (eg, anti-Jo-1), anti-SRP, anti-helicase (anti-Mi-2)	Polymyositis, dermatomyositis
Antimitochondrial	1° biliary cholangitis
Anti-smooth muscle, anti-liver/kidney microsomal-I	Autoimmune hepatitis
Myeloperoxidase-antineutrophil cytoplasmic antibody (MPO-ANCA)/perinuclear ANCA (p-ANCA)	Microscopic polyangiitis, eosinophilic granulomatosis with polyangiitis, ulcerative colitis, 1° sclerosing cholangitis
PR3-ANCA/cytoplasmic ANCA (c-ANCA)	Granulomatosis with polyangiitis
Anti-phospholipase A <sub>2</sub> receptor	1° membranous nephropathy
Anti-hemidesmosome	Bullous pemphigoid
Anti-desmoglein (anti-desmosome)	Pemphigus vulgaris
Antithyroglobulin, antithyroid peroxidase (antimicrosomal)	Hashimoto thyroiditis
Anti-TSH receptor	Graves disease
IgA anti-endomysial, IgA anti-tissue transglutaminase, IgA and IgG deamidated gliadin peptide	Celiac disease
Anti-glutamic acid decarboxylase, islet cell cytoplasmic antibodies	Type 1 diabetes mellitus
Antiparietal cell, anti-intrinsic factor	Pernicious anemia
Anti-glomerular basement membrane	Goodpasture syndrome

**Immunodeficiencies**

DISEASE	DEFECT	PRESENTATION	FINDINGS
<b>B-cell disorders</b>			
<b>X-linked (Bruton) agammaglobulinemia</b>	Defect in <b>BTK</b> , a tyrosine kinase gene → no B-cell maturation; X-linked recessive (↑ in Boys)	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 (1° follicles and germinal centers absent) → live vaccines contraindicated
<b>Selective IgA deficiency</b>	Cause unknown Most common 1° immunodeficiency	Majority <b>Asymptomatic</b> Can see <b>Airway</b> and <b>GI</b> infections, <b>Autoimmune</b> disease, <b>Atopy</b> , <b>Anaphylaxis</b> to IgA in blood products	↓ IgA with normal IgG, IgM levels ↑ susceptibility to giardiasis Can cause false-negative celiac disease test
<b>Common variable immunodeficiency</b>	Defect in B-cell differentiation. Cause unknown in most cases	May present in childhood but usually diagnosed after puberty ↑ risk of autoimmune disease, bronchiectasis, lymphoma, sinopulmonary infections	↓ plasma cells, ↓ immunoglobulins
<b>T-cell disorders</b>			
<b>Thymic aplasia</b>	<b>22q11</b> microdeletion; failure to develop 3rd and 4th pharyngeal pouches → absent thymus and parathyroids <b>DiGeorge syndrome</b> —thymic, parathyroid, cardiac defects <b>Velocardiofacial syndrome</b> —palate, facial, cardiac defects	<b>CATCH-22:</b> Cardiac defects (conotruncal abnormalities [eg, tetralogy of Fallot, truncus arteriosus]), <b>Abnormal facies</b> , <b>Thymic hypoplasia</b> → T-cell deficiency (recurrent viral/fungal infections), <b>Cleft palate</b> , <b>Hypocalcemia</b> 2° to parathyroid aplasia → tetany	↓ T cells, ↓ PTH, ↓ Ca <sup>2+</sup> Thymic shadow absent on CXR
<b>IL-12 receptor deficiency</b>	↓ Th1 response; autosomal recessive	Disseminated mycobacterial and fungal infections; may present after administration of BCG vaccine	↓ IFN-γ Most common cause of Mendelian susceptibility to mycobacterial diseases (MSMD)
<b>Autosomal dominant hyper-IgE syndrome (Job syndrome)</b>	Deficiency of Th17 cells due to <b>STAT3</b> mutation → impaired recruitment of neutrophils to sites of infection	Cold (noninflamed) staphylococcal <b>Abscesses</b> , retained <b>Baby teeth</b> , <b>Coarse</b> facies, <b>Dermatologic</b> problems (eczema), ↑ IgE, bone <b>Fractures</b> from minor trauma	↑ IgE ↑ eosinophils Learn the <b>ABCDEF</b> 's to get a <b>Job!</b>
<b>Chronic mucocutaneous candidiasis</b>	T-cell dysfunction Impaired cell-mediated immunity against <i>Candida</i> sp Classic form caused by defects in <b>AIRE</b>	Persistent 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>B- and T-cell disorders</b>			
<b>Severe combined immunodeficiency</b>	Several types including defective IL-2R gamma chain (most common, X-linked recessive); adenosine deaminase deficiency (autosomal recessive); RAG mutation → VDJ recombination defect	Failure to thrive, chronic diarrhea, thrush Recurrent viral, bacterial, fungal, and protozoal infections	↓ T-cell receptor excision circles (TRECs) Part of newborn screening for SCID Absence of thymic shadow (CXR), germinal centers (lymph node biopsy), and T cells (flow cytometry)
<b>Ataxia-telangiectasia</b> 	Defects in ATM gene → failure to detect DNA damage → failure to halt progression of cell cycle → mutations accumulate; autosomal recessive	Triad: cerebellar defects (Ataxia), spider Angiomas (telangiectasia A), IgA deficiency ↑↑ sensitivity to radiation (limit x-ray exposure)	↑ AFP ↓ IgA, IgG, and IgE Lymphopenia, cerebellar atrophy ↑ risk of lymphoma and leukemia
<b>Hyper-IgM syndrome</b>	Most commonly due to defective CD40L on Th cells → class switching defect; X-linked recessive	Severe pyogenic infections early in life; opportunistic infection with <i>Pneumocystis</i> , <i>Cryptosporidium</i> , CMV	Normal or ↑ IgM ↓ IgG, IgA, IgE Failure to make germinal centers
<b>Wiskott-Aldrich syndrome</b>	Mutation in WAS gene; leukocytes and platelets unable to reorganize actin cytoskeleton → defective antigen presentation; X-linked recessive	<b>WATER:</b> Wiskott-Aldrich: Thrombocytopenia, Eczema, Recurrent (pyogenic) infections ↑ risk of autoimmune disease and malignancy	↓ to normal IgG, IgM ↑ IgE, IgA Fewer and smaller platelets
<b>Phagocyte dysfunction</b>			
<b>Leukocyte adhesion deficiency (type 1)</b>	Defect in LFA-1 integrin (CD18) protein on phagocytes; impaired migration and chemotaxis; autosomal recessive	Late separation (>30 days) of umbilical cord, absent pus, dysfunctional neutrophils → recurrent skin and mucosal bacterial infections	↑ neutrophils in blood Absence of neutrophils at infection sites → impaired wound healing
<b>Chédiak-Higashi syndrome</b> 	Defect in lysosomal trafficking regulator gene (LYST) Microtubule dysfunction in phagosome-lysosome fusion; autosomal recessive	<b>PLAIN:</b> Progressive neurodegeneration, Lymphohistiocytosis, Albinism (partial), recurrent pyogenic Infections, peripheral Neuropathy	Giant granules (B, arrows) in granulocytes and platelets Pancytopenia Mild coagulation defects
<b>Chronic granulomatous disease</b>	Defect of NADPH oxidase → ↓ reactive oxygen species (eg, superoxide) and ↓ respiratory burst in neutrophils; X-linked form most common	↑ susceptibility to catalase + organisms Recurrent infections and granulomas	Abnormal dihydrorhodamine (flow cytometry) test (↓ green fluorescence) Nitroblue tetrazolium dye reduction test (obsolete) fails to turn blue

**Infections in immunodeficiency**

PATHOGEN	↓ T CELLS	↓ B CELLS	↓ GRANULOCYTES	↓ COMPLEMENT
<b>Bacteria</b>	Sepsis	Encapsulated (Please SHINE my SKiS): <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 <i>Streptococcus</i>	Some Bacteria Produce No Serious granules: <i>Staphylococcus,</i> <i>Burkholderia cepacia,</i> <i>Pseudomonas aeruginosa,</i> <i>Nocardia,</i> <i>Serratia</i>	Encapsulated species with early complement deficiencies Neisseria with late complement (C5–C9) deficiencies
<b>Viruses</b>	CMV, EBV, JC virus, VZV, chronic infection with respiratory/GI viruses	Enteroviral encephalitis, poliovirus (live vaccine contraindicated)	N/A	N/A
<b>Fungi/parasites</b>	<i>Candida</i> (local), PCP, <i>Cryptococcus</i>	GI giardiasis (no IgA)	<i>Candida</i> (systemic), <i>Aspergillus, Mucor</i>	N/A

Note: B-cell deficiencies tend to produce recurrent bacterial infections, whereas T-cell deficiencies produce more fungal and viral infections.

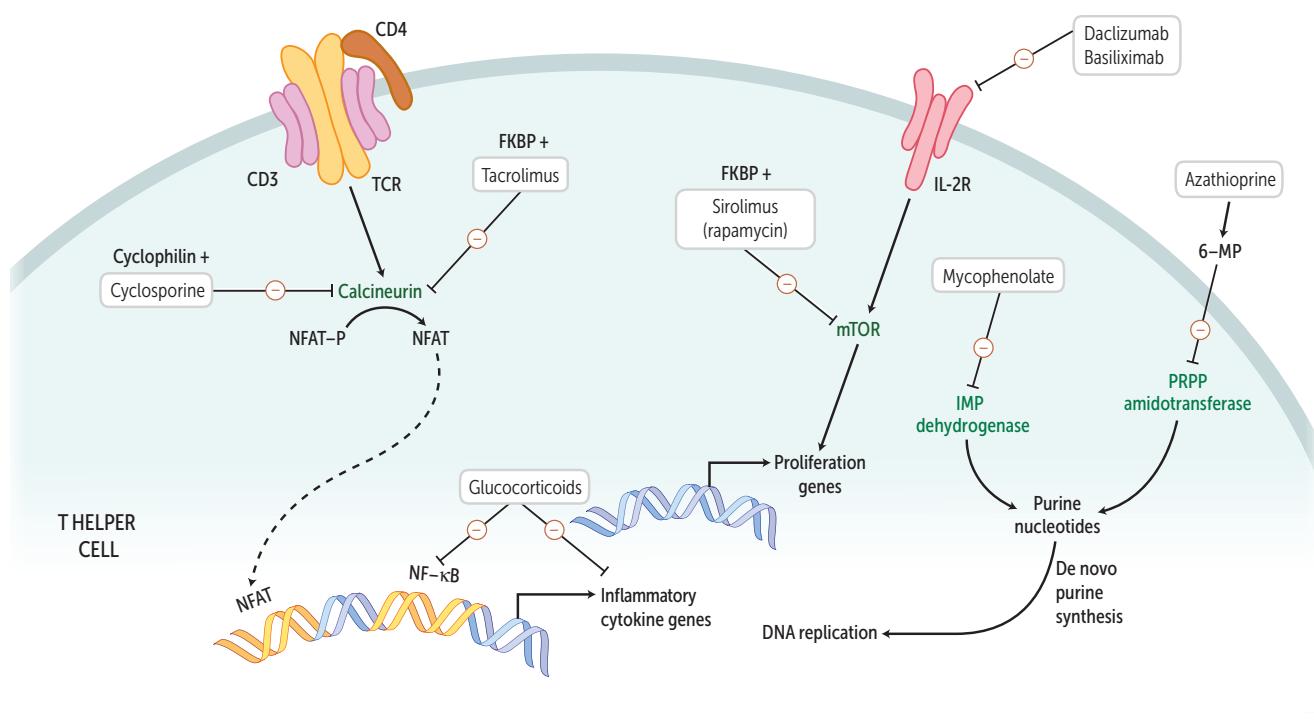
**Transplant rejection**

TYPE OF REJECTION	ONSET	PATHOGENESIS	FEATURES
<b>Hyperacute</b>	Within minutes	Pre-existing recipient antibodies react to donor antigen (type II hypersensitivity reaction), activate complement	Widespread thrombosis of graft vessels (arrows within glomerulus <b>A</b> ) → ischemia and fibrinoid necrosis Graft must be removed
<b>Acute</b>	Weeks to months	Cellular: CD8+ T cells and/or CD4+ T cells activated against donor MHCs (type IV hypersensitivity reaction) Humoral: similar to hyperacute, except antibodies develop after transplant (associated with C4d deposition)	Vasculitis of graft vessels with dense interstitial lymphocytic infiltrate <b>B</b> Prevent/reverse with immunosuppressants
<b>Chronic</b>	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 <b>C</b> Organ-specific examples: <ul style="list-style-type: none"> <li>▪ Chronic allograft nephropathy</li> <li>▪ Bronchiolitis obliterans</li> <li>▪ Accelerated atherosclerosis (heart)</li> <li>▪ Vanishing bile duct syndrome</li> </ul>
<b>Graft-versus-host disease</b>	Varies	Grafted immunocompetent T cells proliferate in the immunocompromised host and reject host cells with “foreign” proteins → severe organ dysfunction Type IV hypersensitivity reaction	Maculopapular rash, jaundice, diarrhea, hepatosplenomegaly Usually in bone marrow and liver transplants (rich in lymphocytes) Potentially beneficial in bone marrow transplant for leukemia (graft-versus-tumor effect) For patients who are immunocompromised, irradiate blood products prior to transfusion to prevent GVHD

## ► IMMUNOLOGY—IMMUNOSUPPRESSANTS

**Immunosuppressants** Agents that block lymphocyte activation and proliferation. Reduce acute transplant rejection by suppressing cellular immunity (used as prophylaxis). Frequently combined to achieve greater efficacy with ↓ toxicity. Chronic suppression ↑ risk of infection and malignancy.

DRUG	MECHANISM	INDICATIONS	TOXICITY	NOTES
<b>Cyclosporine</b>	Calcineurin inhibitor; binds cyclophilin Blocks T-cell activation by preventing IL-2 transcription	Psoriasis, rheumatoid arthritis	Nephrotoxicity, hypertension, hyperlipidemia, neurotoxicity, gingival hyperplasia, hirsutism	Both calcineurin inhibitors are highly nephrotoxic, especially in higher doses or in patients with ↓ renal function
<b>Tacrolimus (FK506)</b>	Calcineurin inhibitor; binds FK506 binding protein (FKBP) Blocks T-cell activation by preventing IL-2 transcription	Immunosuppression after solid organ transplant	Similar to cyclosporine, ↑ risk of diabetes and neurotoxicity; no gingival hyperplasia or hirsutism	
<b>Sirolimus (Rapamycin)</b>	mTOR inhibitor; binds FKBP Blocks T-cell activation and B-cell differentiation by preventing response to IL-2	Kidney transplant rejection prophylaxis specifically Sir Basil's kidney transplant	"Pansirtopenia" (pancytopenia), insulin resistance, hyperlipidemia; <b>not nephrotoxic</b>	Kidney "sir-vives." Synergistic with cyclosporine Also used in drug-eluting stents
<b>Basiliximab</b>	Monoclonal antibody; blocks IL-2R		Edema, hypertension, tremor	
<b>Azathioprine</b>	Antimetabolite precursor of 6-mercaptopurine Inhibits lymphocyte proliferation by blocking nucleotide synthesis	Rheumatoid arthritis, Crohn disease, glomerulonephritis, other autoimmune conditions	Pancytopenia	6-MP degraded by xanthine oxidase; toxicity ↑ by allopurinol Pronounce "azathio-purine"
<b>Mycophenolate Mofetil</b>	Reversibly inhibits IMP dehydrogenase, preventing purine synthesis of B and T cells	Glucocorticoid-sparing agent in rheumatic disease	GI upset, pancytopenia, hypertension, hyperglycemia Less nephrotoxic and neurotoxic	Associated with invasive CMV infection
<b>Glucocorticoids</b>	Inhibit NF-κB Suppress both B- and T-cell function by ↓ transcription of many cytokines Induce T cell apoptosis	Many autoimmune and inflammatory disorders, adrenal insufficiency, asthma, CLL, non-Hodgkin lymphoma	Cushing syndrome, osteoporosis, hyperglycemia, diabetes, amenorrhea, adrenocortical atrophy, peptic ulcers, psychosis, cataracts, avascular necrosis (femoral head)	Demargination of WBCs causes artificial leukocytosis Adrenal insufficiency may develop if drug is stopped abruptly after chronic use

**Immunosuppression targets****Recombinant cytokines and clinical uses**

CYTOKINE	AGENT	CLINICAL USES
<b>Bone marrow stimulation</b>		
Erythropoietin	Epoetin alfa (EPO analog)	Anemias (especially in renal failure) Associated with ↑ risk of hypertension, thromboembolic events
Colony stimulating factors	Filgrastim (G-CSF), Sargramostim (GM-CSF)	Leukopenia; recovery of granulocyte and monocyte counts
Thrombopoietin	Romiplostim (TPO analog), eltrombopag (think “elthrombopag.” TPO receptor agonist)	Autoimmune thrombocytopenia Platelet stimulator
<b>Immunotherapy</b>		
Toll-like receptor 7	Imiquimod	Anogenital warts, actinic keratosis
Interleukin-2	Aldesleukin	Renal cell carcinoma, metastatic melanoma
Interferons	IFN- $\alpha$  IFN- $\beta$  IFN- $\gamma$	Chronic hepatitis C (not preferred) and B, renal cell carcinoma  Multiple sclerosis  Chronic granulomatous disease

**Therapeutic antibodies**

AGENT	TARGET	CLINICAL USE	NOTES
<b>Autoimmune disease therapy</b>			
<b>Adalimumab, infliximab</b>	Soluble TNF- $\alpha$	IBD, rheumatoid arthritis, ankylosing spondylitis, psoriasis	Screen patients for TB due to risk of reactivation Etanercept is a decoy TNF- $\alpha$ receptor and not a monoclonal antibody
<b>Eculizumab</b>	Complement protein C5	Paroxysmal nocturnal hemoglobinuria	
<b>Guselkumab</b>	IL-23	Psoriasis	
<b>Ixekizumab, secukinumab</b>	IL-17A	Psoriasis, psoriatic arthritis	
<b>Natalizumab</b>	$\alpha$ 4-integrin	Multiple sclerosis, Crohn disease	$\alpha$ 4-integrin: WBC adhesion Risk of PML in patients with JC virus
<b>Ustekinumab</b>	IL-12/IL-23	Psoriasis, psoriatic arthritis	
<b>Vedolizumab</b>	$\alpha$ 4-integrin	IBD	Gut-specific anti-integrin, preventing migration of leukocytes to the gastrointestinal tract
<b>Other applications</b>			
<b>Denosumab</b>	RANKL	Osteoporosis; inhibits osteoclast maturation (mimics osteoprotegerin)	<b>Denosumab</b> helps make <b>dense</b> bones
<b>Emicizumab</b>	Factor IXa and X	Hemophilia A	Bispecific; mimics factor VIII
<b>Omalizumab</b>	IgE	Refractory allergic asthma; prevents IgE binding to Fc $\epsilon$ RI	
<b>Palivizumab</b>	RSV F protein	RSV prophylaxis for high-risk infants	<b>Palivizumab</b> —virus

# HIGH-YIELD PRINCIPLES IN

# Microbiology

*“Support bacteria. They’re the only culture some people have.”*

—Steven Wright

*“What lies behind us and what lies ahead of us are tiny matters compared to what lies within us.”*

—Henry S. Haskins

*“Wise and humane management of the patient is the best safeguard against infection.”*

—Florence Nightingale

*“I sing and play the guitar, and I’m a walking, talking bacterial infection.”*

—Kurt Cobain

Microbiology questions on the Step 1 exam often require two (or more) steps: Given a certain clinical presentation, you will first need to identify the most likely causative organism, and you will then need to provide an answer regarding some features of that organism or relevant antimicrobial agents. For example, a description of a child with fever and a petechial rash will be followed by a question that reads, “From what site does the responsible organism usually enter the blood?”

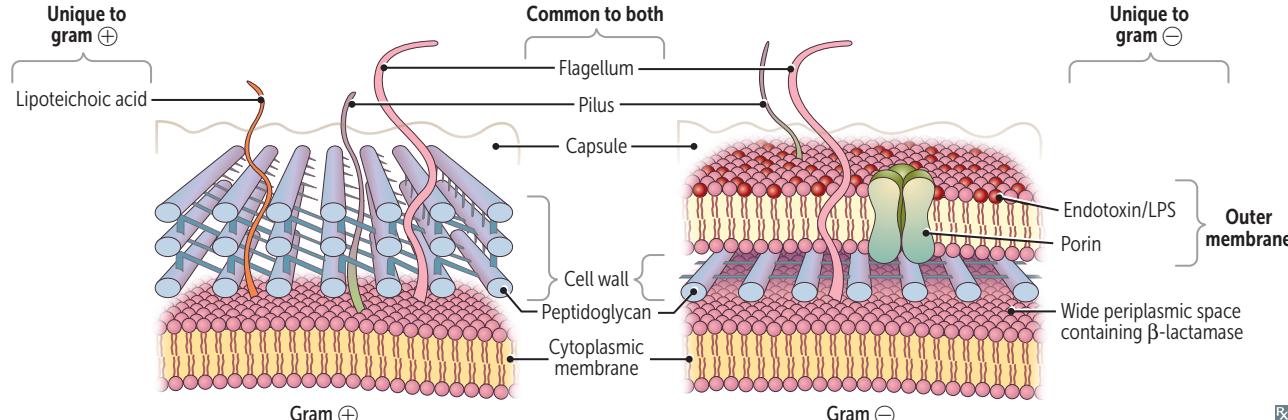
This section therefore presents organisms in two major ways: in individual microbial “profiles” and in the context of the systems they infect and the clinical presentations they produce. You should become familiar with both formats. When reviewing the systems approach, remind yourself of the features of each microbe by returning to the individual profiles. Also be sure to memorize the laboratory characteristics that allow you to identify microbes.

► Basic Bacteriology	124
► Clinical Bacteriology	134
► Mycology	151
► Parasitology	155
► Virology	162
► Systems	178
► Antimicrobials	187

## ► MICROBIOLOGY—BASIC BACTERIOLOGY

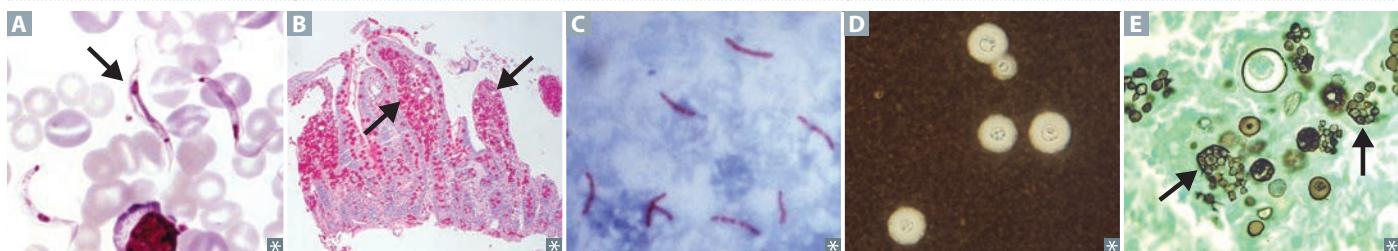
**Bacterial structures**

STRUCTURE	CHEMICAL COMPOSITION	FUNCTION
<b>Appendages</b>		
<b>Flagellum</b>	Proteins	Motility
<b>Pilus/fimbria</b>	Glycoprotein	Mediate adherence of bacteria to cell surface; sex pilus forms during conjugation
<b>Specialized structures</b>		
<b>Spore</b>	Keratin-like coat; dipicolinic acid; peptidoglycan, DNA	Gram $\oplus$ only Survival: resist dehydration, heat, chemicals
<b>Cell envelope</b>		
<b>Capsule</b>	Discrete layer usually made of polysaccharides (and rarely proteins)	Protects against phagocytosis
<b>Slime (S) layer</b>	Loose network of polysaccharides	Mediates adherence to surfaces, plays a role in biofilm formation (eg, indwelling catheters)
<b>Outer membrane</b>	Outer leaflet: contains endotoxin (LPS/LOS) Embedded proteins: porins and other outer membrane proteins (OMPs) Inner leaflet: phospholipids	Gram $\ominus$ only Endotoxin: lipid A induces TNF and IL-1; antigenic O polysaccharide component Most OMPs are antigenic Porins: transport across outer membrane
<b>Periplasm</b>	Space between cytoplasmic membrane and outer membrane in gram $\ominus$ bacteria (peptidoglycan in middle)	Accumulates components exiting gram $\ominus$ cells, including hydrolytic enzymes (eg, $\beta$ -lactamases)
<b>Cell wall</b>	Peptidoglycan is a sugar backbone with peptide side chains cross-linked by transpeptidase	Net-like structure gives rigid support, protects against osmotic pressure damage
<b>Cytoplasmic membrane</b>	Phospholipid bilayer sac with embedded proteins (eg, penicillin-binding proteins [PBPs]) and other enzymes Lipoteichoic acids (gram <b>positive</b> ) only extend from membrane to exterior	Site of oxidative and transport enzymes; PBPs involved in cell wall synthesis Lipoteichoic acids induce TNF- $\alpha$ and IL-1

**Cell envelope**

**Stains**

<b>Gram stain</b>	First-line lab test in bacterial identification. Bacteria with thick peptidoglycan layer retain crystal violet dye (gram $\oplus$ ); bacteria with thin peptidoglycan layer turn red or pink (gram $\ominus$ ) with counterstain. These bugs do not Gram stain well (These Little Microbes May Unfortunately Lack Real Color But Are Everywhere):	
	<i>Treponema, Leptospira</i>	Too thin to be visualized
	<i>Mycobacteria</i>	Cell wall has high lipid content
	<i>Mycoplasma, Ureaplasma</i>	No cell wall
	<i>Legionella, Rickettsia, Chlamydia, Bartonella, Anaplasma, Ehrlichia</i>	Primarily intracellular; also, <i>Chlamydia</i> lack classic peptidoglycan because of $\downarrow$ muramic acid
<b>Giems stain</b>	<i>Chlamydia, Rickettsia, Trypanosomes A, Borrelia, Helicobacter pylori, Plasmodium</i>	<b>Clumsy Rick Tripped on a Borrowed Helicopter Plastered in Gems</b>
<b>Periodic acid-Schiff stain</b>	Stains <b>glycogen</b> , mucopolysaccharides; used to diagnose Whipple disease ( <i>Tropheryma whipplei</i> B)	<b>PaSs the sugar</b>
<b>Ziehl-Neelsen stain (carbol fuchsin)</b>	Acid-fast bacteria (eg, <i>Mycobacteria</i> C, <i>Nocardia</i> ; stains mycolic acid in cell wall); protozoa (eg, <i>Cryptosporidium</i> oocysts)	Auramine-rhodamine stain is more often used for screening (inexpensive, more sensitive)
<b>India ink stain</b>	<i>Cryptococcus neoformans</i> D; mucicarmine can also be used to stain thick polysaccharide capsule red	
<b>Silver stain</b>	Fungi (eg, <i>Coccidioides</i> E, <i>Pneumocystis jirovecii</i> ), <i>Legionella</i> , <i>Helicobacter pylori</i>	
<b>Fluorescent antibody stain</b>	Used to identify many bacteria, viruses, <i>Pneumocystis jirovecii</i> , <i>Giardia</i> , and <i>Cryptosporidium</i>	Example is FTA-ABS for syphilis



**Properties of growth****media****Selective media**

The same type of media can possess both (or neither) of these properties.

**Indicator (differential) media**

Favors the growth of particular organism while preventing growth of other organisms. Example: Thayer-Martin agar contains antibiotics that allow the selective growth of *Neisseria* by inhibiting the growth of other sensitive organisms.

Yields a color change in response to the metabolism of certain organisms. Example: MacConkey agar contains a pH indicator; a lactose fermenter like *E coli* will convert lactose to acidic metabolites → color changes to pink.

**Special culture requirements**

BUG	MEDIA USED FOR ISOLATION	MEDIA CONTENTS/OTHER
<i>H influenzae</i>	Chocolate agar	Factors V ( $\text{NAD}^+$ ) 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 ( <b>Bordet</b> for <i>Bordetella</i> ) Regan-Lowe medium	Potato extract Charcoal, blood, and antibiotic
<i>C diphtheriae</i>	Tellurite agar, Löffler medium	
<i>M tuberculosis</i>	Löwenstein-Jensen medium, Middlebrook medium, rapid automated broth cultures	
<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>Brucella</i> , <i>Francisella</i> , <i>Legionella</i> , <i>Pasteurella</i>	<b>Charcoal</b> yeast extract agar buffered with cysteine and iron	The <b>Ella</b> siblings, <b>Bruce</b> , <b>Francis</b> , a <b>legionnaire</b> , and a <b>pasteur</b> (pastor), built the Sistine ( <b>cysteine</b> ) chapel out of <b>charcoal</b> and <b>iron</b>
Fungi	<b>Sabouraud</b> agar	"Sab's a <b>fun guy!</b> "

**Aerobes**

Use an  $\text{O}_2$ -dependent system to generate ATP.

Examples include *Nocardia*, *Pseudomonas aeruginosa*, *Mycobacterium tuberculosis*, and *Bordetella pertussis*.

Reactivation of *M tuberculosis* (eg, after immunocompromise or TNF- $\alpha$  inhibitor use) has a predilection for the apices of the lung.

**Anaerobes**

Examples include *Clostridium*, *Bacteroides*, *Fusobacterium*, and *Actinomyces israelii*. 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 ( $\text{CO}_2$  and  $\text{H}_2$ ).

**Facultative anaerobes**

May use  $\text{O}_2$  as a terminal electron acceptor to generate ATP, but can also use fermentation and other  $\text{O}_2$ -independent pathways.

Anaerobes Can't Breathe Fresh Air.

Anaerobes are normal flora in GI tract, typically pathogenic elsewhere. Amin $\text{O}_2$ glycosides are ineffective against anaerobes because these antibiotics require  $\text{O}_2$  to enter into bacterial cell.

**Intracellular bacteria****Obligate intracellular**

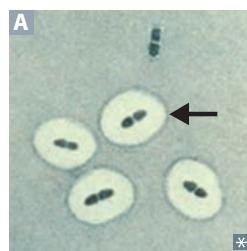
*Rickettsia*, *Chlamydia*, *Coxiella*  
Rely on host ATP

Stay inside (cells) when it is Really Chilly and Cold

**Facultative intracellular**

*Salmonella*, *Neisseria*, *Brucella*, *Mycobacterium*,  
*Listeria*, *Francisella*, *Legionella*, *Yersinia pestis*

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. Asplenics (No Spleen Here) have ↓ opsonizing ability and thus ↑ risk for severe infections; need vaccines to protect against:

- *N meningitidis*
- *S pneumoniae*
- *H influenzae*

**Encapsulated bacteria vaccines**

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

Pneumococcal vaccines: PCV13 (pneumococcal conjugate vaccine), PPSV23 (pneumococcal polysaccharide vaccine with no conjugated protein).

*H influenzae* type b (conjugate vaccine).

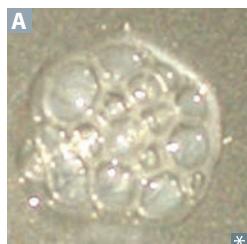
Meningococcal vaccine (conjugate vaccine).

**Urease-positive organisms**

*Proteus*, *Cryptococcus*, *H pylori*, *Ureaplasma*, *Nocardia*, *Klebsiella*, *S epidermidis*, *S saprophyticus*. Urease hydrolyzes urea to release ammonia and  $\text{CO}_2 \rightarrow \uparrow \text{pH}$ . Predisposes to struvite (magnesium ammonium phosphate) stones, particularly *Proteus*.

Pee CHUNKSS.

### Catalase-positive organisms



Catalase degrades H<sub>2</sub>O<sub>2</sub> into H<sub>2</sub>O and bubbles of O<sub>2</sub> **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  $\oplus$  organisms.

Examples: *Nocardia*, *Staphylococci*, *Serratia*, *Candida*, *Listeria*, *E coli*, *Burkholderia cepacia*, *Pseudomonas*, *Aspergillus*, *Helicobacter pylori*, *Bordetella pertussis*.

### Pigment-producing bacteria

*Actinomyces israelii*—yellow “sulfur” granules, which are composed of filaments of bacteria

Israel has yellow sand

*S aureus*—golden yellow pigment

*Aureus* (Latin) = gold

*P aeruginosa*—blue-green pigment (pyocyanin and pyoverdin)

Aerugula is green

*Serratia marcescens*—red pigment

Think red Sriracha hot sauce

### In vivo biofilm-producing bacteria

*S epidermidis*

Catheter and prosthetic device infections

Viridans streptococci (*S mutans*, *S sanguinis*)

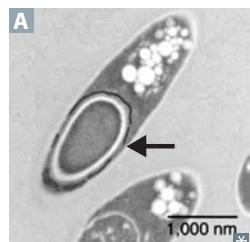
Dental plaques, infective endocarditis

*P aeruginosa*

Respiratory tree colonization in patients with cystic fibrosis, ventilator-associated pneumonia  
Contact lens–associated keratitis

Nontypeable (unencapsulated) *H influenzae*

Otitis media

**Spore-forming bacteria**

Some gram  $\oplus$  bacteria can form spores **A** when nutrients are limited. Spores lack metabolic activity and are highly resistant to heat and chemicals. Core contains dipicolinic acid (responsible for heat resistance). Must autoclave to kill spores (as is done to surgical equipment) by steaming at 121°C for 15 minutes. Hydrogen peroxide and iodine-based agents are also sporicidal.

Examples: *B anthracis* (anthrax), *B cereus* (food poisoning), *C botulinum* (botulism), *C difficile* (pseudomembranous colitis), *C perfringens* (gas gangrene), *C tetani* (tetanus).

**Bacterial virulence factors****Protein A**

These promote evasion of host immune response.

Binds Fc region of IgG. Prevents opsonization and phagocytosis. Expressed by *S aureus*.

**IgA protease**

Enzyme that cleaves IgA, allowing bacteria to adhere to and colonize mucous membranes. Secreted by *S pneumoniae*, *H influenzae* type b, and *Neisseria* (SHiN).

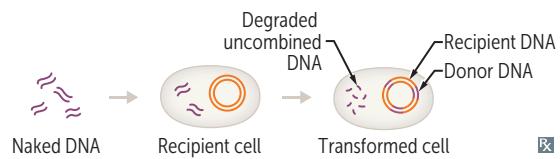
**M protein**

Helps prevent phagocytosis. Expressed by group A streptococci. Sequence homology with human tropomyosin and myosin (molecular mimicry); possibly underlies the autoimmune response seen in acute rheumatic fever.

## Bacterial genetics

### Transformation

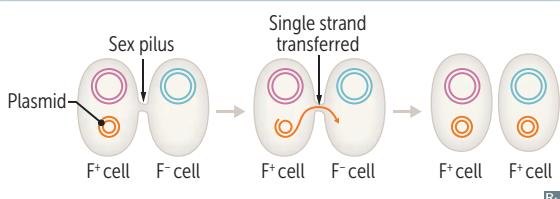
Competent bacteria can bind and import short pieces of environmental naked bacterial chromosomal DNA (from bacterial cell lysis). The transfer and expression of newly transferred genes is called transformation. A feature of many bacteria, especially *S. pneumoniae*, *H. influenzae* type b, and *Neisseria* (**SHiN**). Adding deoxyribonuclease degrades naked DNA, preventing transformation.



### Conjugation

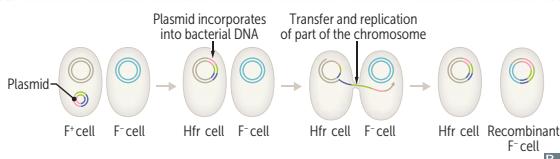
#### $F^+ \times F^-$

$F^+$  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.



#### $Hfr \times F^-$

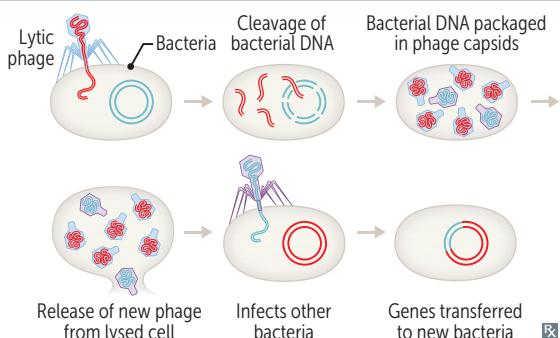
$F^+$  plasmid can become incorporated into bacterial chromosomal DNA, termed high-frequency recombination ( $Hfr$ ) cell. Transfer of leading part of plasmid and a few flanking chromosomal genes. High-frequency recombination may integrate some of those bacterial genes. Recipient cell remains  $F^-$  but now may have new bacterial genes.



### Transduction

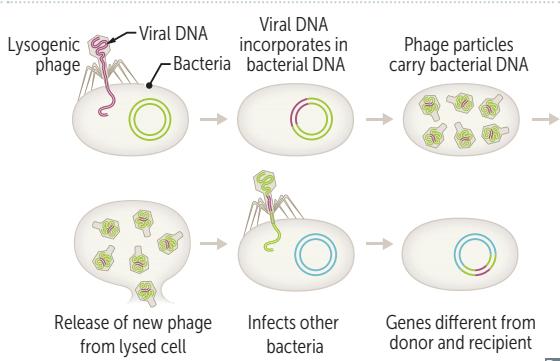
#### Generalized

A "packaging" error. Lytic phage infects 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.



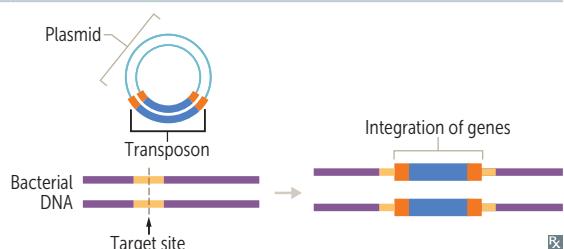
#### Specialized

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.

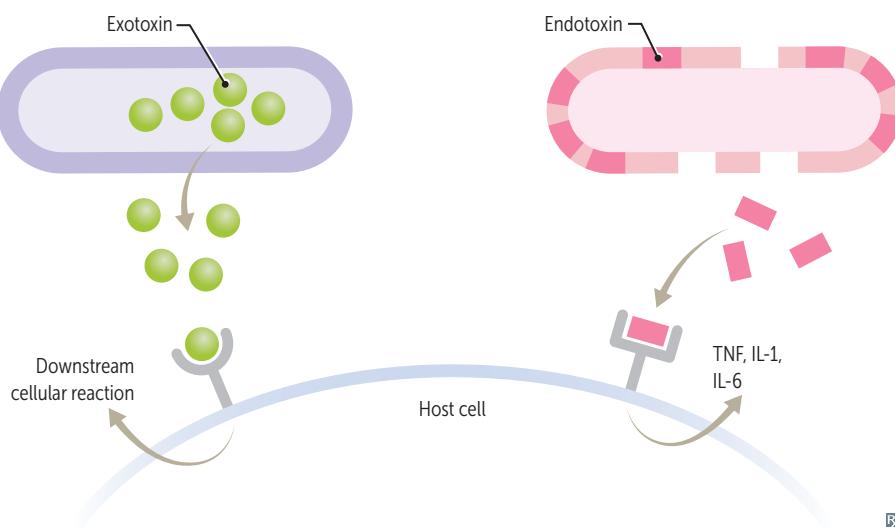


**Bacterial genetics (continued)****Transposition**

A “jumping” process involving a transposon (specialized segment of DNA), which can copy and excise itself and then insert into the same DNA molecule or an unrelated DNA (eg, plasmid or chromosome). Critical in creating plasmids with multiple drug resistance and transfer across species lines (eg, Tn1546 with *vanA* from *Enterococcus* to *S aureus*).

**Main features of exotoxins and endotoxins**

	<b>Exotoxins</b>	<b>Endotoxins</b>
<b>SOURCE</b>	Certain species of gram $\oplus$ and gram $\ominus$ bacteria	Outer cell membrane of most gram $\ominus$ bacteria
<b>SECRETED FROM CELL</b>	Yes	No
<b>CHEMISTRY</b>	Polypeptide	Lipid A component of LPS (structural part of bacteria; released when lysed)
<b>LOCATION OF GENES</b>	Plasmid or bacteriophage	Bacterial chromosome
<b>TOXICITY</b>	High (fatal dose on the order of 1 $\mu\text{g}$ )	Low (fatal dose on the order of hundreds of micrograms)
<b>CLINICAL EFFECTS</b>	Various effects (see following pages)	Fever, shock (hypotension), DIC
<b>MODE OF ACTION</b>	Various modes (see following pages)	Induces TNF, IL-1, and IL-6
<b>ANTIGENICITY</b>	Induces high-titer antibodies called antitoxins	Poorly antigenic
<b>VACCINES</b>	Toxoids used as vaccines	No toxoids formed and no vaccine available
<b>HEAT STABILITY</b>	Destroyed rapidly at 60°C (except staphylococcal enterotoxin and <i>E coli</i> heat-stable toxin)	Stable at 100°C for 1 hr
<b>TYPICAL DISEASES</b>	Tetanus, botulism, diphtheria, cholera	Meningococcemia; sepsis by gram $\ominus$ rods



**Bacteria with exotoxins**

BACTERIA	TOXIN	MECHANISM	MANIFESTATION
<b>Inhibit protein synthesis</b>			
<i>Corynebacterium diphtheriae</i>	Diphtheria toxin <sup>a</sup>	Inactivate elongation factor (EF-2)	Pharyngitis with pseudomembranes in throat and severe lymphadenopathy (bull neck), myocarditis
<i>Pseudomonas aeruginosa</i>	Exotoxin A <sup>a</sup>		Host cell death
<i>Shigella</i> spp <i>Enterohemorrhagic E. coli</i>	Shiga toxin <sup>a</sup>	Inactivate 60S ribosome by removing adenine from rRNA	Damages GI mucosa → dysentery Enhances cytokine release → hemolytic-uremic syndrome (HUS; prototypically in EHEC serotype O157:H7) Unlike <i>Shigella</i> , EHEC does not invade host cells
<b>Increase fluid secretion</b>			
<i>Enterotoxigenic E. coli</i>	Heat-labile toxin (LT) <sup>a</sup>	Overactivates adenylate cyclase ( $\uparrow$ cAMP) → $\uparrow$ Cl <sup>-</sup> secretion in gut and H <sub>2</sub> O efflux	Watery diarrhea: “ <b>lable</b> in the <b>Air</b> ( <b>Adenylate cyclase</b> ), <b>stable</b> on the <b>Ground</b> ( <b>Guanylate cyclase</b> )” Bacteria that $\uparrow$ cAMP include <b>Cholera</b> , <b>Anthracis</b> , <b>Pertussis</b> , <b>E. coli</b> ; “ <b>Increase cAMP with CAPE</b>
	Heat-stable toxin (ST)	Overactivates guanylate cyclase ( $\uparrow$ cGMP) → $\downarrow$ resorption of NaCl and H <sub>2</sub> O in gut	
<i>Bacillus anthracis</i>	Anthrax toxin <sup>a</sup>	Mimics adenylate cyclase ( $\uparrow$ cAMP)	Likely responsible for characteristic edematous borders of black eschar in cutaneous anthrax
<i>Vibrio cholerae</i>	Cholera toxin <sup>a</sup>	Overactivates adenylate cyclase ( $\uparrow$ cAMP) by permanently activating G <sub>s</sub>	Voluminous “rice-water” diarrhea
<b>Inhibit phagocytic ability</b>			
<i>Bordetella pertussis</i>	Pertussis toxin <sup>a</sup>	Inactivates inhibitory G subunit (G <sub>i</sub> ) → activation of adenylate cyclase → $\uparrow$ cAMP	<b>Whooping cough</b> —child coughs on expiration and “whoops” on inspiration; can cause “100-day cough” in adults; associated with posttussive emesis
<b>Inhibit release of neurotransmitter</b>			
<i>Clostridium tetani</i>	Tetanospasmin <sup>a</sup>	Both are proteases that cleave SNARE (soluble NSF attachment protein receptor), a set of proteins required for neurotransmitter release via vesicular fusion	Toxin prevents release of <b>inhibitory</b> (GABA and glycine) neurotransmitters from Renshaw cells in spinal cord → spastic paralysis, risus sardonicus, trismus (lockjaw), opisthotonus
<i>Clostridium botulinum</i>	Botulinum toxin <sup>a</sup>		Infant botulism—caused by ingestion of spores (eg, from soil, raw honey). Toxin produced <i>in vivo</i> Foodborne botulism—caused by ingestion of preformed toxin (eg, from canned foods)

<sup>a</sup> An AB toxin (aka, two-component toxin [or three for anthrax]) with **B** enabling **Binding** and triggering uptake (endocytosis) of the **Active A** component. The A components are usually ADP ribosyltransferases; others have enzymatic activities as listed in chart.

**Bacteria with exotoxins (continued)**

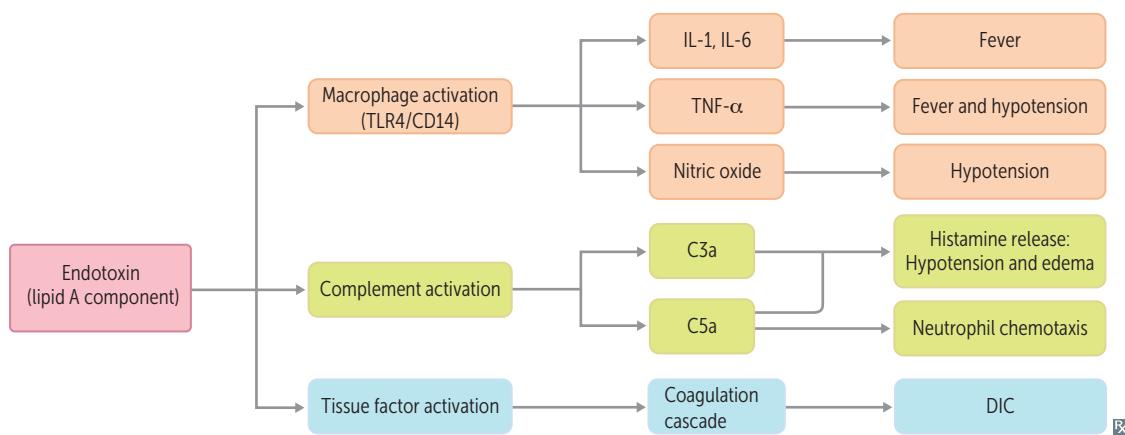
BACTERIA	TOXIN	MECHANISM	MANIFESTATION
<b>Lyse cell membranes</b>			
<i>Clostridium perfringens</i>	Alpha toxin	Phospholipase (lecithinase) that degrades tissue and cell membranes	Degradation of phospholipids → myonecrosis (“gas gangrene”) and hemolysis (“double zone” of hemolysis on blood agar)
<i>Streptococcus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

**Endotoxin**

LPS found in outer membrane of gram  $\ominus$  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/CD14), complement activation, and tissue factor activation.

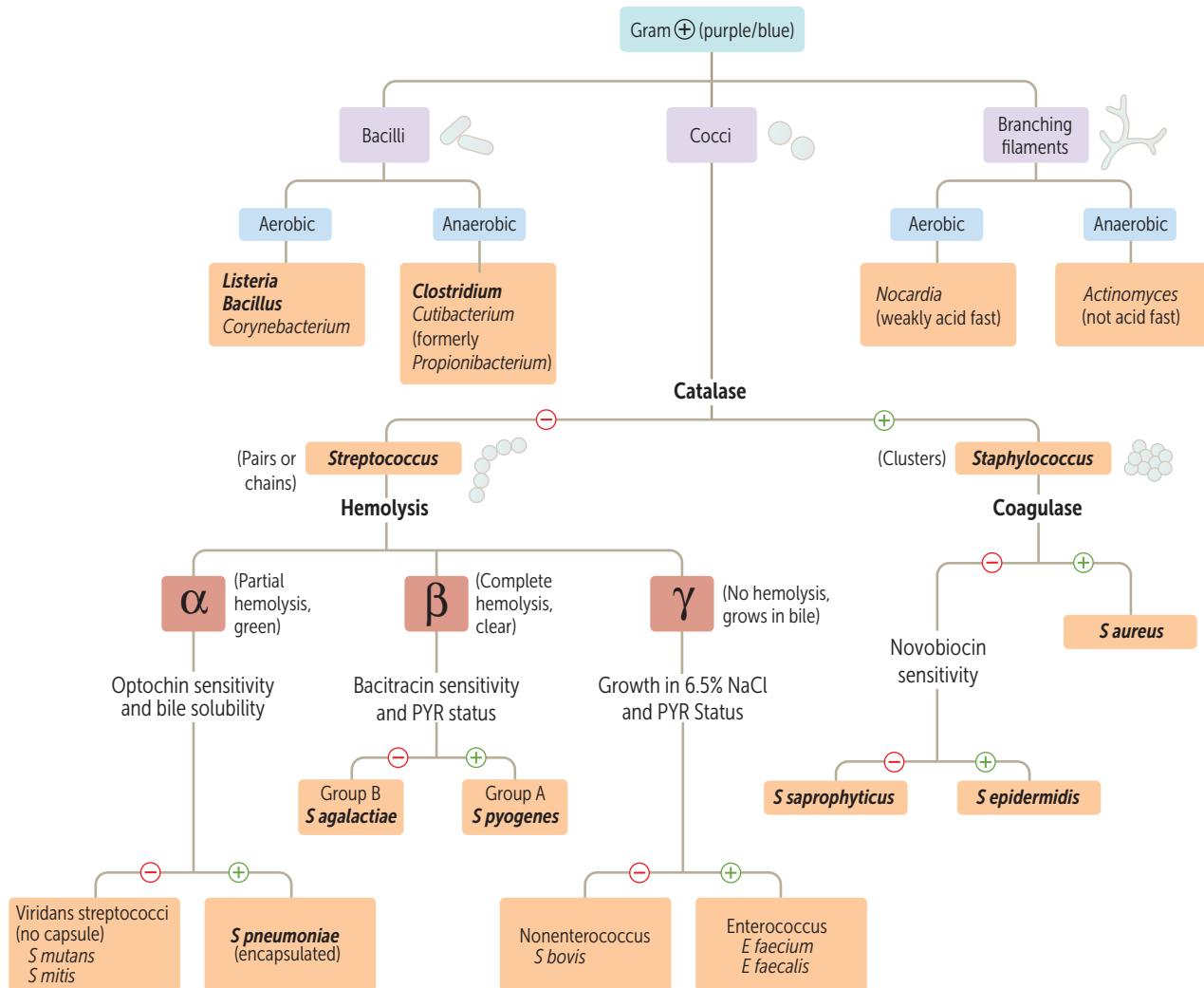
**ENDOTOXINS:**

**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

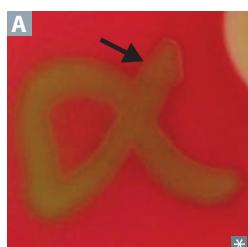


Important tests are in **bold**. Important **pathogens** are in **bold italics**.  
Note: Enterococcus is either  $\alpha$ - or  $\gamma$ -hemolytic.



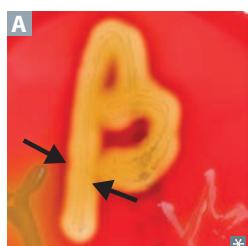
## Gram-positive cocci antibiotic tests

**Staphylococci**Novobiocin—**Saprophyticus** is resistant;  
**epidermidis** is sensitive**Sapro** is a no-go on **Novo****Streptococci**Optochin—**Viridans** is **Resistant**; **Pneumoniae** is **Sensitive****OVRPS** (overpass)Bacitracin—group **B** strep are **Resistant**; group **A** strep are **Sensitive****B-BRAS**

***α*-hemolytic bacteria**

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

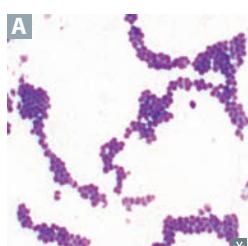
- *Streptococcus pneumoniae* (catalase  $\ominus$  and optochin sensitive)
- Viridans streptococci (catalase  $\ominus$  and optochin resistant)

***β*-hemolytic bacteria**

Gram  $\oplus$  cocci. Complete lysis of RBCs  $\rightarrow$  pale/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  $\oplus$ ,  $\beta$ -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, ears, axilla, and groin.

Causes:

- Inflammatory disease—skin infections, organ abscesses, pneumonia (often after influenza virus infection), endocarditis, septic arthritis, and osteomyelitis.
- Toxin-mediated disease—toxic shock syndrome (TSST-1), scalded skin syndrome (exfoliative toxin), rapid-onset food poisoning (enterotoxins).

**MRSA (methicillin-resistant *S. aureus*)**—important cause of serious nosocomial and community-acquired infections. Resistance due to altered penicillin-binding proteins (conferred by *mecA* gene). Some strains release Panton-Valentine leukocidin (PVL), which kills leukocytes and causes tissue necrosis.

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

**Staphylococcal toxic shock syndrome (TSS)**—fever, vomiting, diarrhea, 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.

*S. aureus* makes coagulase and toxins. Forms fibrin clot around itself  $\rightarrow$  abscess.

***Staphylococcus epidermidis***

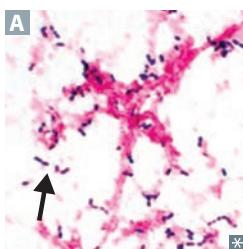
Gram  $\oplus$ , catalase  $\oplus$ , coagulase  $\ominus$ , urease  $\oplus$  cocci in clusters. Novobiocin sensitive. Does not ferment mannitol (vs *S. aureus*).

Normal flora of skin; contaminates blood cultures.

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

***Staphylococcus saprophyticus***

Gram  $\oplus$ , catalase  $\oplus$ , coagulase  $\ominus$ , urease  $\oplus$  cocci in clusters. Novobiocin resistant.  
Normal flora of female genital tract and perineum.  
Second most common cause of uncomplicated UTI in young females (most common is *E coli*).

***Streptococcus pneumoniae***

Gram  $\oplus$ ,  $\alpha$ -hemolytic, lancet-shaped diplococci **A**.  
Encapsulated. IgA protease. Optochin sensitive and bile soluble.

Most commonly causes **MOPS**:

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

Pneumococcus is associated with “rusty” sputum, patients with hyposplenia or asplenia. No virulence without capsule.

***Viridans group streptococci***

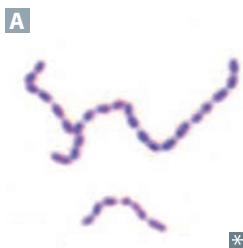
Gram  $\oplus$ ,  $\alpha$ -hemolytic cocci. Optochin resistant and bile insoluble. Normal flora of the oropharynx.

*Streptococcus mutans* and *S mitis* cause dental caries.

*S sanguinis* makes dextrans that bind to fibrin-platelet aggregates on damaged **heart** valves, causing subacute bacterial endocarditis.

Viridans group strep live in the mouth, because they are not afraid **of-the-chin** (**op-to-chin** resistant).

*Sanguinis* = **blood**. Think, “there is lots of **blood** in the **heart**” (endocarditis).

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

Gram  $\oplus$  cocci in chains **A**. Group A strep cause:

- Pyogenic—pharyngitis, cellulitis, impetigo (“honey-crusted” lesions), erysipelas
- Toxigenic—scarlet fever, toxic shock-like syndrome, necrotizing fasciitis
- Immunologic—rheumatic fever, glomerulonephritis

Bacitracin sensitive,  $\beta$ -hemolytic, pyrrolidonyl arylamidase (PYR)  $\oplus$ . Hyaluronic acid capsule and M protein inhibit phagocytosis. Antibodies to M protein enhance host defenses against *S pyogenes* but can give rise to rheumatic fever.

Diagnose strep pharyngitis via throat swab, which can be tested with an antigen detection assay (rapid, in-office results) or cultured on blood agar (results in 48 hours).

“**Ph**”ogenes **pharyngitis** can result in rheumatic “**pfever**” and glomerulone**phritis**.

Strains causing impetigo can induce glomerulonephritis.

Key virulence factors include DNase, erythrogenic exotoxin, streptokinase, streptolysin O. ASO titer or anti-DNase B antibodies indicate recent *S pyogenes* infection.

**Scarlet fever**—blanching, sandpaper-like body rash, strawberry tongue, and circumoral pallor in the setting of group A streptococcal pharyngitis (erythrogenic toxin  $\oplus$ ).

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

Gram  $\oplus$  cocci, bacitracin resistant,  $\beta$ -hemolytic, Group **B** for Babies! colonizes vagina; causes pneumonia, meningitis, and sepsis, mainly in **babies**. Polysaccharide capsule confers virulence. 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 patients at 35–37 weeks' gestation with rectal and vaginal swabs. Patients with  $\oplus$  culture receive intrapartum penicillin/ampicillin prophylaxis.

***Streptococcus bovis***

Gram  $\oplus$  cocci, colonizes the gut. *S gallolyticus* (*S bovis* biotype 1) can cause bacteremia and subacute endocarditis. Patients with *S bovis* endocarditis have  $\uparrow$  incidence of colon cancer.

**Bovis** in the **blood** = **cancer** in the **colon**.

***Enterococci***

Gram  $\oplus$  cocci. Enterococci (*E faecalis* and *E faecium*) are normal colonic flora that are penicillin G resistant and cause UTI, biliary tract infections, and subacute endocarditis (following GI/GU procedures). Catalase  $\ominus$ , PYR  $\oplus$ , typically nonhemolytic. VRE (vancomycin-resistant enterococci) are an important cause of nosocomial infection.

Enterococci are more resilient than streptococci, can grow in 6.5% NaCl and bile (lab test).

*Enter* = intestine, *faecalis* = feces, *strepto* = twisted (chains), *coccus* = berry.

***Bacillus anthracis***

Gram  $\oplus$ , spore-forming rod that produces anthrax toxin (an exotoxin consisting of protective antigen, lethal factor, and edema factor). Has a polypeptide capsule (poly D-glutamate). Colonies show a halo of projections, sometimes referred to as “medusa head” appearance.

**Cutaneous anthrax**

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

**Pulmonary anthrax**

Inhalation of spores, most commonly from contaminated animals or animal products, although also a potential bioweapon  $\rightarrow$  flu-like symptoms that rapidly progress to fever, pulmonary hemorrhage, mediastinitis (CXR may show widened mediastinum), and shock. Also called woolsorter's disease. Prophylaxis with ciprofloxacin or doxycycline when exposed.

***Bacillus cereus***

Gram  $\oplus$  rod. Causes food poisoning. Spores survive cooking rice (reheated rice syndrome). Keeping rice warm results in germination of spores and enterotoxin formation. Emetic type causes nausea and vomiting within 1–5 hours. Caused by cereulide, a preformed toxin. Diarrheal type causes watery, nonbloody diarrhea and GI pain within 8–18 hours. Management: supportive care (antibiotics are ineffective against toxins).

**Clostridia**

Gram  $\ominus$ , spore-forming, obligate anaerobic rods. Tetanus toxin and botulinum toxin are proteases that cleave SNARE proteins involved in neurotransmission.

***Clostridium tetani***

Pathogen is noninvasive and remains localized to wound site. Produces tetanospasmin, an exotoxin causing tetanus. Tetanospasmin spreads by retrograde axonal transport to CNS and blocks release of GABA and glycine from Renshaw cells in spinal cord. Causes spastic paralysis, trismus (lockjaw), risus sardonicus (raised eyebrows and open grin), opisthotonus (spasms of spinal extensors).

Tetanus is tetanic paralysis.

Prevent with tetanus vaccine. Treat with antitoxin +/- vaccine booster, antibiotics, diazepam (for muscle spasms), and wound debridement.

***Clostridium botulinum***

Produces a heat-labile toxin that inhibits ACh release at the neuromuscular junction, causing botulism. In babies, ingestion of spores (eg, in honey) leads to disease (floppy baby syndrome). In adults, disease is caused by ingestion of preformed toxin (eg, in canned food). Symptoms of botulism (the 5 D's): diplopia, dysarthria, dysphagia, dyspnea, descending flaccid paralysis. Does not present with sensory deficits.

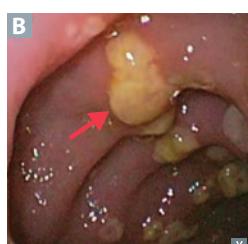
Botulinum is from bad bottles of food, juice, and honey.

Treatment: human botulinum immunoglobulin. Local botulinum toxin A (Botox) injections used to treat focal dystonia, hyperhidrosis, muscle spasms, and cosmetic reduction of facial wrinkles.

***Clostridium perfringens***

Produces  $\alpha$ -toxin (lecithinase, a phospholipase) that can cause myonecrosis (gas gangrene A; presents as soft tissue crepitus) and hemolysis. If heavily spore-contaminated food is cooked but left standing too long at  $< 60^{\circ}\text{C}$ , spores germinate  $\rightarrow$  vegetative bacteria  $\rightarrow$  heat-labile enterotoxin  $\rightarrow$  late-onset (10–12 hours) food poisoning symptoms, resolution in 24 hours.

*Perfringens* perforates a gangrenous leg.

***Clostridioides difficile***

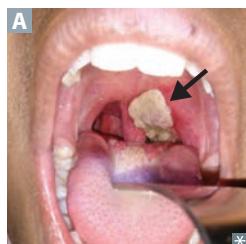
Produces toxins A and B, which damage enterocytes. Both toxins lead to watery diarrhea  $\rightarrow$  pseudomembranous colitis B. Often 2° to antibiotic use, especially clindamycin, ampicillin, cephalosporins, fluoroquinolones; associated with PPIs. Fulminant infection: toxic megacolon, ileus, shock.

*Difficile* causes diarrhea.

Diagnosed by PCR or antigen detection of one or both toxins in stool.

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

### **Corynebacterium diphtheriae**



Gram  $\oplus$  rods occurring in angular arrangements; transmitted via respiratory droplets. Causes diphtheria via exotoxin encoded by  $\beta$ -prophage. Potent exotoxin inhibits protein synthesis via ADP-ribosylation of EF-2, leading to possible necrosis in pharynx, cardiac, and CNS tissue. Symptoms include pseudomembranous pharyngitis (grayish-white membrane **A**) with lymphadenopathy ("bull's neck" appearance). Toxin dissemination may cause myocarditis, arrhythmias, neuropathies. Lab diagnosis based on gram  $\oplus$  rods with metachromatic (blue and red) granules and  $\oplus$  Elek test for toxin. Toxoid vaccine prevents diphtheria.

**Coryne** = club shaped (metachromatic granules on Löffler media).

Black colonies on cystine-tellurite agar.

#### **ABCDEFG:**

**A**DP-ribosylation

**B**-prophage

**C**orynebacterium

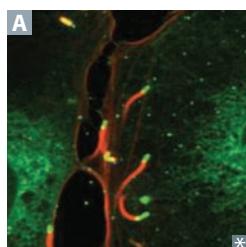
**D**iphtheriae

**E**longation Factor 2

**G**ranules

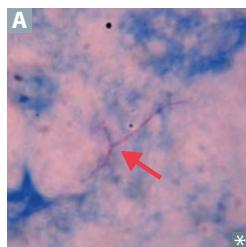
Treatment: diphtheria antitoxin  $+/-$  erythromycin or penicillin.

### **Listeria monocytogenes**



Gram  $\oplus$ , facultative intracellular rod; acquired by ingestion of unpasteurized dairy products and cold deli meats, transplacental transmission, by vaginal transmission during birth. Grows well at refrigeration temperatures ("cold enrichment"). Forms "rocket tails" (red in **A**) via actin polymerization that allow intracellular movement and cell-to-cell spread across cell membranes, thereby avoiding antibody. Characteristic tumbling motility in broth. Can cause amnionitis, septicemia, and spontaneous abortion in pregnant patients; granulomatosis infantiseptica; meningitis in immunocompromised patients, neonates, and older adults; mild, self-limited gastroenteritis in healthy individuals. Treatment: ampicillin.

### **Nocardia vs Actinomyces**



Both are gram  $\oplus$  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  $\ominus$  PPD); cutaneous infections after trauma in immunocompetent; can spread to CNS  $\rightarrow$  cerebral abscess

Treat with sulfonamides (TMP-SMX)

Treatment is a **SNAP**: Sulfonamides—**N**ocardia; **A**ctinomyces—**P**enicillin

#### **Actinomyces**

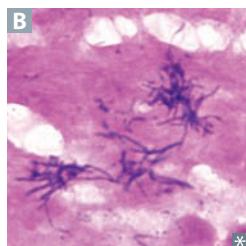
Anaerobe

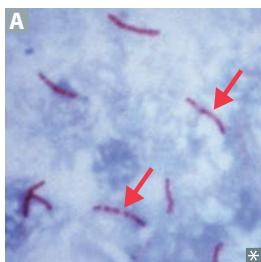
Not acid fast **B**

Normal oral, reproductive, and GI flora

Causes oral/facial abscesses that drain through sinus tracts; often associated with dental caries/extraction and other maxillofacial trauma; forms yellow "sulfur granules"; can also cause PID with IUDs

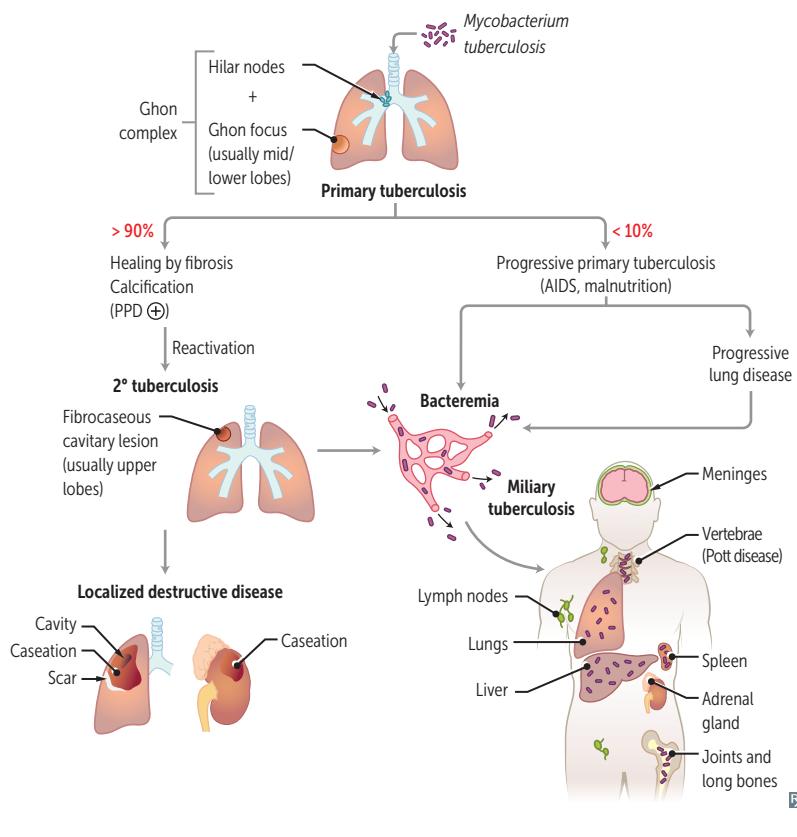
Treat with penicillin



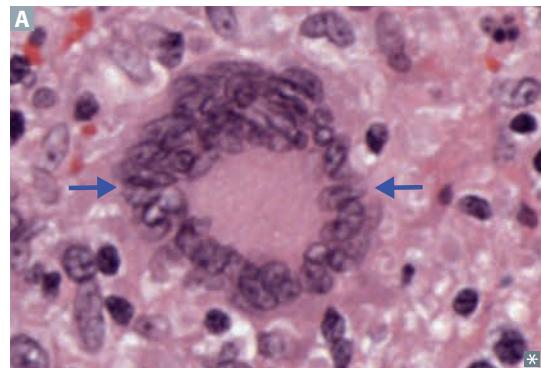
**Mycobacteria**

- Acid-fast rods (pink rods, arrows in A).  
*Mycobacterium tuberculosis* (TB, often resistant to multiple drugs).  
*M avium-intracellulare* (causes disseminated, non-TB disease in AIDS; often resistant to multiple drugs). Prophylaxis with azithromycin when CD4+ count < 50 cells/mm<sup>3</sup>.  
*M scrofulaceum* (cervical lymphadenitis in children).  
*M marinum* (hand infection in aquarium handlers).

TB symptoms include fever, night sweats, weight loss, cough (nonproductive or productive), hemoptysis. Cord factor creates a “serpentine cord” appearance in virulent *M tuberculosis* strains; activates macrophages (promoting granuloma formation) and induces release of TNF- $\alpha$ . Sulfatides (surface glycolipids) inhibit phagolysosomal fusion.

**Tuberculosis**

PPD + if current infection or past exposure.  
 PPD - if no infection and in immunocompromised patients (especially with low CD4+ cell count).  
 Interferon- $\gamma$  release assay (IGRA) has fewer false positives from BCG vaccination.  
 Caseating granulomas with central necrosis and Langhans giant cell (single example in A) are characteristic of 2° tuberculosis. Do not confuse Langhans giant cell with Langerhans cell, an APC.  
 TB reactivation risk highest in immunocompromised individuals (eg, HIV, organ transplant recipients).



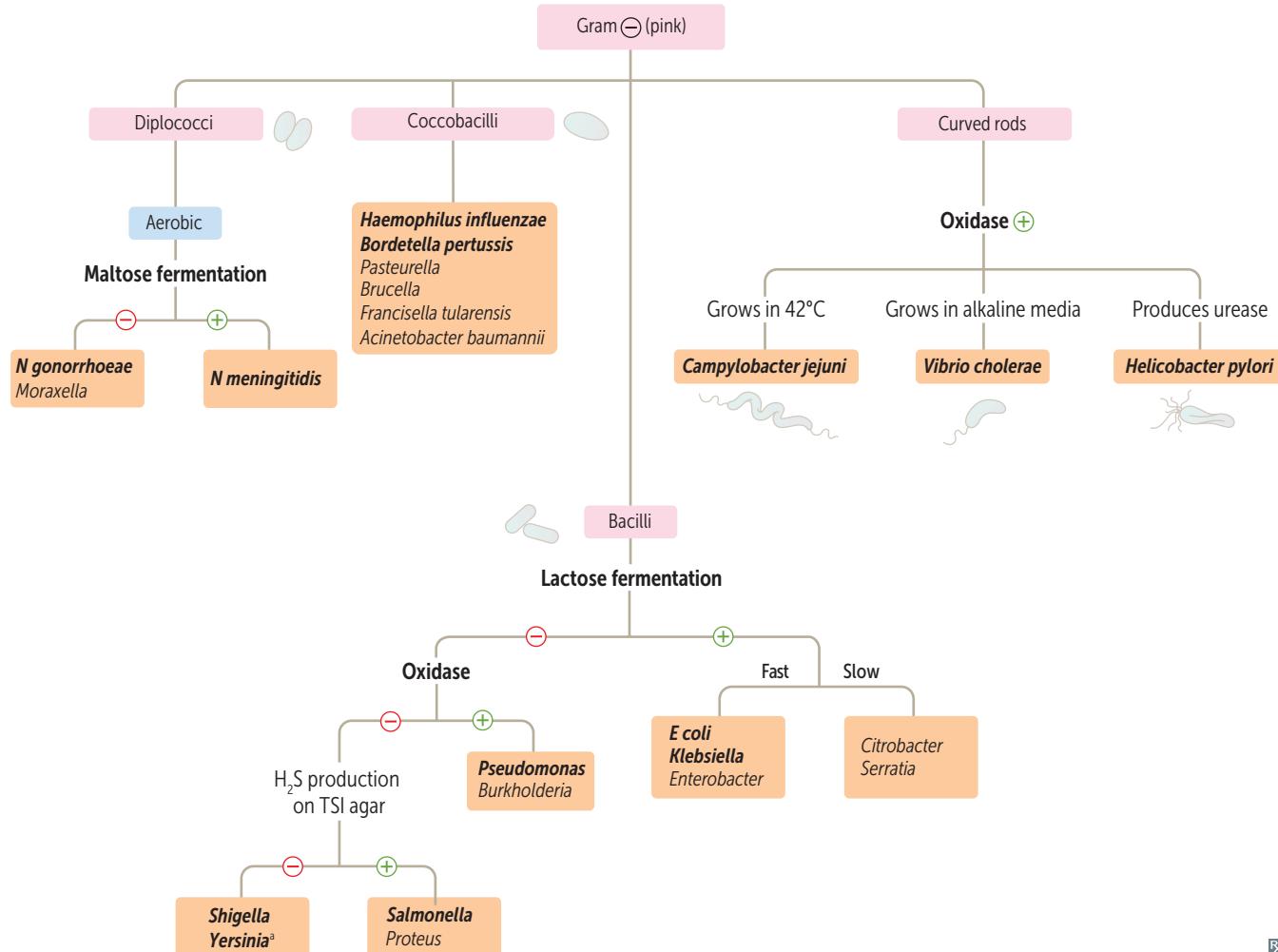
**Leprosy**

Also called Hansen disease. Caused by *Mycobacterium leprae*, an acid-fast bacillus that likes cool temperatures (infects skin and superficial nerves—"glove and stocking" loss of sensation **A**) and cannot be grown in vitro. Diagnosed via skin biopsy or tissue PCR. Reservoir in United States: armadillos.

Leprosy has 2 forms (many cases fall temporarily between two extremes):

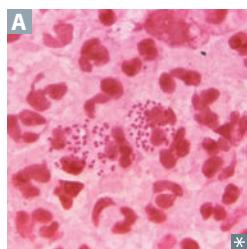
- **Lepromatous**—presents diffusely over the skin, with leonine (lion-like) facies **B**, and is communicable (high bacterial load); characterized by low cell-mediated immunity with a largely Th2 response. Lepromatous form can be **lethal**.
- **Tuberculoid**—limited to a few hypoesthetic, hairless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

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

**Gram-negative lab algorithm**

Important **tests** are in **bold**. Important **pathogens** are in ***bold italic***.

<sup>a</sup>Pleomorphic rod/coccobacillus

***Neisseria***

Gram  $\ominus$  diplococci. Metabolize glucose and produce IgA proteases. Contain lipooligosaccharides (LOS) with strong endotoxin activity.

**Gonococci**

- No polysaccharide capsule
- No maltose acid detection
- No vaccine due to antigenic variation of pilus proteins
- Sexually or perinatally transmitted

Causes gonorrhea, septic arthritis, neonatal conjunctivitis (2–5 days after birth), pelvic inflammatory disease (PID), and Fitz-Hugh-Curtis syndrome

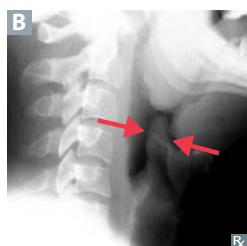
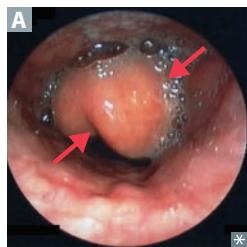
- Diagnosed with NAT
- Condoms  $\downarrow$  sexual transmission, erythromycin eye ointment prevents neonatal blindness
- Treatment: ceftriaxone + azithromycin (to cover possible chlamydial coinfection, ceftriaxone-resistant strains)

*N gonorrhoeae* is often intracellular (within neutrophils) **A**.

Acid production: meningococci—maltose and glucose; gonococci—glucose.

**Meningococci**

- Polysaccharide capsule
- Maltose acid detection
- Vaccine (type B vaccine available for at-risk individuals)
- Transmitted via respiratory and oral secretions. More common among individuals in close quarters (eg, army barracks, college dorms)
- Causes meningococcemia with petechial hemorrhages and gangrene of toes **B**, meningitis, Waterhouse-Friderichsen syndrome (adrenal insufficiency, fever, DIC)
- Diagnosed via culture-based tests or PCR
- 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 via RBC hemolysis.

*Haemophilus* causes epiglottitis (endoscopic appearance in **A**, can be “cherry red” in children; “thumb sign” on lateral neck x-ray **B**), meningitis, otitis media, and pneumonia.

Vaccine contains type b capsular polysaccharide (polyribosylribitol phosphate) conjugated to diphtheria toxoid or other protein. Given between 2 and 18 months of age.

Does not cause the flu (influenza virus does).

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

***Burkholderia cepacia* complex**

Gram  $\ominus$  bacilli. Causes pneumonia in and can be transmitted between patients with cystic fibrosis. Often multidrug resistant. Infection is a relative contraindication to undergoing lung transplant due to its association with poor outcomes.

***Bordetella pertussis***

Gram  $\ominus$ , aerobic coccobacillus. Virulence factors include pertussis toxin (disables G<sub>i</sub>), adenylate cyclase toxin ( $\uparrow$  cAMP), and tracheal cytotoxin. Three clinical stages:

- Catarrhal—low-grade fevers, coryza.
- Paroxysmal—paroxysms of intense cough followed by inspiratory “whoop” (“whooping cough”), posttussive vomiting.
- Convalescent—gradual recovery of chronic cough.

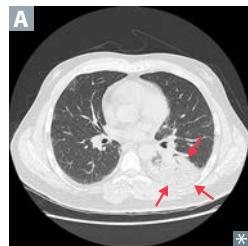
Prevented by Tdap, DTaP vaccines.

Treatment: macrolides; if allergic use TMP-SMX.

***Brucella***

Gram  $\ominus$ , aerobic coccobacillus. Transmitted via ingestion of contaminated animal products (eg, unpasteurized milk). Survives in macrophages in the reticuloendothelial system. Can form non-caseating granulomas. Typically presents with undulant fever, night sweats, and arthralgia.

Treatment: doxycycline + rifampin or streptomycin.

***Legionella pneumophila***

Gram  $\ominus$  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.

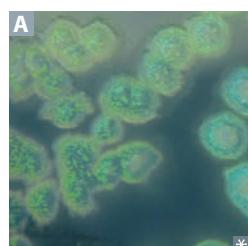
Aerosol transmission from environmental water source habitat (eg, air conditioning systems, hot water tanks). Outbreaks associated with cruise ships, nursing homes. No person-to-person transmission.

Treatment: macrolide or quinolone.

Think of a French **legionnaire** (soldier) with his **silver** helmet, sitting around a campfire (**charcoal**) with his **iron** dagger—he is missing his **sister** (cysteine).

**Legionnaires' disease**—severe pneumonia (often unilateral and lobar **A**), fever, GI and CNS symptoms. Risk factors include older age, tobacco smoking, chronic lung disease.

**Pontiac fever**—mild flu-like symptoms.

***Pseudomonas aeruginosa***

**Aeruginosa**—aerobic; motile, catalase  $\oplus$ , gram  $\ominus$  rod. Non-lactose fermenting.

Oxidase  $\oplus$ . Frequently found in water. Has a grape-like odor.

**PSEUDOMONAS** is associated with:

**Pneumonia, Sepsis, Ecthyma gangrenosum, UTIs, Diabetes, Osteomyelitis, Mucoid polysaccharide capsule, Otitis externa (swimmer's ear), Nosocomial infections (eg, catheters, equipment), Addiction (people who inject drugs), Skin infections (eg, hot tub folliculitis, wound infection in burn victims).** Mucoid polysaccharide capsule may contribute to chronic pneumonia in patients with cystic fibrosis due to biofilm formation.

Produces **PEEP**: Phospholipase C (degrades cell membranes); **Endotoxin** (fever, shock); **Exotoxin A** (inactivates EF-2); **Pigments**: pyoverdine and pyocyanin (blue-green pigment **A**; also generates ROS).

Corneal ulcers/keratitis in contact lens wearers/ minor eye trauma.

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

Treatments:

- Antipseudomonal penicillins in combination with  $\beta$ -lactamase inhibitor (eg, piperacillin-tazobactam)
- 3rd- and 4th-generation cephalosporins (eg, ceftazidime, cefepime)
- Monobactams
- Fluoroquinolones
- Carbapenems



**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> (ty-Vi)	<i>Salmonella</i> spp. except <i>S typhi</i>	<i>Shigella</i>
RESERVOIRS	Humans only	Humans and animals	Humans only
SPREAD	Hematogenous spread	Hematogenous spread	Cell to cell; no hematogenous spread
H <sub>2</sub> S PRODUCTION	Yes	Yes	No
FLAGELLA	Yes ( <i>salmon swim</i> )	Yes ( <i>salmon swim</i> )	No
VIRULENCE FACTORS	Endotoxin; <b>Vi</b> capsule (pronounce “ty <b>Vi</b> ”)	Endotoxin	Endotoxin; Shiga toxin (enterotoxin)
INFECTIOUS DOSE (ID <sub>50</sub> )	High—large inoculum required; acid-labile (inactivated by gastric acids)	High	Low—very small inoculum required; acid stable (resistant to gastric acids)
EFFECT OF ANTIBIOTICS ON FECAL EXCRETION	Prolongs duration	Prolongs duration	Shortens duration
IMMUNE RESPONSE	Primarily monocytes	PMNs in disseminated disease	Primarily PMN infiltration
GI MANIFESTATIONS	Constipation, followed by diarrhea	Diarrhea (possibly bloody)	Crampy abdominal pain → tenesmus, bloody mucoid stools (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"> <li>▪ Causes typhoid fever (rose spots on abdomen, constipation, abdominal pain, fever [pulse-temperature dissociation]; later GI ulceration and hemorrhage); treat with ceftriaxone or fluoroquinolone</li> <li>▪ Carrier state with gallbladder colonization</li> </ul>	<ul style="list-style-type: none"> <li>▪ Poultry, eggs, pets, and turtles are common sources</li> <li>▪ Antibiotics not indicated</li> <li>▪ Gastroenteritis is usually caused by non-typhoidal <i>Salmonella</i></li> </ul>	<ul style="list-style-type: none"> <li>▪ <b>4 F's:</b> fingers, flies, food, feces</li> <li>▪ In order of decreasing severity (less toxin produced): <i>S dysenteriae</i>, <i>S flexneri</i>, <i>S boydii</i>, <i>S sonnei</i></li> <li>▪ Invasion of M cells is key to pathogenicity: organisms that produce little toxin can cause disease</li> </ul>

### ***Yersinia enterocolitica***

Gram  $\ominus$  pleomorphic rod/coccobacillus. Usually transmitted from pet feces (eg, cats, dogs), contaminated milk, or pork. Can cause acute bloody diarrhea, pseudoappendicitis (right lower abdominal pain due to mesenteric adenitis and/or terminal ileitis), reactive arthritis in adults.

### **Lactose-fermenting enteric bacteria**

Fermentation of **lactose** → pink colonies on Mac**Con**key agar. Examples include *Citrobacter*, *E coli*, *Enterobacter*, *Klebsiella*, *Serratia*. *E coli* produces  $\beta$ -galactosidase, which breaks down lactose into glucose and galactose.

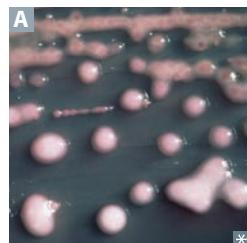
McCowkey **CEEKS** milk.

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

***Escherichia coli***

Gram  $\ominus$ , indole  $\oplus$  rod. *E coli* virulence factors: fimbriae—cystitis and pyelonephritis (P pili); K capsule—pneumonia, neonatal meningitis; LPS endotoxin—septic shock.

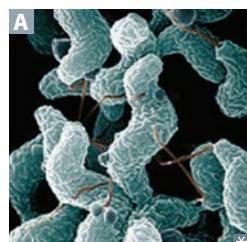
STRAIN	TOXIN AND MECHANISM	PRESOLUTION
<b>Enteroinvasive <i>E coli</i></b>	Microbe invades intestinal mucosa and causes necrosis and inflammation.	EIEC is Invasive; dysentery. Clinical manifestations similar to <i>Shigella</i> .
<b>Enterotoxigenic <i>E coli</i></b>	Produces heat-labile and heat-stable enterotoxins. No inflammation or invasion.	ETEC; Traveler's diarrhea (watery).
<b>Enteropathogenic <i>E coli</i></b>	No toxin produced. Adheres to apical surface, flattens villi, prevents absorption.	Diarrhea, usually in children (think EPEC and Pediatrics).
<b>Enterohemorrhagic <i>E coli</i></b>	O157:H7 is most common serotype in US. Often transmitted via undercooked meat, raw leafy vegetables. Shiga toxin causes <b>hemolytic-uremic syndrome</b> —triad of anemia, thrombocytopenia, and acute kidney injury due to microthrombi forming on damaged endothelium → mechanical hemolysis (with schistocytes on peripheral blood smear), platelet consumption, and ↓ renal blood flow.	Dysentery (toxin alone causes necrosis and inflammation). Does not ferment sorbitol (vs other <i>E coli</i> ). EHEC associated with hemorrhage, hamburgers, hemolytic-uremic syndrome.

***Klebsiella***

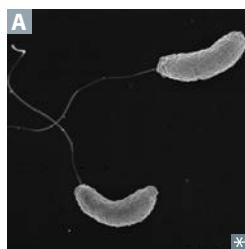
Gram  $\ominus$  rod; intestinal flora that causes lobar pneumonia in patients with alcohol overuse and patients with diabetes when aspirated. Very mucoid colonies **A** caused by abundant polysaccharide capsules. Dark red “currant jelly” sputum (blood/mucus). Also cause of nosocomial UTIs. Associated with evolution of multidrug resistance (MDR).

**ABCDE's of Klebsiella:**

- A**spiration pneumonia
- B**scess in lungs and liver
- C**urrent jelly sputum
- D**iabetes mellitus
- E**tOH overuse

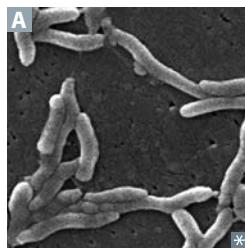
***Campylobacter jejuni***

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.

***Vibrio cholerae***

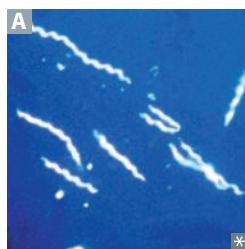
Gram  $\ominus$ , flagellated, comma shaped **A**, oxidase  $\oplus$ , grows in alkaline media. Endemic to developing countries. Produces profuse rice-water diarrhea via enterotoxin that permanently activates G<sub>s</sub>,  $\uparrow$  cAMP. Sensitive to stomach acid (acid labile); requires large inoculum (high ID<sub>50</sub>) unless host has  $\downarrow$  gastric acidity. Transmitted via ingestion of contaminated water or uncooked food (eg, raw shellfish). Treat promptly with oral rehydration solution.

***Vibrio vulnificus***—gram  $\ominus$  bacillus, usually found in marine environments. Causes severe wound infections or septicemia due to exposure to contaminated sea water. Presents as cellulitis that can progress to necrotizing fasciitis in high-risk patients, especially those with liver disease (eg, cirrhosis). Serious wound infection requires surgical debridement.

***Helicobacter pylori***

Curved, flagellated (motile), 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: amoxicillin (metronidazole if penicillin allergy) + clarithromycin + proton pump inhibitor; antibiotics **cure** *Pylori*. Bismuth-based quadruple therapy if concerned about macrolide resistance.

**Spirochetes**

Spiral-shaped bacteria **A** with axial filaments. Includes *Leptospira*, *Treponema*, and *Borrelia*. 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.

**Little Twirling Bacteria****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; deer are essential to tick life cycle but do not harbor *Borrelia*.

Common in northeastern United States. Stage 1—early localized: erythema migrans (typical “bulls-eye” configuration **B** is pathognomonic but not always present), flu-like symptoms.

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

Stage 3—late disseminated: encephalopathy, chronic arthritis, peripheral neuropathy.

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

**F**acial nerve palsy (typically bilateral)

**A**rthritis

**C**ardiac block

**E**rythema migrans

Treatment: doxycycline (1st line); amoxicillin (pregnant patients, children  $< 8$  years old); ceftriaxone if IV therapy required



**Leptospira interrogans** Spirochete with hook-shaped ends found in water contaminated with animal urine.

**Leptospirosis**—flu-like symptoms, myalgias (classically of calves), jaundice, photophobia with conjunctival suffusion (erythema without exudate). Prevalent among surfers and in tropics (eg, Hawaii).

**Weil disease** (icterohemorrhagic leptospirosis)—severe form with jaundice and azotemia from liver and kidney dysfunction, fever, hemorrhage, and anemia.

### Syphilis

Caused by spirochete *Treponema pallidum*. Treatment: penicillin G.

#### Primary syphilis

Localized disease presenting with painless chancre **A**. Use fluorescent or dark-field microscopy to visualize treponemes in fluid from chancre **B**. VDRL  $\oplus$  in  $\sim 80\%$ .

#### Secondary syphilis

Disseminated disease with constitutional symptoms, maculopapular rash **C** (including palms **D** and soles), condylomata lata **E** (smooth, painless, wart-like white lesions on genitals), lymphadenopathy, patchy hair loss; also confirmable with dark-field microscopy. Serologic testing: VDRL/RPR (nonspecific), confirm diagnosis with specific test (eg, FTA-ABS). Secondary syphilis = systemic. Latent syphilis ( $\oplus$  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).

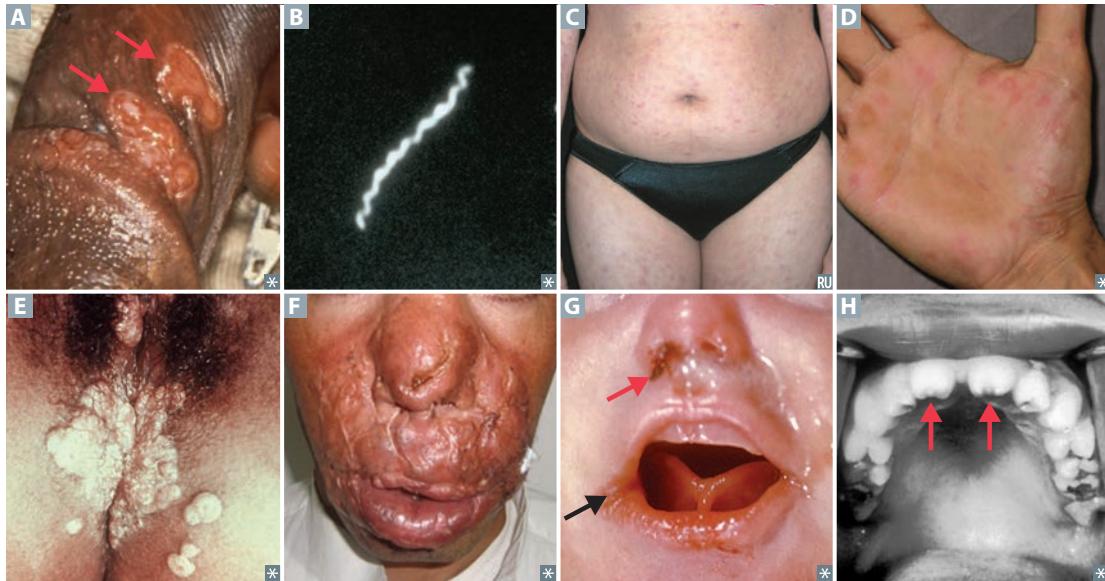
Signs: broad-based ataxia,  $\oplus$  Romberg, Charcot joint, stroke without hypertension.

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.

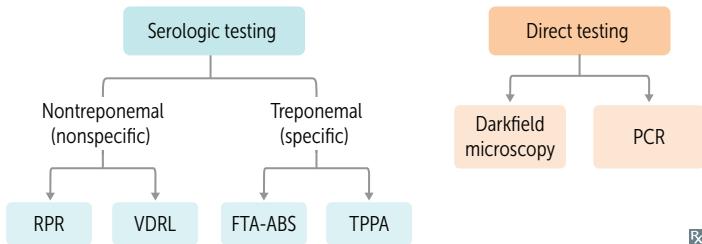
To prevent, treat patient early in pregnancy, as placental transmission typically occurs after first trimester.



**Diagnosing syphilis**

VDRL and RPR detects nonspecific antibody that reacts with beef cardiolipin. Quantitative, inexpensive, and widely available test for syphilis (sensitive but not specific).

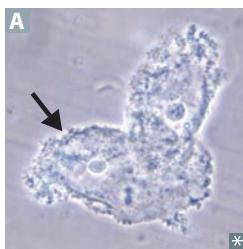
False-Positive results on **VDRL** with:  
**P**regnancy  
**V**iral infection (eg, EBV, hepatitis)  
**D**rugs (eg, chlorpromazine, procainamide)  
**R**heumatic fever (rare)  
**L**upus (anticardiolipin antibody) and **L**eprsy



Rx

**Jarisch-Herxheimer reaction**

Flu-like symptoms (fever, chills, headache, myalgia) after antibiotics are started due to host response to sudden release of bacterial antigens.

**Gardnerella vaginalis**

A pleomorphic, gram-variable rod involved in bacterial vaginosis. Presents as a gray vaginal discharge with a fishy smell; nonpainful (vs vaginitis). Associated with sexual activity, but not sexually transmitted. Bacterial vaginosis is also characterized by overgrowth of certain anaerobic bacteria in vagina (due to ↓ lactobacilli). Clue cells (vaginal epithelial cells covered with *Gardnerella*) have stippled appearance along outer margin (arrow in A).

Amine whiff test—mixing discharge with 10% KOH enhances fishy odor.  
 Vaginal pH >4.5 during infection.  
 Treatment: metronidazole or clindamycin.

**Chlamydiae**

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

- Elementary body (small, dense) is “enfectious” and enters cell via endocytosis; transforms into reticulate body.
- Reticulate body replicates in cell by fission; reorganizes into elementary bodies.

*Chlamydia trachomatis* causes neonatal and follicular adult conjunctivitis A, nongonococcal urethritis, PID, and reactive arthritis.

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

Chlamydial cell wall lacks classic peptidoglycan (due to reduced muramic acid), rendering β-lactam antibiotics ineffective.

*Chlamys* = cloak (intracellular).

C *psittaci*—has an avian reservoir (parrots), causes atypical pneumonia.

Lab diagnosis: PCR, nucleic acid amplification test. Cytoplasmic inclusions (reticulate bodies) seen on Giemsa or fluorescent antibody-stained smear.

Treatment: azithromycin (favored because one-time treatment) or doxycycline. Add ceftriaxone for possible concomitant gonorrhea.

***Chlamydia trachomatis* serotypes**

<b>Types A, B, and C</b>	Chronic infection, cause blindness due to follicular conjunctivitis in resource-limited areas.	<b>ABC</b> = Africa, Blindness, Chronic infection.
<b>Types D–K</b>	Urethritis/PID, ectopic pregnancy, neonatal pneumonia (staccato cough) with eosinophilia, neonatal conjunctivitis (1–2 weeks after birth).	D–K = everything else. Neonatal disease can be acquired during vaginal birth if pregnant patient is infected.
<b>Types L1, L2, and L3</b>	<b>Lymphogranuloma venereum</b> —small, painless ulcers on genitals → swollen, painful inguinal lymph nodes that ulcerate (bubo). Treat with doxycycline.	

**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	Unpasteurized 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)

**Rickettsial diseases  
and vector-borne  
illnesses**

RASH COMMON

**Rocky Mountain  
spotted fever**

Treatment: doxycycline.

*Rickettsia rickettsii*, vector is tick. Despite its name, disease occurs primarily in the South Atlantic states, especially North Carolina. Rash typically starts at wrists **A** and ankles and then spreads to trunk, palms, and soles.

Classic triad—headache, fever, rash (vasculitis).

**Palms and soles** rash is seen in Coxsackievirus

**A** infection (hand, foot, and mouth disease), Rocky Mountain spotted fever, and 2° Syphilis (you drive CARS using your **palms** and **soles**).

**Typhus**

Endemic (fleas)—*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. Monocytes with morulae **B** (mulberry-like inclusions) in cytoplasm.

**MEGA:**

Monocytes = Ehrlichiosis

Granulocytes = Anaplasmosis

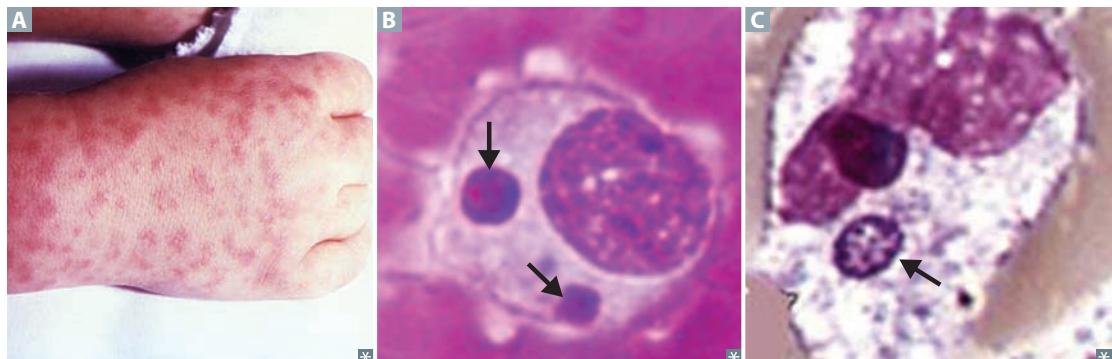
**Anaplasmosis**

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

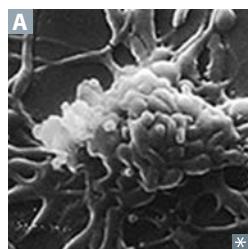
**Q fever**

*Coxiella burnetii*, no arthropod vector. Bacterium inhaled as aerosols from cattle/sheep amniotic fluid. Presents with headache, cough, influenza-like symptoms, pneumonia, possibly in combination with hepatitis. Common cause of culture ⊖ endocarditis.

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



**Mycoplasma  
pneumoniae**



Classic cause of atypical “walking pneumonia” (insidious onset, headache, nonproductive cough, patchy or diffuse interstitial infiltrate, macular rash).

Occurs frequently in those <30 years old; outbreaks in military recruits, prisons, colleges. Treatment: macrolides, doxycycline, or fluoroquinolone (penicillin ineffective since *Mycoplasma* has no cell wall).

Not seen on Gram stain. Pleiomorphic **A**.

Bacterial membrane contains sterols for stability. Grown on Eaton agar.

CXR appears more severe than patient presentation. High titer of **cold** agglutinins (IgM), which can agglutinate RBCs. *Mycoplasma* gets **cold** without a **coat** (no cell wall).

Can cause atypical variant of Stevens-Johnson syndrome, typically in children and adolescents.

## ► MICROBIOLOGY—MYCOLOGY

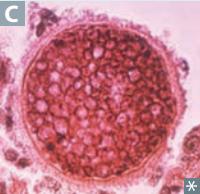
**Systemic mycoses**

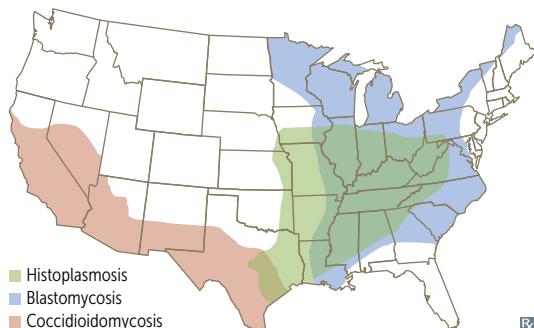
All of the following can cause pneumonia and can disseminate.

All are caused by dimorphic fungi: **cold** ( $20^{\circ}\text{C}$ ) = **mold**; **heat** ( $37^{\circ}\text{C}$ ) = **yeast**. Only exception is *Coccidioides*, which is a spherule (not yeast) in tissue.

Systemic mycoses can form granulomas (like TB); cannot be transmitted person-to-person (unlike TB).

Treatment: fluconazole or itraconazole for **local** infection; amphotericin B for **systemic** infection.

DISEASE	ENDEMIC LOCATION	PATHOLOGIC FEATURES	UNIQUE SIGNS/SYMPOMS	NOTES
<b>Histoplasmosis</b> 	Mississippi and Ohio River Valleys	Macrophage filled with <i>Histoplasma</i> (smaller than RBC) <b>A</b>	Palatal/tongue ulcers, splenomegaly, pancytopenia, erythema nodosum	<b>Histo</b> hides (within macrophages) Associated with bird or bat droppings (eg, caves) Diagnosis via urine/serum antigen
<b>Blastomycosis</b> 	Eastern and Central US, Great Lakes	Broad-based budding of <i>Blastomyces</i> (same size as RBC) <b>B</b>	Inflammatory lung disease Disseminates to bone/skin ( verrucous lesions, may mimic SCC).	<b>Blasto</b> buds broadly
<b>Coccidioidomycosis</b> 	Southwestern US, California	Spherule (much larger than RBC) filled with endospores of <i>Coccidioides</i> <b>C</b>	Disseminates to bone/skin Erythema nodosum (desert bumps) or multiforme Arthralgias (desert rheumatism) Can cause meningitis	Associated with dust exposure in endemic areas (eg, archeological excavations, earthquakes)
<b>Paracoccidioidomycosis</b> 	Latin America	Budding yeast of <i>Paracoccidioides</i> with “ <b>captain’s wheel</b> ” formation (much larger than RBC) <b>D</b>	Similar to blastomycosis, males > females	<b>Paracoccidio</b> parasails with the <b>captain’s wheel</b> all the way to <b>Latin America</b>



### Cutaneous mycoses

<b>Tinea (dermatophytes)</b>	Clinical name for dermatophyte (cutaneous fungal) infections. Dermatophytes include <i>Microsporum</i> , <i>Trichophyton</i> , and <i>Epidermophyton</i> . Branching septate hyphae visible on KOH preparation with blue fungal stain <b>A</b> . Associated with pruritus.
<b>Tinea capitis</b>	Occurs on head, scalp. Associated with lymphadenopathy, alopecia, scaling <b>B</b> .
<b>Tinea corporis</b>	Occurs on body (usually torso). Characterized by enlarging erythematous, scaly rings (“ringworm”) with central clearing <b>C</b> . Can be acquired from contact with infected pets or farm animals.
<b>Tinea cruris</b>	Occurs in inguinal area (“jock itch”) <b>D</b> . Often does not show the central clearing seen in tinea corporis.
<b>Tinea pedis</b>	Three varieties (“athlete’s foot”): <ul style="list-style-type: none"> <li>▪ Interdigital <b>E</b>; most common</li> <li>▪ Moccasin distribution <b>F</b></li> <li>▪ Vesicular type</li> </ul>
<b>Tinea unguium</b>	Onychomycosis; occurs on nails.
<b>Tinea ( pityriasis) versicolor</b>	Caused by <i>Malassezia</i> spp. ( <i>Pityrosporum</i> spp.), a yeast-like fungus (not a dermatophyte despite being called tinea). Degradation of lipids produces acids that inhibit tyrosinase (involved in melanin synthesis) → hypopigmentation <b>G</b> ; hyperpigmentation and/or pink patches can also occur due to inflammatory response. Less pruritic than dermatophytes. Can occur any time of year, but more common in summer (hot, humid weather). “Spaghetti and meatballs” appearance on microscopy <b>H</b> . 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 (people who inject drugs), disseminated candidiasis (especially in neutropenic patients), chronic mucocutaneous candidiasis.

Treatment: oral fluconazole/topical azoles for vaginal; nystatin, azoles, or, rarely, echinocandins for oral; fluconazole, echinocandins, or amphotericin B for esophageal or systemic disease.

#### *Aspergillus fumigatus*

Septate hyphae that branch at 45° Acute Angle **D E**.

Causes invasive aspergillosis in immunocompromised patients, especially those with neutrophil dysfunction (eg, chronic granulomatous disease) because *Aspergillus* is catalase  $\oplus$ .

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

Some species of *Aspergillus* produce Aflatoxins (associated with hepatocellular carcinoma). Treatment: voriconazole or echinocandins (2nd-line).

**Allergic bronchopulmonary aspergillosis (ABPA)**—hypersensitivity response to *Aspergillus* growing in lung mucus. Associated with asthma and cystic fibrosis; may cause bronchiectasis and eosinophilia.

#### *Cryptococcus neoformans*

5–10  $\mu\text{m}$  with narrow budding. Heavily encapsulated yeast. Not dimorphic.

Found in soil, pigeon droppings. Acquired through inhalation with hematogenous dissemination to meninges. Highlighted with India ink (clear halo **G**) and mucicarmine (red inner capsule **H**).

Latex agglutination test detects polysaccharide capsular antigen and is more sensitive and specific. Causes cryptococcosis, cryptococcal meningitis, cryptococcal encephalitis (“soap bubble” lesions in brain), primarily in immunocompromised.

Treatment: amphotericin B + flucytosine followed by fluconazole for cryptococcal meningitis.

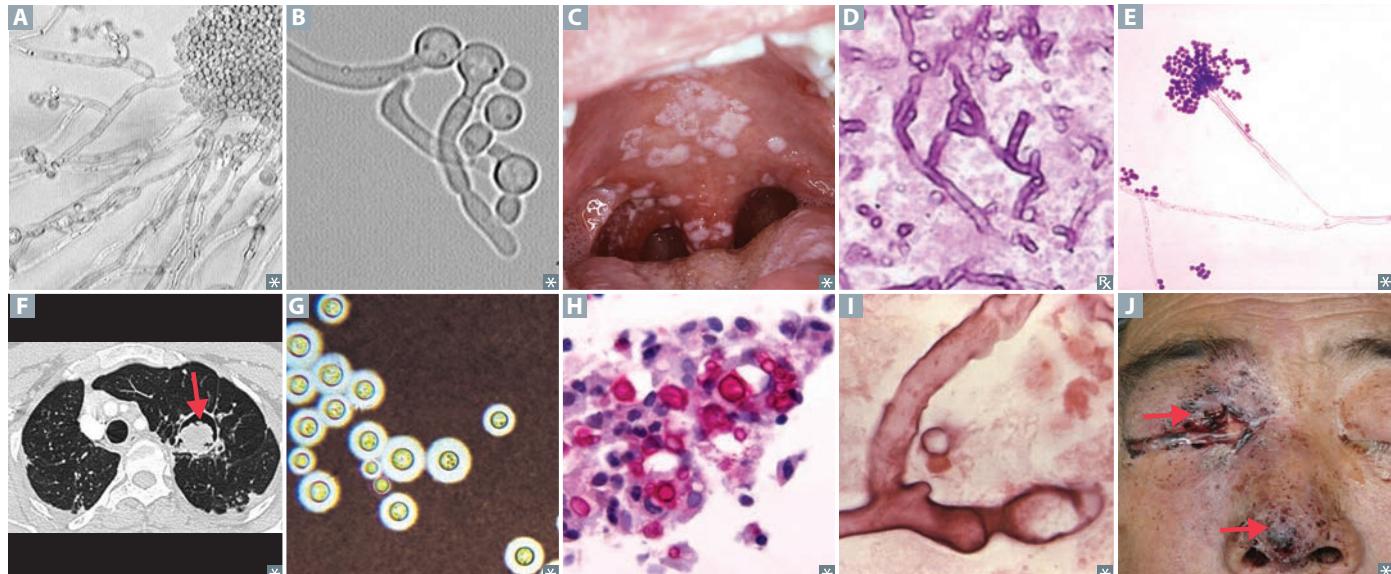
#### *Mucor and Rhizopus spp*

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

Causes mucormycosis, mostly in patients with DKA and/or neutropenia (eg, leukemia). Inhalation of spores  $\rightarrow$  fungi proliferate in blood vessel walls, penetrate cribriform plate, and enter brain.

Rhinocerebral, frontal lobe abscess; cavernous sinus thrombosis. Headache, facial pain, black necrotic eschar on face **J**; may have cranial nerve involvement.

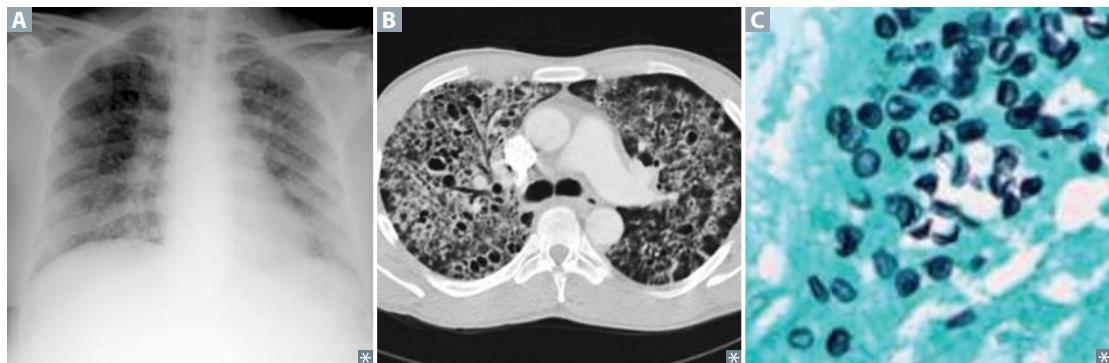
Treatment: surgical debridement, amphotericin B or isavuconazole.



***Pneumocystis jirovecii***

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

Treatment/prophylaxis: TMP-SMX, pentamidine, dapsone (prophylaxis as single agent, or treatment in combination with TMP), atovaquone. Start prophylaxis when CD4+ cell count drops to < 200 cells/mm<sup>3</sup> in people living with HIV.

***Sporothrix schenckii***

Causes sporotrichosis. Dimorphic fungus. Exists as a **cigar**-shaped yeast at 37 °C in the human body and as hyphae with spores in soil (conidia). Lives on vegetation. When spores are traumatically introduced into the skin, typically by a thorn ("**rose gardener's disease**"), causes local pustule or ulcer with nodules along draining lymphatics (ascending lymphangitis **A**). Disseminated disease possible in immunocompromised host.

Treatment: itraconazole or **potassium iodide** (only for cutaneous/lymphocutaneous). Think of a **rose gardener** who smokes a **cigar** and **pot**.

## ► MICROBIOLOGY—PARASITOLOGY

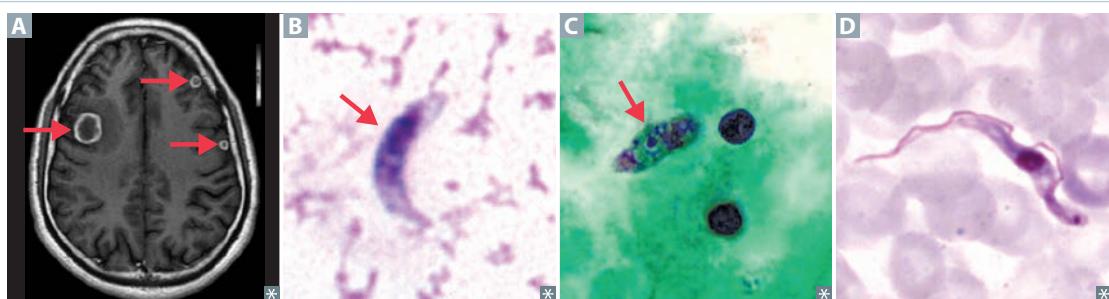
## Protozoa—gastrointestinal infections

ORGANISM	DISEASE	TRANSMISSION	DIAGNOSIS	TREATMENT
<i>Giardia lamblia</i>	<b>Giardiasis</b> —bloating, flatulence, foul-smelling, nonbloody, fatty diarrhea (often seen in campers/hikers)—think <b>fat-rich Ghirardelli chocolates</b> for <b>fatty stools</b> of <i>Giardia</i>	Cysts in water	Multinucleated trophozoites <b>A</b> or cysts <b>B</b> in stool, antigen detection, PCR	Metronidazole
<i>Entamoeba histolytica</i>	<b>Amebiasis</b> —bloody diarrhea (dysentery), liver abscess (“anchovy paste” exudate), RUQ pain; histology of colon biopsy shows flask-shaped ulcers	Cysts in water	Serology, antigen testing, PCR, and/or trophozoites (with engulfed RBCs <b>C</b> in the cytoplasm) or cysts with up to 4 nuclei in stool <b>D</b> ; <b>Entamoeba Eats Erythrocytes</b>	Metronidazole; paromomycin or 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 <b>E</b> , antigen detection, PCR	Prevention (by filtering city water supplies); nitazoxanide in immunocompetent hosts

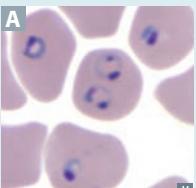


**Protozoa—CNS infections**

ORGANISM	DISEASE	TRANSMISSION	DIAGNOSIS	TREATMENT
<i>Toxoplasma gondii</i>	Immunocompetent: mononucleosis-like symptoms, ⊖ heterophile antibody test Reactivation in AIDS → brain abscesses usually seen as multiple ring-enhancing lesions on MRI <b>A</b> Congenital toxoplasmosis: classic triad of chorioretinitis, hydrocephalus, and intracranial calcifications	Cysts in meat (most common); oocysts in cat feces; crosses placenta (pregnant patients should avoid cats)	Serology, biopsy (tachyzoite) <b>B</b> ; PCR of amniotic fluid for possible intrauterine disease	Sulfadiazine + pyrimethamine Prophylaxis with TMP-SMX when CD4+ cell count < 100 cells/mm <sup>3</sup>
<i>Naegleria fowleri</i>	Rapidly fatal meningoencephalitis	Swimming in warm freshwater; enters via cribriform plate	Amoebas in CSF <b>C</b>	Amphotericin B has been effective for a few survivors
<i>Trypanosoma brucei</i>	<b>African sleeping sickness</b> — enlarged lymph nodes, recurring fever (due to antigenic variation), somnolence, coma	Tsetse fly, a painful bite	Trypomastigote in blood smear <b>D</b>	Suramin for blood- borne disease or <b>melarsoprol</b> for CNS penetration (“I <b>sure</b> am <b>mellow</b> when I’m <b>sleeping</b> ”)

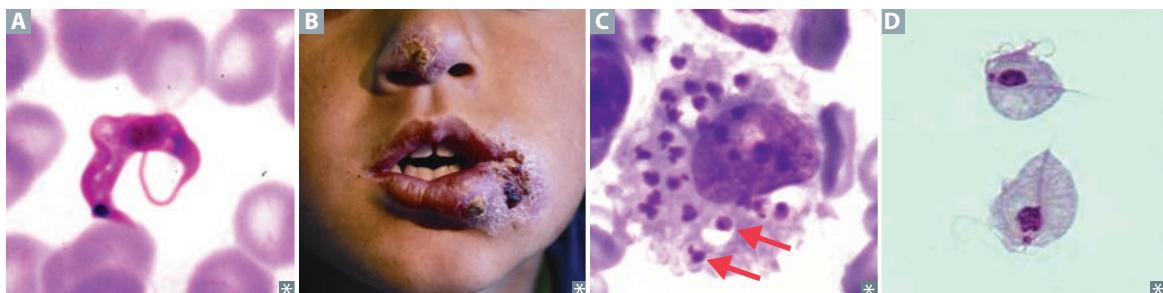


**Protozoa—hematologic infections**

ORGANISM	DISEASE	TRANSMISSION	DIAGNOSIS	TREATMENT
<i>Plasmodium</i> <i>P vivax/ovale</i> <i>P falciparum</i> <i>P malariae</i>	<p><b>Malaria</b>—fever, headache, anemia, splenomegaly; hypoglycemia in severe disease</p> <p><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</p> <p><i>P falciparum</i>—severe; irregular fever patterns; parasitized RBCs occlude capillaries in brain (cerebral malaria), kidneys, lungs</p> <p><i>P malariae</i>—72-hr cycle (quartan)</p>	<i>Anopheles</i> mosquito	Blood smear: trophozoite ring form within RBC <b>A</b> , schizont containing merozoites; red granules (Schüffner stippling) <b>B</b> throughout RBC cytoplasm seen with <i>P vivax/ovale</i>	Chloroquine (for sensitive species); if resistant, use mefloquine or atovaquone/proguanil If life-threatening, use intravenous quinidine or artesunate (test for G6PD deficiency) For <i>P vivax/ovale</i> , add primaquine for hypnozoite (test for G6PD deficiency)
<b>A</b> 				
<b>B</b> 				
<i>Babesia</i> <b>C</b> 	<b>Babesiosis</b> —fever and hemolytic anemia; predominantly in northeastern and north central United States; asplenia ↑ risk of severe disease due to inability to clear infected RBCs	<i>Ixodes</i> tick (also vector for <i>Borrelia burgdorferi</i> and <i>Anaplasma</i> spp)	Blood smear: ring form <b>C1</b> , “Maltese cross” <b>C2</b> ; PCR	Atovaquone + azithromycin

**Protozoa—others**

ORGANISM	DISEASE	TRANSMISSION	DIAGNOSIS	TREATMENT
<b>Visceral infections</b>				
<i>Trypanosoma cruzi</i>	<b>Chagas disease</b> —dilated cardiomyopathy with apical atrophy, megacolon, megaesophagus; predominantly in South America  Unilateral periorbital swelling (Romaña sign) characteristic of acute stage	Triatomine insect (kissing bug) bites and defecates around the mouth or eyes → fecal transmission into bite site or mucosa	Trypomastigote in blood smear <b>A</b>	<b>Benznidazole</b> or <b>nifurtimox</b> ; <b>cruzing</b> in my <b>Benz</b> , with a <b>fur</b> coat on
<i>Leishmania</i> spp	<b>Visceral leishmaniasis</b> ( <b>kala-azar</b> )—spiking fevers, hepatosplenomegaly, pancytopenia  <b>Cutaneous leishmaniasis</b> —skin ulcers <b>B</b>	Sandfly	Macrophages containing amastigotes <b>C</b>	Amphotericin B, sodium stibogluconate
<b>Sexually transmitted infections</b>				
<i>Trichomonas vaginalis</i>	<b>Vaginitis</b> —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) <b>D</b> on wet mount; punctate cervical hemorrhages (“strawberry cervix”)	Metronidazole for patient and partner(s) (prophylaxis; check for STI)

**Nematode routes of infection**

Ingested—*Enterobius*, *Ascaris*, *Toxocara*, *Trichinella*, *Trichuris*  
 Cutaneous—*Strongyloides*, *Ancylostoma*, *Necator*  
 Bites—*Loa loa*, *Onchocerca volvulus*, *Wuchereria bancrofti*

You'll get sick if you **EATTT** these!

These get into your feet from the **SAND**

Lay **LOW** to avoid getting bitten

**Nematodes (roundworms)**

ORGANISM	DISEASE	TRANSMISSION	TREATMENT
<b>Intestinal</b>			
<i>Enterobius vermicularis</i> <b>(pinworm)</b>	Causes anal pruritus (diagnosed by seeing egg <b>A</b> via the tape test).	Fecal-oral.	Bendazoles, pyrantel pamoate.
<i>Ascaris lumbricoides</i> <b>(giant roundworm)</b>	May cause obstruction at ileocecal valve, biliary obstruction, intestinal perforation, migrates from nose/mouth. Migration of larvae to alveoli → Löeffler syndrome (pulmonary eosinophilia).	Fecal-oral; knobby-coated, oval eggs seen in feces under microscope <b>B</b> .	Bendazoles.
<i>Strongyloides stercoralis</i> <b>(threadworm)</b>	GI (eg, duodenitis), pulmonary (eg, dry cough, hemoptysis), and cutaneous (eg, pruritus) symptoms. Hyperinfection syndrome caused by autoinfection (larvae enter bloodstream).	Larvae in soil penetrate skin; rhabditiform larvae seen in feces under microscope.	Ivermectin or bendazoles.
<i>Ancylostoma</i> spp., <i>Necator americanus</i> <b>(hookworms)</b>	Cause microcytic anemia by sucking blood from intestinal wall. <b>Cutaneous larva migrans</b> —pruritic, serpiginous rash <b>C</b> .	Larvae penetrate skin from walking barefoot on contaminated beach/soil.	Bendazoles or pyrantel pamoate.
<i>Trichinella spiralis</i>	Larvae enter bloodstream, encyst in striated muscle <b>D</b> → myositis. <b>Trichinosis</b> —fever, vomiting, nausea, periorbital edema, myalgia.	Undercooked meat (especially pork); fecal-oral (less likely).	Bendazoles.
<i>Trichuris trichiura</i> <b>(whipworm)</b>	Often asymptomatic; loose stools, anemia, rectal prolapse in children.	Fecal-oral.	Bendazoles.
<b>Tissue</b>			
<i>Toxocara canis</i>	<b>Visceral larva migrans</b> —migration into blood → inflammation of liver, eyes (visual impairment, blindness), CNS (seizures, coma), heart (myocarditis). Patients often asymptomatic.	Fecal-oral.	Bendazoles.
<i>Onchocerca volvulus</i>	Skin changes, loss of elastic fibers, river blindness ( <b>black</b> skin nodules, “ <b>black</b> sight”); allergic reaction possible.	Female <b>black</b> fly.	Ivermectin ( <b>iver</b> mectin for <b>riv</b> er blindness).
<i>Loa loa</i>	Swelling in skin, worm in conjunctiva.	Deer fly, horse fly, mango fly.	Diethylcarbamazine.
<i>Wuchereria bancrofti</i> , <i>Brugia malayi</i>	<b>Lymphatic filariasis (elephantiasis)</b> —worms invade lymph nodes. → inflammation → lymphedema <b>E</b> ; symptom onset after 9 mo–1 yr.	Female mosquito.	Diethylcarbamazine.



**Cestodes (tapeworms)**

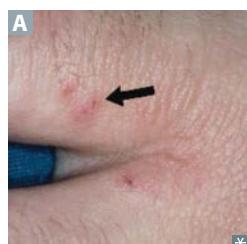
ORGANISM	DISEASE	TRANSMISSION	TREATMENT
<i>Taenia solium</i> <b>A</b>	Intestinal tapeworm	Ingestion of larvae encysted in undercooked pork	Praziquantel
	Cysticercosis, neurocysticercosis (cystic CNS lesions, seizures) <b>B</b>	Ingestion of eggs in food contaminated with human feces	Praziquantel; albendazole for neurocysticercosis
<i>Diphyllobothrium latum</i>	Vitamin B <sub>12</sub> deficiency (tapeworm competes for B <sub>12</sub> in intestine) → megaloblastic anemia	Ingestion of larvae in raw freshwater fish	Praziquantel, niclosamide
<i>Echinococcus granulosus</i> <b>C</b>	Hydatid cysts <b>D</b> (“eggshell calcification”) in liver <b>E</b> ; cyst rupture can cause anaphylaxis	Ingestion of eggs in food contaminated with dog feces Sheep are an intermediate host	Albendazole; surgery for complicated cysts

**Trematodes (flukes)**

ORGANISM	DISEASE	TRANSMISSION	TREATMENT
<i>Schistosoma</i>	Liver and spleen enlargement ( <b>A</b> shows <i>S mansoni</i> egg with lateral spine), fibrosis, inflammation, portal hypertension	Snails are intermediate host; cercariae penetrate skin of humans in contact with contaminated fresh water (eg, swimming or bathing)	Praziquantel
	Chronic infection with <i>S haematobium</i> (egg with terminal spine <b>B</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

## Ectoparasites

### *Sarcoptes scabiei*

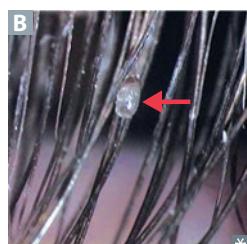


Mites burrow into stratum corneum and cause **scabies**—pruritus (worse at night) and serpiginous burrows (lines) often between fingers and toes **A**.

Common in children, crowded populations (jails, nursing homes); transmission through skin-to-skin contact (most common) or via fomites.

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

### *Pediculus humanus*/ *Phthirus pubis*



Blood-sucking lice that cause intense pruritus with associated excoriations, commonly on scalp and neck (head lice), waistband and axilla (body lice), or pubic and perianal regions (pubic lice).

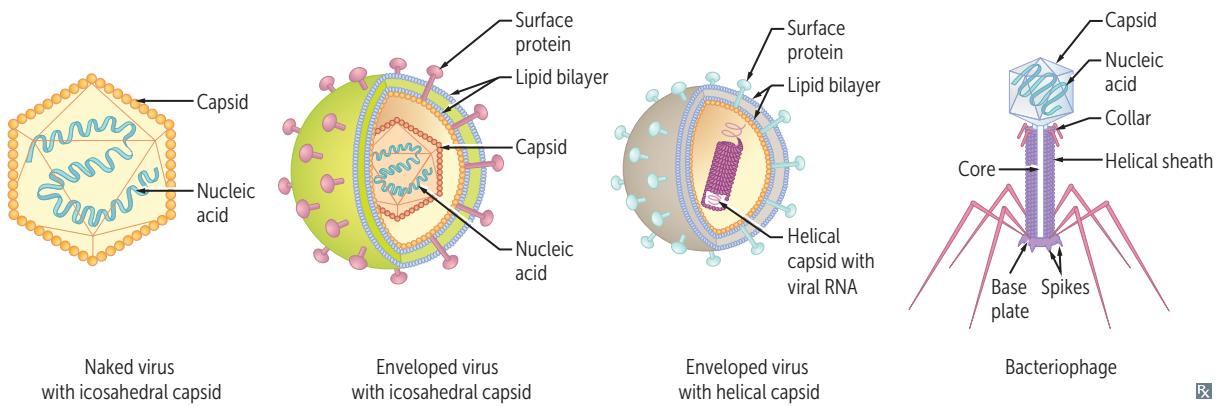
Body lice can transmit *Rickettsia prowazekii* (epidemic typhus), *Borrelia recurrentis* (relapsing fever), *Bartonella quintana* (trench fever).

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

## Parasite hints

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

## ► MICROBIOLOGY—VIROLOGY

**Viral structure—general features****Viral genetics****Recombination**

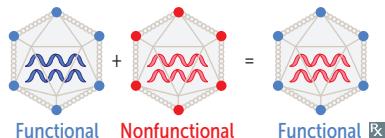
Exchange of genes between 2 chromosomes by crossing over within regions of significant base sequence homology.

**Reassortment**

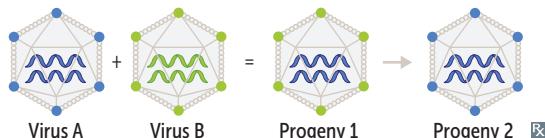
When viruses with segmented genomes (eg, influenza virus) exchange genetic material. For example, the 2009 novel H1N1 influenza A pandemic emerged via complex viral reassortment of genes from human, swine, and avian viruses. Has potential to cause antigenic shift.

**Complementation**

When 1 of 2 viruses that infect the cell has a mutation that results in a nonfunctional protein, the nonmutated virus “complements” the mutated one by making a functional protein that serves both viruses. For example, hepatitis D virus requires the presence of replicating hepatitis B virus to supply HBsAg, the envelope protein for HDV.

**Phenotypic mixing**

Occurs with simultaneous infection of a cell with 2 viruses. For progeny 1, genome of virus A can be partially or completely coated (forming pseudovirion) with the surface proteins of virus B. Type B protein coat determines the tropism (infectivity) of the hybrid virus. Progeny from subsequent infection of a cell by progeny 1 will have a type A coat that is encoded by its type A genetic material.



**DNA viral genomes**

All DNA viruses have dsDNA genomes except Parvoviridae (ssDNA). All are linear except papilloma-, polyoma-, and hepadnaviruses (circular).

All are dsDNA (like our cells), except “**part-of-a-virus**” (**parvovirus**) is ssDNA. *Parvus* = small.

**RNA viral genomes**

All RNA viruses have ssRNA genomes except Reoviridae (dsRNA). ⊕ stranded RNA viruses: I went to a **retro** (**retrovirus**) **toga** (**togavirus**) party, where I drank **flavored** (**flavivirus**) **Corona** (**coronavirus**) and ate **hippie** (**hepevirus**) **California** (**calicivirus**) **pickles** (**picornavirus**).

All are ssRNA, except “**repeato**-virus” (**reovirus**) is dsRNA.

**Naked viral genome infectivity**

Purified nucleic acids of most dsDNA viruses (except poxviruses and HBV) and ⊕ strand ssRNA (≈ mRNA) viruses are infectious. Naked nucleic acids of ⊖ strand ssRNA and dsRNA viruses are not infectious. They require polymerases contained in the complete virion.

**Viral envelopes**

Generally, enveloped viruses acquire their envelopes from plasma membrane when they exit from cell. Exceptions include herpesviruses, which acquire envelopes from nuclear membrane. Naked (nonenveloped) viruses include papillomavirus, adenovirus, parvovirus, polyomavirus, calicivirus, picornavirus, reovirus, and hepevirus.

Enveloped DNA viruses (**herpesvirus**, **hepatnavirus**, **poxvirus**) **have helpful** protection.

**DNA virus characteristics**

Some general rules—all DNA viruses:

GENERAL RULE	COMMENTS
Are <b>HHAPPPP</b> y viruses	Hepadna, Herpes, Adeno, Pox, Parvo, Papilloma, Polyoma.
Are double stranded	Except parvo (single stranded).
Have linear genomes	Except papilloma and polyoma (circular, supercoiled) and hepatna (circular, incomplete).
Are icosahedral	Except pox (complex).
Replicate in the nucleus	Except pox (carries own DNA-dependent RNA polymerase).

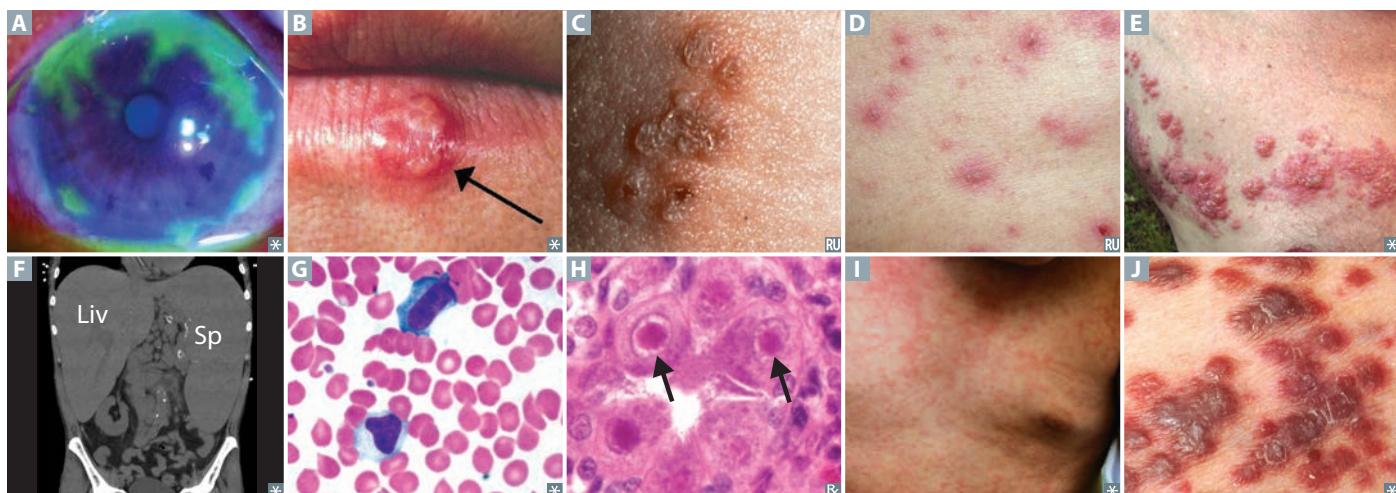
<b>DNA viruses</b>		All replicate in the nucleus (except poxvirus). “Pox is out of the box (nucleus).”	
VIRAL FAMILY	ENVELOPE	DNA STRUCTURE	MEDICAL IMPORTANCE
<b>Herpesviruses</b>	Yes	DS and linear	See Herpesviruses entry
<b>Poxvirus</b>	Yes	DS and linear (largest DNA virus)	Smallpox eradicated world wide by use of the live-attenuated vaccine Cowpox (“milkmaid blisters”) <b>Molluscum contagiosum</b> —flesh-colored papule with central umbilication
<b>Hepadnavirus</b>	Yes	Partially DS and circular	HBV: <ul style="list-style-type: none"><li>▪ Acute or chronic hepatitis</li><li>▪ Not a retrovirus but has reverse transcriptase</li></ul>
<b>Adenovirus</b> 	No	DS and linear	Febrile pharyngitis <b>A</b> —sore throat Acute hemorrhagic cystitis Pneumonia Conjunctivitis—“pink eye” Gastroenteritis Myocarditis
<b>Papillomavirus</b>	No	DS and circular	HPV—warts, cancer (cervical, anal, penile, or oropharyngeal); serotypes 1, 2, 6, 11 associated with warts; serotypes 16, 18 associated with cancer
<b>Polyomavirus</b>	No	DS and circular	JC virus—progressive multifocal leukoencephalopathy (PML) in HIV BK virus—transplant patients, commonly targets kidney <b>JC</b> : Junky Cerebrum; <b>BK</b> : Bad Kidney
<b>Parvovirus</b>	No	SS and linear (smallest DNA virus)	B19 virus—aplastic crises in sickle cell disease, “slapped cheek” rash in children (erythema infectiosum, or fifth disease); infects RBC precursors and endothelial cells → RBC destruction → hydrops fetalis and death in fetus, pure RBC aplasia and rheumatoid arthritis-like symptoms in adults

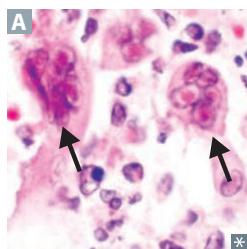
### **Herpesviruses** Enveloped, DS, and linear viruses

VIRUS	ROUTE OF TRANSMISSION	CLINICAL SIGNIFICANCE	NOTES
<b>Herpes simplex virus-1</b>	Respiratory secretions, saliva	Gingivostomatitis, keratoconjunctivitis <b>A</b> , herpes labialis (cold sores) <b>B</b> , herpetic whitlow on finger, temporal lobe encephalitis, esophagitis, erythema multiforme	Most commonly latent in trigeminal ganglia Most common cause of sporadic encephalitis, can present as altered mental status, seizures, and/or aphasia
<b>Herpes simplex virus-2</b>	Sexual contact, perinatal	Herpes genitalis <b>C</b> , neonatal herpes	Most commonly latent in sacral ganglia Viral meningitis more common with HSV-2 than with HSV-1

**Herpesviruses (continued)**

VIRUS	ROUTE OF TRANSMISSION	CLINICAL SIGNIFICANCE	NOTES
<b>Varicella-Zoster virus (HHV-3)</b>	Respiratory secretions, contact with fluid from vesicles	Varicella-zoster (chickenpox <b>D</b> , shingles <b>E</b> ), encephalitis, pneumonia Most common complication of shingles is post-herpetic neuralgia	Latent in dorsal root or trigeminal ganglia; CN V <sub>1</sub> branch involvement can cause herpes zoster ophthalmicus
<b>Epstein-Barr virus (HHV-4)</b>	Respiratory secretions, saliva; aka “kissing disease,” (common in teens, young adults)	<b>Mononucleosis</b> —fever, hepatosplenomegaly <b>F</b> , pharyngitis, and lymphadenopathy (especially posterior cervical nodes); avoid contact sports until resolution due to risk of splenic rupture Associated with lymphomas (eg, endemic Burkitt lymphoma), nasopharyngeal carcinoma (especially Asian adults), lymphoproliferative disease in transplant patients	Infects <b>B</b> cells through CD21, “Must be <b>21</b> to drink <b>Beer</b> in a <b>Barr</b> ” Atypical lymphocytes on peripheral blood smear <b>G</b> —not infected <b>B</b> cells but reactive cytotoxic T cells ⊕ Monospot test—heterophile antibodies detected by agglutination of sheep or horse RBCs Use of amoxicillin (eg, for presumed strep pharyngitis) can cause maculopapular rash
<b>Cytomegalovirus (HHV-5)</b>	Congenital, transfusion, sexual contact, saliva, urine, transplant	Mononucleosis (⊖ Monospot) in immunocompetent patients; infection in immunocompromised, especially pneumonia in transplant patients; esophagitis; AIDS <b>retinitis</b> (“ <b>sight</b> omegalovirus”): hemorrhage, cotton-wool exudates, vision loss Congenital CMV	Infected cells have characteristic “owl eye” intranuclear inclusions <b>H</b> Latent in mononuclear cells
<b>Human herpesviruses 6 and 7</b>	Saliva	Roseola infantum (exanthem subitum): high fevers for several days that can cause seizures, followed by diffuse macular rash (starts on trunk then spreads to extremities) <b>I</b> ; usually seen in children <2 years old	<b>Roseola</b> : fever first, <b>Rosy</b> (rash) later Self-limited illness HHV-7—less common cause of roseola
<b>Human herpesvirus 8</b>	Sexual contact	Kaposi sarcoma (neoplasm of endothelial cells). Seen in HIV/AIDS and transplant patients. Dark/violaceous plaques or nodules <b>J</b> representing vascular proliferations	Can also affect GI tract and lungs



**HSV identification**

PCR of skin lesions is test of choice.

CSF PCR for herpes encephalitis.

Tzanck test (outdated)—a smear of an opened skin vesicle to detect multinucleated giant cells **A** commonly seen in HSV-1, HSV-2, and VZV infection.

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

**Receptors used by viruses**

VIRUS	RECEPTORS
CMV	Integrins (heparan sulfate)
EBV	CD21
HIV	CD4, CXCR4, CCR5
Parvovirus B19	P antigen on RBCs
Rabies	Nicotinic AChR
<b>Rhinovirus</b>	<b>ICAM-1 (I CAMe to see the rhino)</b>

RNA viruses				
VIRAL FAMILY	ENVELOPE	RNA STRUCTURE	CAPSID SYMMETRY	MEDICAL IMPORTANCE
<b>Reoviruses</b>	No	DS linear Multisegmented	Icosahedral (double)	Coltivirus <sup>a</sup> —Colorado tick fever Rotavirus—cause of fatal diarrhea in children
<b>Picornaviruses</b>	No	SS $\oplus$ linear	Icosahedral	Poliovirus—polio-Salk/Sabin vaccines—IPV/OPV Echovirus—aseptic meningitis Rhinovirus—“common cold” Coxsackievirus—aseptic meningitis; herpangina (mouth blisters, fever); hand, foot, and mouth disease; myocarditis; pericarditis HAV—acute viral hepatitis
				PERCH
<b>Hepeviruses</b>	No	SS $\oplus$ linear	Icosahedral	HEV
<b>Caliciviruses</b>	No	SS $\oplus$ linear	Icosahedral	Norovirus—viral gastroenteritis
<b>Flaviviruses</b>	Yes	SS $\oplus$ linear	Icosahedral	HCV Yellow fever <sup>a</sup> Dengue <sup>a</sup> St. Louis encephalitis <sup>a</sup> West Nile virus <sup>a</sup> —meningoencephalitis, flaccid paralysis Zika virus <sup>a</sup>
<b>Togaviruses</b>	Yes	SS $\oplus$ linear	Icosahedral	Toga CREW—Chikungunya virus <sup>a</sup> (co-infection with dengue virus can occur), Rubella, Eastern and Western equine encephalitis
<b>Retroviruses</b>	Yes	SS $\oplus$ linear 2 copies	Icosahedral (HTLV), complex and conical (HIV)	Have reverse transcriptase HTLV—T-cell leukemia HIV—AIDS
<b>Coronaviruses</b>	Yes	SS $\oplus$ linear	Helical	“Common cold,” SARS, MERS, COVID-19
<b>Orthomyxoviruses</b>	Yes	SS $\ominus$ linear 8 segments	Helical	Influenza virus
<b>Paramyxoviruses</b>	Yes	SS $\ominus$ linear Nonsegmented	Helical	PaRaMyxovirus: Parainfluenza—croup RSV—bronchiolitis in babies Measles, Mumps
<b>Rhabdoviruses</b>	Yes	SS $\ominus$ linear	Helical	Rabies
<b>Filoviruses</b>	Yes	SS $\ominus$ linear	Helical	Ebola/Marburg hemorrhagic fever—often fatal.
<b>Arenaviruses</b>	Yes	SS $\oplus$ and $\ominus$ circular 2 segments	Helical	LCMV—lymphocytic choriomeningitis virus Lassa fever encephalitis—spread by rodents
<b>Bunyaviruses</b>	Yes	SS $\ominus$ circular 3 segments	Helical	California encephalitis <sup>a</sup> Sandfly/Rift Valley fevers <sup>a</sup> Crimean-Congo hemorrhagic fever <sup>a</sup> Hantavirus—hemorrhagic fever, pneumonia
<b>Delta virus</b>	Yes	SS $\ominus$ circular	Uncertain	HDV is a “Defective” virus that requires the presence of HBV to replicate

SS, single-stranded; DS, double-stranded;  $\oplus$ , positive sense;  $\ominus$ , negative sense; <sup>a</sup>= arbovirus, arthropod borne (mosquitoes, ticks).

**Negative-stranded viruses**

Must transcribe  $\ominus$  strand to  $\oplus$ . Virion brings its own RNA-dependent RNA polymerase. They include **arenaviruses**, **bunyaviruses**, **paramyxoviruses**, **orthomyxoviruses**, **filoviruses**, and **rhabdoviruses**.

Always bring polymerase or fail replication.

**Segmented viruses**

All are RNA viruses. They include **Bunyaviruses** (3 segments), **Orthomyxoviruses** (influenza viruses) (8 segments), **Arenaviruses** (2 segments), and **Reoviruses** (10–12 segments).

**BOARDing flight 382** in 10–12 minutes.

**Picornavirus**

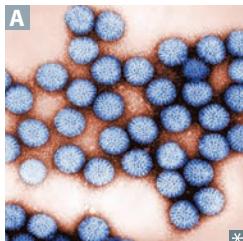
Includes **Poliovirus**, **Echovirus**, **Rhinovirus**, **Coxsackievirus**, and **HAV**. RNA is translated into 1 large polypeptide that is cleaved by virus-encoded proteases into functional viral proteins. Poliovirus, echovirus, and coxsackievirus are enteroviruses and can cause aseptic (viral) meningitis.

**PicoRNAvirus** = small **RNA** virus.  
**PERCH** on a “peak” (pico).

**Rhinovirus**

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

**Rhino** has a runny **nose**.

**Rotavirus**

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

**Rotavirus** = **right out the anus**. CDC recommends routine vaccination of all infants except those with a history of intussusception (rare adverse effect of rotavirus vaccination) or SCID.

**Influenza viruses**

Orthomyxoviruses. Enveloped,  $\ominus$  ssRNA viruses with segmented genome. Contain hemagglutinin (binds sialic acid and promotes viral entry) and neuraminidase (promotes progeny virion release) antigens. Patients at risk for fatal bacterial superinfection, most commonly *S. aureus*, *S. pneumoniae*, and *H. influenzae*. Treatment: supportive +/- neuraminidase inhibitor (eg, oseltamivir, zanamivir).

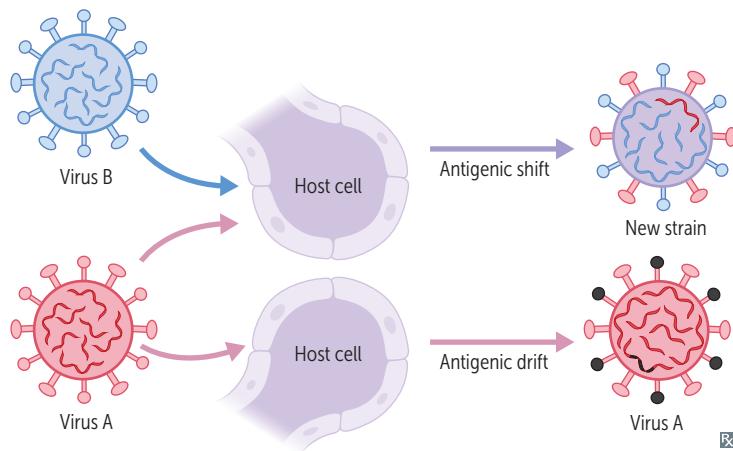
**Hemagglutinin:** lets the virus **in**  
**Neuraminidase:** sends the virus **away**  
 Reformulated vaccine ("the flu shot") contains viral strains most likely to appear during the flu season, due to the virus' rapid genetic change. Killed viral vaccine is most frequently used. Live attenuated vaccine contains temperature-sensitive mutant that replicates in the nose but not in the lung; administered intranasally. **Sudden shift** is more deadly than **gradual drift**.

**Genetic/antigenic shift**

Infection of 1 cell by 2 different segmented viruses (eg, swine influenza and human influenza viruses) → RNA segment reassortment → dramatically different virus (genetic shift) → major global outbreaks (pandemics).

**Genetic/antigenic drift**

Random mutation in hemagglutinin (HA) or neuraminidase (NA) genes → minor changes in HA or NA protein (drift) occur frequently → major global outbreaks (pandemics).

**Rubella virus**

A togavirus. Causes rubella, once known as German (3-day) measles. Fever, postauricular and other lymphadenopathy, arthralgias, and fine, maculopapular rash that starts on face and spreads centrifugally to involve trunk and extremities **A**.

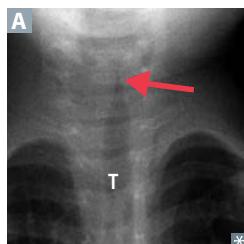
Causes mild disease in children but serious congenital disease (a TORCH infection). Congenital rubella findings include classic triad of sensorineural deafness, cataracts, and patent ductus arteriosus. "Blueberry muffin" appearance may be seen due to dermal extramedullary hematopoiesis.

**Paramyxoviruses**

Paramyxoviruses cause disease in children. They include those that cause parainfluenza (croup), mumps, measles, RSV, and human metapneumovirus. All subtypes can cause respiratory tract infection (bronchiolitis, pneumonia) in infants. All contain surface F (fusion) protein, which causes respiratory epithelial cells to fuse and form multinucleated cells. Palivizumab (monoclonal antibody against F protein) prevents pneumonia caused by RSV infection in premature infants.

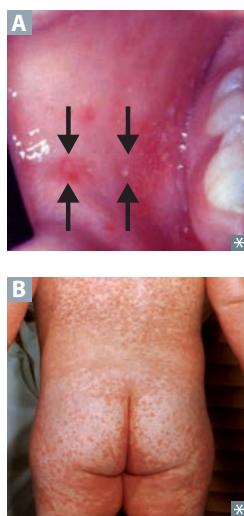
**Palivizumab** for paramyxovirus (RSV) prophylaxis in preemies.

### Acute laryngotracheobronchitis



Also called croup. Caused by parainfluenza viruses. Virus membrane contains hemagglutinin (binds sialic acid and promotes viral entry) and neuraminidase (promotes progeny virion release) antigens. Results in a “seal-like” barking cough and inspiratory stridor. Narrowing of upper trachea and subglottis leads to characteristic steeple sign on x-ray **A**.

### Measles (rubeola) virus



Usual presentation involves prodromal fever with cough, coryza, and conjunctivitis, then eventually Koplik spots (bright red spots with blue-white center on buccal mucosa **A**), followed 1–2 days later by a maculopapular rash **B** that starts at the head/neck and spreads downward.

Lymphadenitis with Warthin-Finkeldey giant cells (fused lymphocytes) in a background of paracortical hyperplasia. Possible sequelae:

- Subacute sclerosing panencephalitis (SSPE): personality changes, dementia, autonomic dysfunction, death (occurs years later)
- Encephalitis (1:1000): symptoms appear within few days of rash
- Giant cell pneumonia (rare except in immunosuppressed)

#### 4 C's of measles:

- Cough
- Coryza
- Conjunctivitis
- “C”oplik spots

Vitamin A supplementation can reduce morbidity and mortality from measles, particularly in malnourished children. Pneumonia is the most common cause of measles-associated death in children.

### Mumps virus



Uncommon due to effectiveness of MMR vaccine.

Symptoms: Parotitis **A**, Orchitis (inflammation of testes), aseptic Meningitis, and Pancreatitis. Can cause sterility (especially after puberty).

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

### Chikungunya virus

An alphavirus member of togavirus family, transmitted by *Aedes* mosquito. Systemic infection that produces inflammatory polyarthritides that can become chronic. Other symptoms include high fever, maculopapular rash, headache, lymphadenopathy. Hemorrhagic manifestations are uncommon (vs dengue fever). Diagnosed with RT-PCR or serology. No antiviral therapy and no vaccine.

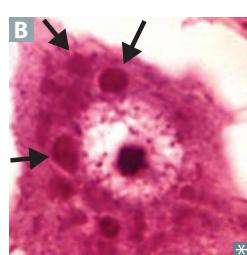
**Dengue virus**

A flavivirus, transmitted by *Aedes* mosquito; most common mosquito-borne viral disease in the world. Can present as dengue fever (fever, rash, headache, myalgias, arthralgias, neutropenia), dengue hemorrhagic fever (dengue fever + bleeding and plasma leakage due to thrombocytopenia and extremely high or low hematocrit), or dengue shock syndrome (plasma leakage leading to circulatory collapse). Diagnosed by PCR or serology.

Dengue hemorrhagic fever is most common in patients infected with a different serotype after their initial infection due to antibody-dependent enhancement of disease.

Presents similarly to Chikungunya virus and is transmitted by the same mosquito vector; coinfections can occur. Dengue virus is more likely to cause neutropenia, thrombocytopenia, hemorrhage, shock, and death.

Live, recombinant vaccine uses yellow fever virus as a backbone into which the genes for the envelope and premembrane proteins of dengue virus have been inserted.

**Rabies virus**

Bullet-shaped virus **A**. Negri bodies (cytoplasmic inclusions **B**) commonly found in Purkinje cells of cerebellum and in hippocampal neurons. Rabies has long incubation period (weeks to months) before symptom onset. Postexposure prophylaxis is wound cleaning plus immunization with killed vaccine and rabies immunoglobulin. Example of passive-active immunity.

Travels to the CNS by migrating in a retrograde fashion (via dynein motors) up nerve axons after binding to ACh receptors.

Progression of disease: fever, malaise → agitation, photophobia, hydrophobia, hypersalivation → paralysis, coma → death.

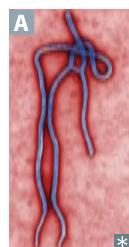
Infection more commonly from bat, raccoon, and skunk bites than from dog bites in the United States; aerosol transmission (eg, bat caves) also possible.

**Yellow fever virus**

A flavivirus (also an arbovirus) transmitted by *Aedes* mosquitoes. Virus has a monkey or human reservoir.

Symptoms: high fever, black vomitus, jaundice, hemorrhage, backache. May see Councilman bodies (eosinophilic apoptotic globules) on liver biopsy.

*Flavi* = yellow, jaundice.

**Ebola virus**

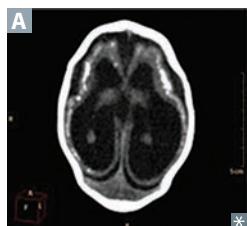
A filovirus **A**. Following an incubation period of up to 21 days, presents with abrupt onset of flu-like symptoms, diarrhea/vomiting, high fever, myalgia. Can progress to DIC, diffuse hemorrhage, shock.

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.

Vaccination of contacts, strict isolation of infected individuals, and barrier practices for health care workers are key to preventing transmission.

**Zika virus**

A flavivirus most commonly transmitted by *Aedes* mosquito bites. Causes conjunctivitis, low-grade pyrexia, and itchy rash in 20% of cases. Outbreaks more common in tropical and subtropical climates. Supportive care, no definitive treatment. Diagnose with RT-PCR or serology.

Sexual and vertical transmission occurs. Can lead to miscarriage or congenital Zika syndrome: brain imaging **A** shows ventriculomegaly, subcortical calcifications. Clinical features include:

- Microcephaly
- Ocular anomalies
- Motor abnormalities (spasticity, seizures)

**Severe acute respiratory syndrome coronavirus 2**

SARS-CoV-2 is a novel  $\oplus$  ssRNA coronavirus and the cause of the ongoing COVID-19 pandemic. Spreads primarily through respiratory droplets and aerosols. Host cell entry occurs by attachment of viral spike protein to angiotensin-converting enzyme 2 receptor on cell membranes.

Clinical course varies; often asymptomatic. Symptoms include

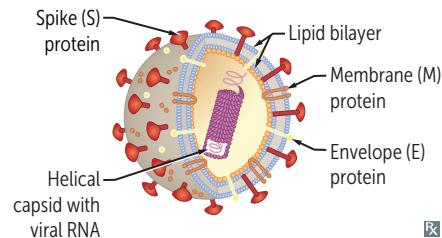
- Common: fever, dry cough, shortness of breath, fatigue.
- More specific: anosmia (loss of smell), dysgeusia (altered taste).

Potential complications include respiratory failure, hypercoagulability, shock, organ failure, death.

Risk factors for severe illness or death include increasing age, obesity, diabetes, hypertension, chronic kidney disease, and severe cardiopulmonary illness.

Diagnosed by RT-PCR (most common); antigen and antibody tests are available.

Treatment options for hospitalized adults include remdesivir (nucleoside analog), convalescent plasma, and dexamethasone (to treat cytokine release syndrome).



**Hepatitis viruses**

Signs and symptoms of all hepatitis viruses: episodes of fever, jaundice, ↑ ALT and AST. Naked viruses (HAV and HEV) lack an envelope and are not destroyed by the gut: the **vowels** hit your **bowels**.

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

HCV lacks 3'-5' exonuclease activity → no proofreading ability → antigenic variation of HCV envelope proteins. Host antibody production lags behind production of new mutant strains of HCV.

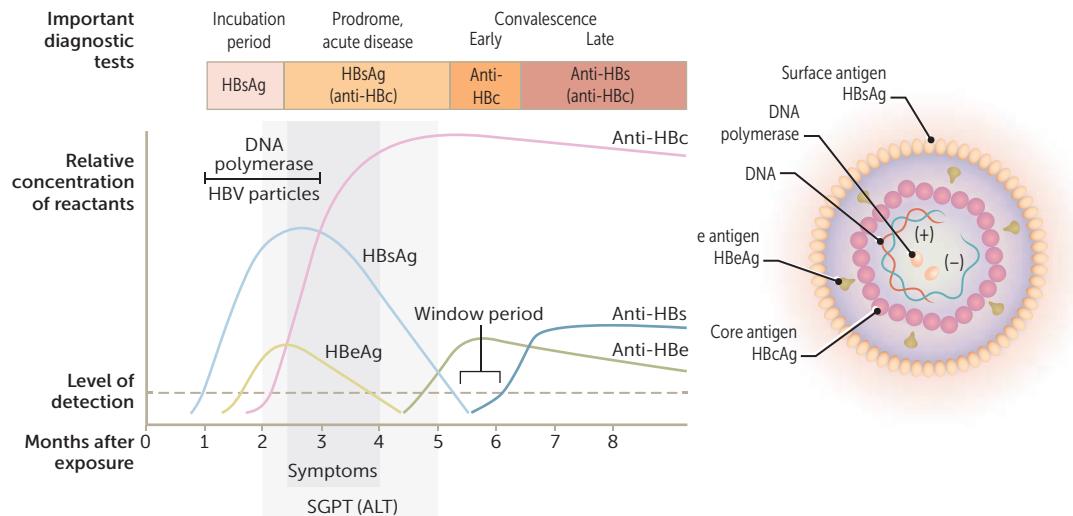
Virus	HAV	HBV	HCV	HDV	HEV
FAMILY	RNA picornavirus	DNA hepadnavirus	RNA flavivirus	RNA deltavirus	RNA hepevirus
TRANSMISSION	Fecal-oral (shellfish, travelers, day care)	Parenteral (Blood), sexual (Bedroom), perinatal (Birthing)	Primarily blood (IV drugs, posttransfusion)	Parenteral, sexual, perinatal	Fecal-oral, especially waterborne
INCUBATION	Short (weeks)	Long (months)	Long	Superinfection (HDV after HBV) = short Coinfection (HDV with HBV) = long	Short
CLINICAL COURSE	Acute and self-limiting (adults), Asymptomatic (children)	Initially like serum sickness (fever, arthralgias, rash); may progress to carcinoma	May progress to Cirrhosis or Carcinoma	Similar to HBV	Fulminant hepatitis in Expectant (pregnant) patients
PROGNOSIS	Good	Adults → mostly full resolution; neonates → worse prognosis	Majority develop stable, Chronic hepatitis C	Superinfection → worse prognosis	High mortality in pregnant patients
HCC RISK	No	Yes	Yes	Yes	No
LIVER BIOPSY	Hepatocyte swelling, monocyte infiltration, Councilman bodies	Granular eosinophilic “ground glass” appearance due to accumulation of surface antigen within infected hepatocytes; cytotoxic T cells mediate damage	Lymphoid aggregates with focal areas of macrovesicular steatosis	Similar to HBV	Patchy necrosis
NOTES	No carrier state	Carrier state common	Carrier state very common	Defective virus, Depends on HBV HBsAg coat for entry into hepatocytes	Enteric, Epidemic (eg, in parts of Asia, Africa, Middle East), no carrier state

### Extrahepatic manifestations of hepatitis B and C

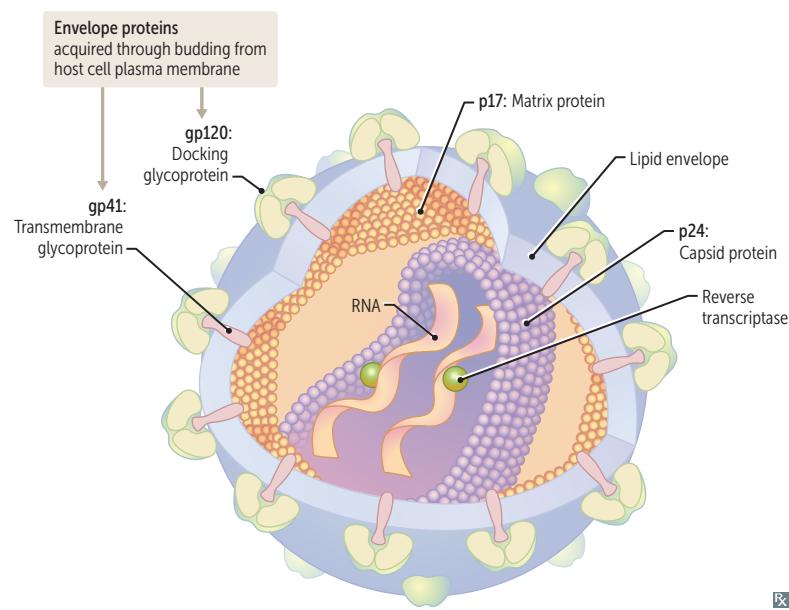
	Hepatitis B	Hepatitis C
HEMATOLOGIC	Aplastic anemia	Essential mixed cryoglobulinemia, ↑ risk B-cell NHL, ITP, autoimmune hemolytic anemia
RENAL	Membranous GN > membranoproliferative GN	Membranoproliferative GN > membranous GN
VASCULAR	Polyarteritis nodosa	Leukocytoclastic vasculitis
DERMATOLOGIC		Sporadic porphyria cutanea tarda, lichen planus
ENDOCRINE		↑ risk of diabetes mellitus, autoimmune hypothyroidism

### Hepatitis serologic markers

Anti-HAV (IgM)	IgM antibody to HAV; best test to detect acute hepatitis A.
Anti-HAV (IgG)	IgG antibody indicates prior HAV infection and/or prior vaccination; protects against reinfection.
HBsAg	Antigen found on surface of HBV; indicates hepatitis B infection.
Anti-HBs	Antibody to HBsAg; indicates immunity to hepatitis B due to vaccination or recovery from infection.
HBcAg	Antigen associated with core of HBV.
Anti-HBc	Antibody to HBcAg; IgM = acute/recent infection; IgG = prior exposure or chronic infection. IgM anti-HBc may be the sole + marker of infection during window period.
HBeAg	Secreted by infected hepatocyte into circulation. Not part of mature HBV virion. Indicates active viral replication and therefore high transmissibility and poorer prognosis.
Anti-HBe	Antibody to HBeAg; indicates low transmissibility.



	HBsAg	Anti-HBs	HBeAg	Anti-HBe	Anti-HBc
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, Integrase, Protease; RIP “Pol” (Paul)

Reverse transcriptase synthesizes dsDNA from genomic RNA; dsDNA integrates into host genome.

Virus binds CD4 as well as a coreceptor, either CCR5 on macrophages (early infection) or CXCR4 on T cells (late infection).

Homozygous CCR5 mutation = immunity.

Heterozygous CCR5 mutation = slower course.

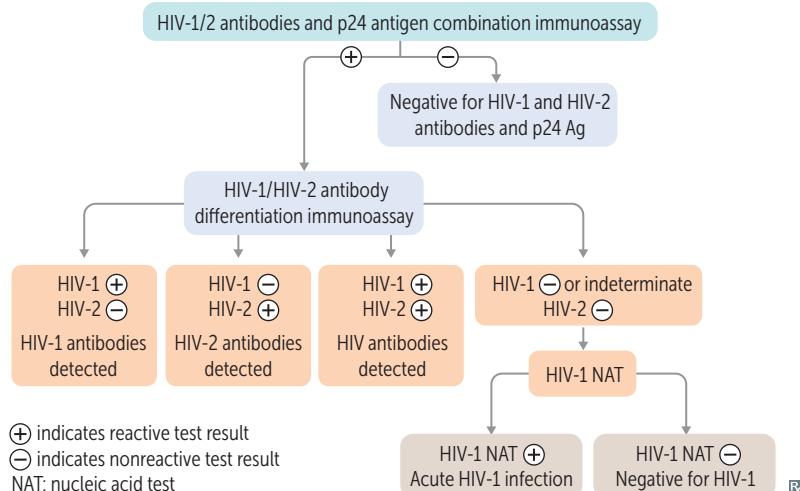
**HIV diagnosis**

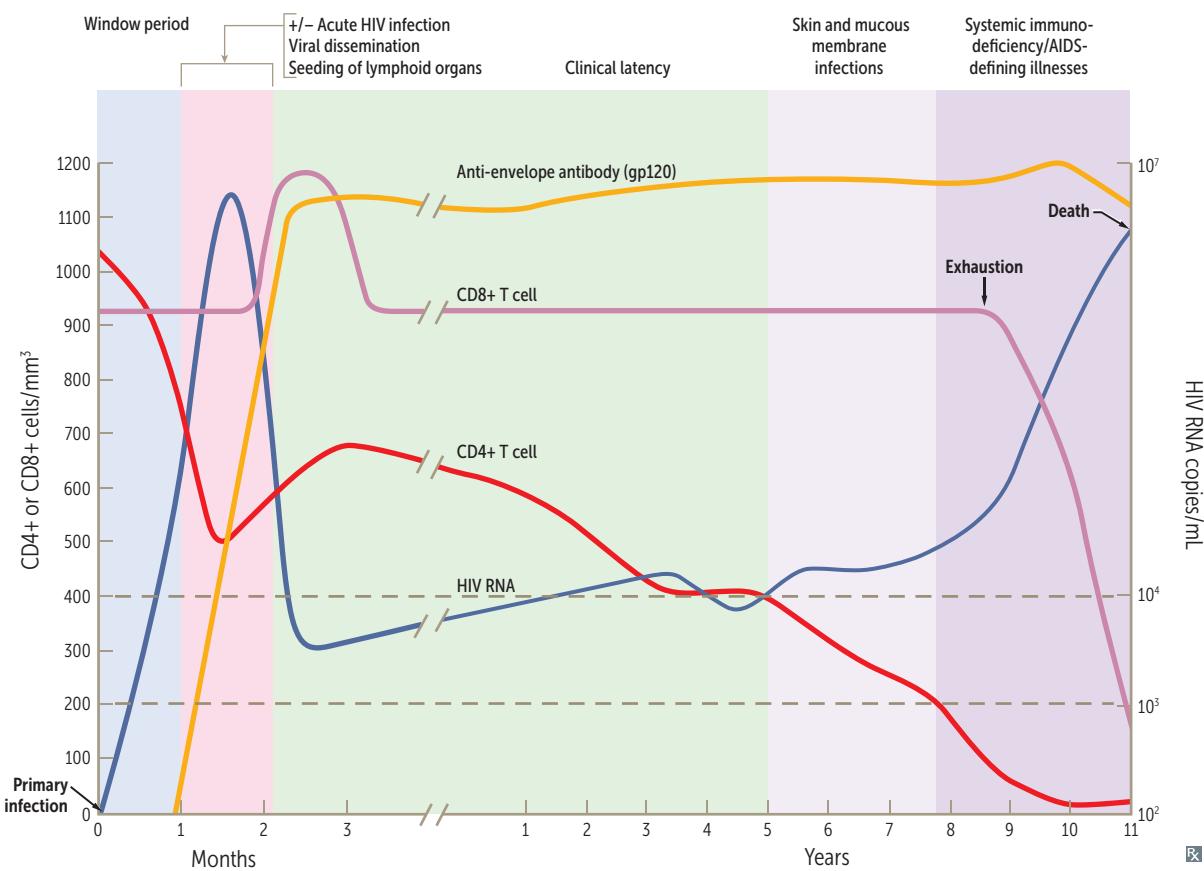
Diagnosis made with HIV-1/2 Ag/Ab immunoassays. These immunoassays detect viral p24 Ag capsid protein and IgG Abs to HIV-1/2. Very high sensitivity/specifity. Viral load tests determine the amount of viral RNA in the plasma. Use viral load to monitor effect of drug therapy. Use HIV genotyping to determine appropriate therapy.

AIDS diagnosis:  $\leq 200$  CD4+ cells/mm<sup>3</sup> (normal: 500–1500 cells/mm<sup>3</sup>) or HIV + with AIDS-defining condition (eg, *Pneumocystis* pneumonia).

Western blot tests are no longer recommended by the CDC for confirmatory testing.

HIV-1/2 Ag/Ab testing is not recommended in babies with suspected HIV due to maternally transferred antibody. Use HIV viral load instead.



**Time course of untreated HIV infection**

Dashed lines on CD4+ cell count axis indicate moderate immunocompromise ( $< 400$  CD4+ cells/mm<sup>3</sup>) and when AIDS-defining illnesses emerge ( $< 200$  CD4+ cells/mm<sup>3</sup>).

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

**Four stages of untreated infection:**

1. Flu-like (acute)
2. Feeling fine (latent)
3. Falling count
4. Final crisis

During clinical latency phase, virus replicates in lymph nodes

**Common diseases of HIV-positive adults**

↓ CD4+ cell count → reactivation of past infections (eg, TB, HSV, shingles), dissemination of bacterial infections and fungal infections (eg, coccidioidomycosis), and non-Hodgkin lymphomas.

PATHOGEN	PRESENTATION	FINDINGS
<b>CD4+ cell count &lt; 500/mm<sup>3</sup></b>		
<i>Candida albicans</i>	Oral thrush	Scrapable white plaque, pseudohyphae on microscopy
EBV	Oral hairy leukoplakia	Unscrapable white plaque on lateral tongue
HHV-8	Kaposi sarcoma	Perivascular spindle cells invading and forming vascular tumors on histology
HPV	Squamous cell carcinoma at site(s) of sexual contact (most commonly anus, cervix, oropharynx)	
<b>CD4+ cell count &lt; 200/mm<sup>3</sup></b>		
<i>Histoplasma capsulatum</i>	Fever, weight loss, fatigue, cough, dyspnea, nausea, vomiting, diarrhea	Oval yeast cells within macrophages
HIV	Dementia	Cerebral atrophy on neuroimaging
JC virus (reactivation)	Progressive multifocal leukoencephalopathy	Nonenhancing areas of demyelination on MRI
<i>Pneumocystis jirovecii</i>	<i>Pneumocystis</i> pneumonia	“Ground-glass” opacities on chest imaging
<b>CD4+ cell count &lt; 100/mm<sup>3</sup></b>		
<i>Aspergillus fumigatus</i>	Hemoptysis, pleuritic pain	Cavitation or infiltrates on chest imaging
<i>Bartonella</i> spp	Bacillary angiomatosis	Multiple red to purple papules or nodules Biopsy with neutrophilic inflammation
<i>Candida albicans</i>	Esophagitis	White plaques on endoscopy; yeast and pseudohyphae on biopsy
CMV	Colitis, Retinitis, Esophagitis, Encephalitis, Pneumonitis (CREEP)	Linear ulcers on endoscopy, cotton-wool spots on fundoscopy Biopsy reveals cells with intranuclear (owl eye) inclusion bodies
<i>Cryptococcus neoformans</i>	Meningitis	Encapsulated yeast on India ink stain or capsular antigen +
<i>Cryptosporidium</i> spp	Chronic, watery diarrhea	Acid-fast oocysts in stool
EBV	B-cell lymphoma (eg, non-Hodgkin lymphoma, CNS lymphoma)	CNS lymphoma—ring enhancing, may be solitary (vs <i>Toxoplasma</i> )
<i>Mycobacterium avium-intracellulare</i> , <i>Mycobacterium avium</i> complex	Nonspecific systemic symptoms (fever, night sweats, weight loss) or focal lymphadenitis	Most common if CD4+ cell count < 50/mm <sup>3</sup>
<i>Toxoplasma gondii</i>	Brain abscesses	Multiple ring-enhancing lesions on MRI

**Prions**

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

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

**Bovine spongiform encephalopathy**—also called “mad cow disease.”

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

## ► MICROBIOLOGY—SYSTEMS

**Normal flora: dominant**

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

LOCATION	MICROORGANISM
Skin	<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

**Bugs causing food-borne illness**

*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>L monocytogenes</i>	Deli meats, soft cheeses
<i>Salmonella</i>	Poultry, meat, and eggs
<i>S aureus</i>	Meats, mayonnaise, custard; preformed toxin
<i>V parahaemolyticus</i> and <i>V vulnificus</i> <sup>a</sup>	Raw/undercooked seafood

<sup>a</sup>*V vulnificus* predominantly causes 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 toxin
Enteroinvasive <i>E coli</i>	Invades colonic mucosa
<i>Salmonella</i> (non-typoidal)	Lactose $\ominus$ ; flagellar motility; has animal reservoir, especially poultry and eggs
<i>Shigella</i>	Lactose $\ominus$ ; very low ID <sub>50</sub> ; produces Shiga toxin; human reservoir only; bacillary dysentery
<i>Y enterocolitica</i>	Day care outbreaks; pseudoappendicitis

**Watery diarrhea**

<i>C difficile</i>	Pseudomembranous colitis; associated with antibiotics and PPIs; 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, Cryptosporidium</i>
<i>V cholerae</i>	Comma-shaped organisms; rice-water diarrhea; often from infected seafood
Viruses	Norovirus (most common cause in developed countries), rotavirus ( $\downarrow$ incidence in developed countries due to vaccination), enteric 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>	<i>Mycoplasma</i>	<i>C pneumoniae</i>	<i>H influenzae</i>	Influenza virus
	<i>C trachomatis</i>	<i>S pneumoniae</i>	Anaerobes	Anaerobes
	(infants–3 yr)	Viruses (eg, influenza)	Viruses	<i>H influenzae</i>
	<i>C pneumoniae</i> (school-aged children)		<i>Mycoplasma</i>	Gram $\ominus$ rods
	<i>S pneumoniae</i>			
	Runts May Cough			
	Chunky Sputum			

**Special groups**

Alcohol overuse	<i>Klebsiella</i> , anaerobes usually due to aspiration (eg, <i>Peptostreptococcus</i> , <i>Fusobacterium</i> , <i>Prevotella</i> , <i>Bacteroides</i> )
IV drug use	<i>S pneumoniae</i> , <i>S aureus</i>
Aspiration	Anaerobes
Atypical	<i>Mycoplasma</i> , <i>Chlamydophila</i> , <i>Legionella</i> , viruses (RSV, CMV, influenza, adenovirus)
Cystic fibrosis	<i>Pseudomonas</i> , <i>S aureus</i> , <i>S pneumoniae</i> , <i>Burkholderia cepacia</i>
Immunocompromised	<i>S aureus</i> , enteric gram $\ominus$ rods, fungi, viruses, <i>P jirovecii</i> (with HIV)
Nosocomial	<i>S aureus</i> , <i>Pseudomonas</i> , other enteric gram $\ominus$ rods
Postviral	<i>S pneumoniae</i> , <i>S aureus</i> , <i>H influenzae</i>
COPD	<i>S pneumoniae</i> , <i>H influenzae</i> , <i>M catarrhalis</i> , <i>Pseudomonas</i>

**Common causes of meningitis**

NEWBORN (0–6 MO)	CHILDREN (6 MO–6 YR)	6–60 YR	60 YR +
Group B <i>Streptococcus</i>	<i>S pneumoniae</i>	<i>S pneumoniae</i>	<i>S pneumoniae</i>
<i>E coli</i>	<i>N meningitidis</i>	<i>N meningitidis</i>	<i>N meningitidis</i>
<i>Listeria</i>	<i>H influenzae</i> type b	Enteroviruses	<i>H influenzae</i> type b
	Group B <i>Streptococcus</i>	HSV	Group B <i>Streptococcus</i>
	Enteroviruses		<i>Listeria</i>

Give ceftriaxone and vancomycin empirically (add ampicillin if *Listeria* is suspected).

Viral causes of meningitis: enteroviruses (especially coxsackievirus), HSV-2 (HSV-1 = encephalitis), HIV, West Nile virus (also causes encephalitis), VZV.

In HIV: *Cryptococcus* spp.

Note: Incidence of Group B streptococcal meningitis in neonates has ↓ greatly due to screening and antibiotic prophylaxis in pregnancy. Incidence of *H influenzae* meningitis has ↓ greatly due to conjugate *H influenzae* vaccinations. Today, cases are usually seen in unimmunized children.

**Cerebrospinal fluid findings in meningitis**

	OPENING PRESSURE	CELL TYPE	PROTEIN	GLUCOSE
Bacterial	↑	↑ 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>M tuberculosis</i> (Pott disease)
Cat and dog bites	<i>Pasteurella multocida</i>
IV drug use	<i>S aureus</i> ; also <i>Pseudomonas</i> , <i>Candida</i>

Elevated ESR and CRP sensitive but not specific.

Radiographs are insensitive early but can be useful in chronic osteomyelitis (A, left). MRI is best for detecting acute infection and detailing anatomic involvement (A, right). Biopsy or aspiration with culture necessary to identify organism.

## Urinary tract infections

Cystitis presents with dysuria, frequency, urgency, suprapubic pain, and WBCs (but not WBC casts) in urine. Primarily caused by ascension of microbes from urethra to bladder. Ascension to kidney results in pyelonephritis, which presents with fever, chills, flank pain, costovertebral angle tenderness, hematuria, and WBC casts.

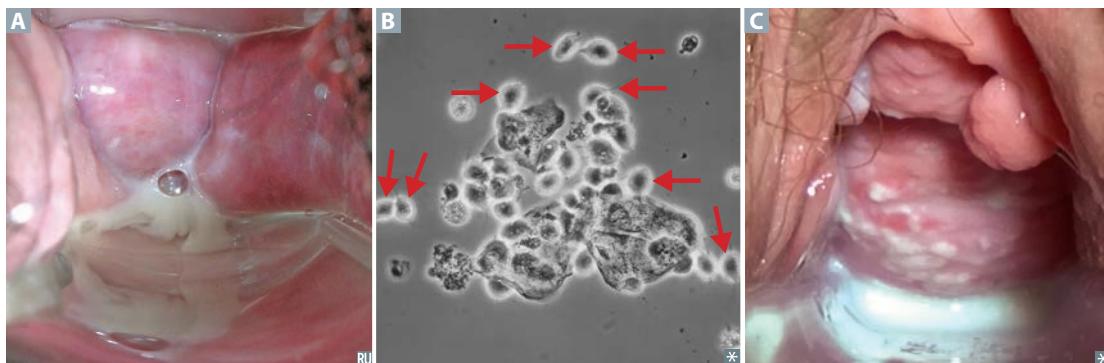
Ten times more common in females (shorter urethras colonized by fecal flora).

Risk factors: obstruction (eg, kidney stones, enlarged prostate), kidney surgery, catheterization, congenital GU malformation (eg, vesicoureteral reflux), diabetes, pregnancy.

SPECIES	FEATURES	COMMENTS
<i>Escherichia coli</i>	Leading cause of UTI. Colonies show strong pink lactose-fermentation on MacConkey agar.	Diagnostic markers: ⊕ Leukocyte esterase = evidence of WBC activity.
<i>Staphylococcus saprophyticus</i>	2nd leading cause of UTI, particularly in young, sexually active females.	⊕ Nitrite test = reduction of urinary nitrates by gram ⊥ bacterial species (eg, <i>E coli</i> ).
<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; associated with struvite stones. Produces urease.	
<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 <b>A</b> with fishy odor	Inflammation (“strawberry cervix”) Frothy, yellow-green, foul-smelling discharge	Inflammation Thick, white, “cottage cheese” discharge <b>C</b>
LAB FINDINGS	Clue cells pH > 4.5 ⊕ KOH whiff test	Motile pear-shaped trichomonads <b>B</b> pH > 4.5	Pseudohyphae pH normal (4.0–4.5)
TREATMENT	Metronidazole or clindamycin	Metronidazole Treat sexual partner(s)	Azoles



**TORCH infections**

Microbes that may pass from mother to fetus. Transmission is transplacental in most cases, or via vaginal delivery (especially HSV-2). Nonspecific signs common to many **ToRCHHeS** infections include hepatosplenomegaly, jaundice, thrombocytopenia, and growth restriction.

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	MATERNAL ACQUISITION	MATERNAL MANIFESTATIONS	NEONATAL MANIFESTATIONS
<b>Toxoplasma gondii</b>	Cat feces or ingestion of undercooked meat	Usually asymptomatic; lymphadenopathy (rarely)	Classic triad: chorioretinitis, hydrocephalus, and intracranial calcifications, +/− “blueberry muffin” rash <b>A</b>
<b>Rubella</b>	Respiratory droplets	Rash, lymphadenopathy, polyarthritides, polyarthralgia	Classic triad: abnormalities of <b>eye</b> (cataracts <b>B</b> ) and <b>ear</b> (deafness) and congenital <b>heart</b> disease (PDA); +/− “blueberry muffin” rash. “ <b>I</b> (eye) <b>♥</b> <b>rub</b> y ( <b>rubella</b> ) <b>ear</b> ings”
<b>Cytomegalovirus</b>	Sexual contact, organ transplants	Usually asymptomatic; mononucleosis-like illness	Hearing loss, seizures, petechial rash, “blueberry muffin” rash, chorioretinitis, periventricular calcifications <b>C</b>
<b>HIV</b>	Sexual contact, needlestick	Variable presentation depending on CD4+ cell count	Recurrent infections, chronic diarrhea
<b>Herpes simplex virus-2</b>	Skin or mucous membrane contact	Usually asymptomatic; herpetic (vesicular) lesions	Meningoencephalitis, herpetic (vesicular) lesions
<b>Syphilis</b>	Sexual contact	Chancres (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**

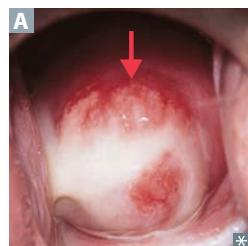
AGENT	ASSOCIATED SYNDROME/DISEASE	CLINICAL PRESENTATION
Coxsackievirus type A	Hand-foot-mouth disease	Oval-shaped vesicles on palms and soles <b>A</b> ; vesicles and ulcers in oral mucosa (herpangina)
Human herpesvirus 6	Roseola (exanthem subitum)	Asymptomatic rose-colored macules appear on body after several days of high fever; can present with febrile seizures; usually affects infants
Measles virus	Measles (rubeola)	Confluent rash beginning at head and moving down; preceded by cough, coryza, conjunctivitis, and blue-white (Koplik) spots on buccal mucosa
Parvovirus B19	Erythema infectiosum (fifth disease)	“Slapped cheek” rash on face <b>B</b> (can cause hydrops fetalis in pregnant patients)
Rubella virus	Rubella	Pink macules and papules begin at head and move down, remain discrete → fine desquamating truncal rash; postauricular lymphadenopathy
<i>Streptococcus pyogenes</i>	Scarlet fever	Sore throat, <b>Circumoral pallor</b> <b>C</b> , group <b>A</b> strep, <b>Rash</b> (sandpaper-like, from neck to trunk and extremities), <b>Lymphadenopathy</b> , <b>Erythrogenic toxin</b> , <b>strawberry Tongue (SCARLET)</b>
Varicella-Zoster virus	Chickenpox	Vesicular rash begins on trunk; spreads to face <b>D</b> and extremities with lesions of different stages



**Sexually transmitted infections**

DISEASE	CLINICAL FEATURES	PATHOGEN
AIDS	Opportunistic infections, Kaposi sarcoma, lymphoma	HIV
Chancroid	Painful genital ulcer with exudate, inguinal adenopathy <b>A</b>	<i>Haemophilus ducreyi</i> (it's so painful, you “ <b>do cry</b> ”)
		
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>
		
Granuloma inguinale (Donovanosis)	Painless, beefy red ulcer that bleeds readily on contact <b>B</b> Uncommon in US	<i>Klebsiella (Calymmatobacterium) granulomatis</i> ; cytoplasmic Donovan bodies (bipolar staining) seen on microscopy
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

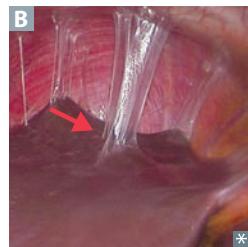


Top bugs—*Chlamydia trachomatis* (subacute, often undiagnosed), *Neisseria gonorrhoeae* (acute).

*C. trachomatis*—most common bacterial STI in the United States.

Signs include cervical motion tenderness, adnexal tenderness, purulent cervical discharge **A**.

PID may include salpingitis, endometritis, hydrosalpinx, and tubo-ovarian abscess.



Salpingitis is a risk factor for ectopic pregnancy, infertility, chronic pelvic pain, and adhesions. Can lead to perihepatitis (**Fitz-Hugh-Curtis syndrome**)—infection and inflammation of liver capsule and “violin string” adhesions of peritoneum to liver **B**.

### Nosocomial infections

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

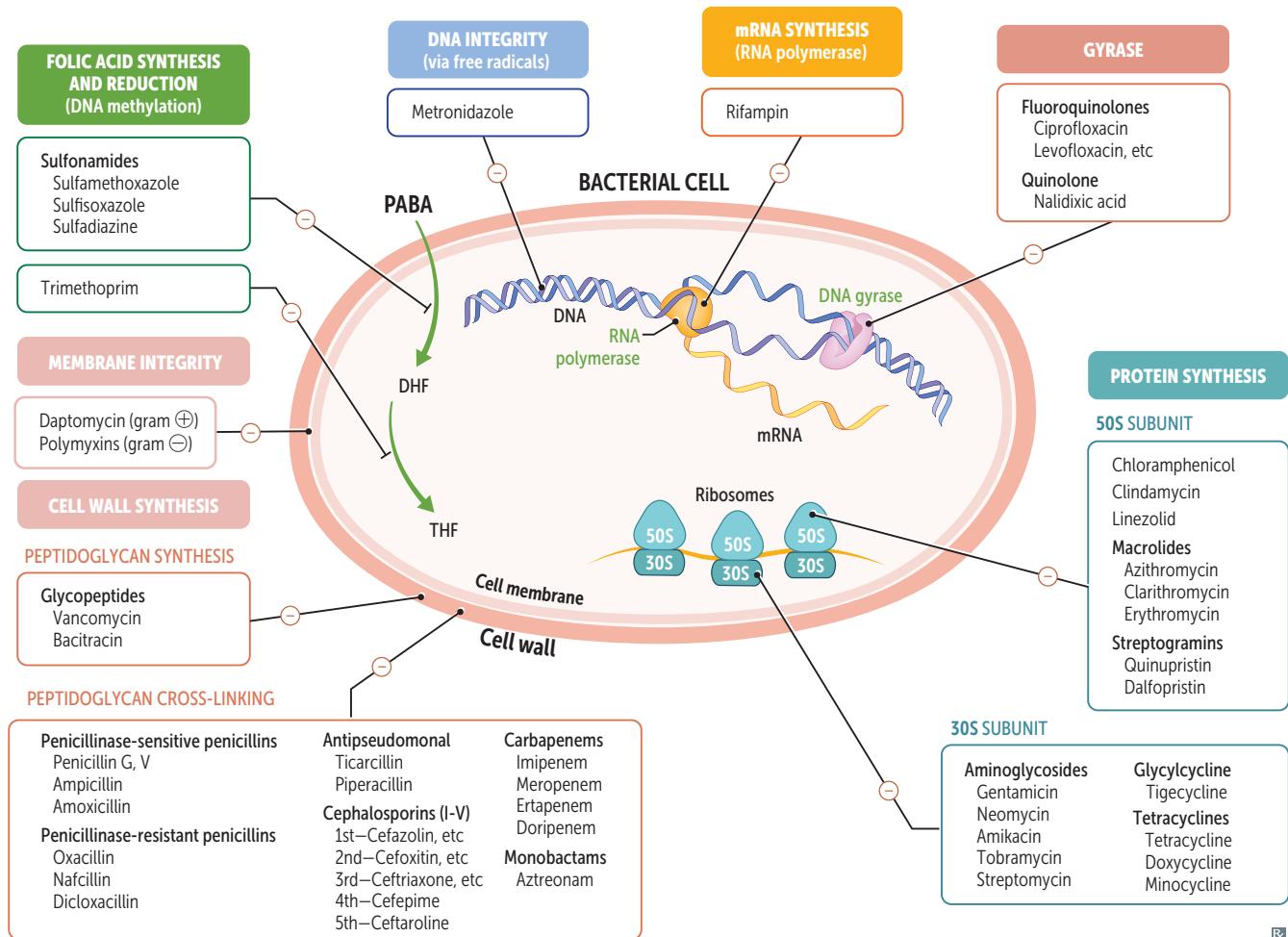
RISK FACTOR	PATHOGEN	UNIQUE SIGNS/SYMPOMTS
Antibiotic use	<i>Clostridium difficile</i>	Watery diarrhea, leukocytosis
Aspiration (2° to altered mental status, old age)	Polymicrobial, gram ⊖ bacteria, often anaerobes	Right lower lobe infiltrate or right upper/middle lobe (patient recumbent); purulent malodorous sputum
Decubitus ulcers, surgical wounds, drains	<i>S. aureus</i> (including MRSA), gram ⊖ anaerobes ( <i>Bacteroides, Prevotella, Fusobacterium</i> )	Erythema, tenderness, induration, drainage from surgical wound sites
Intravascular catheters	<i>S. aureus</i> (including MRSA), <i>S. epidermidis</i> (long term)	Erythema, induration, tenderness, drainage from access sites
Mechanical ventilation, endotracheal intubation	Late onset: <i>P. aeruginosa, Klebsiella, Acinetobacter, S. aureus</i>	New infiltrate on CXR, ↑ sputum production; sweet odor ( <i>Pseudomonas</i> )
Renal dialysis unit, needlestick	HBV, HCV	
Urinary catheterization	<i>Proteus</i> spp, <i>E. coli, Klebsiella (PEcK)</i>	Dysuria, leukocytosis, flank pain or costovertebral angle tenderness
Water aerosols	<i>Legionella</i>	Signs of pneumonia, GI symptoms (diarrhea, nausea, vomiting), neurologic abnormalities

**Bugs affecting unvaccinated children**

CLINICAL PRESENTATION	FINDINGS/LABS	PATHOGEN
<b>Dermatologic</b>		
<b>Rash</b>	Beginning at head and moving down with postauricular lymphadenopathy	Rubella virus
	Beginning at head and moving down; preceded by cough, coryza, conjunctivitis, and Koplik spots	Measles virus
<b>Neurologic</b>		
<b>Meningitis</b>	Microbe colonizes nasopharynx Can also lead to myalgia and paralysis	<i>H influenzae</i> type b Poliovirus
<b>Tetanus</b>	Muscle spasms and spastic paralysis (eg, lockjaw, opisthotonus)	<i>Clostridium tetani</i>
<b>Respiratory</b>		
<b>Epiglottitis</b>	Fever with dysphagia, drooling, and difficulty breathing due to edema	<i>H influenzae</i> type b (also capable of causing epiglottitis in fully immunized children)
<b>Pertussis</b>	Low-grade fevers, coryza → whooping cough, posttussive vomiting → gradual recovery	<i>Bordetella pertussis</i>
<b>Pharyngitis</b>	Grayish pseudomembranes (may obstruct airways)	<i>Corynebacterium diphtheriae</i>

## ► MICROBIOLOGY—ANTIMICROBIALS

## Antimicrobial therapy

**Penicillin G, V**

Penicillin G (IV and IM form), penicillin V (oral). Prototype  $\beta$ -lactam antibiotics.

## MECHANISM

D-Ala-D-Ala structural analog. Bind penicillin-binding proteins (transpeptidases). Block transpeptidase cross-linking of peptidoglycan in cell wall. Activate autolytic enzymes.

## CLINICAL USE

Mostly used for gram + organisms (*S pneumoniae*, *S pyogenes*, *Actinomyces*). Also used for gram - cocci (mainly *N meningitidis*) and spirochetes (mainly *T pallidum*). Bactericidal for gram + cocci, gram + rods, gram - cocci, and spirochetes.  $\beta$ -lactamase sensitive.

## ADVERSE EFFECTS

Hypersensitivity reactions, direct Coombs + hemolytic anemia, drug-induced interstitial nephritis.

## RESISTANCE

$\beta$ -lactamase cleaves the  $\beta$ -lactam ring. Mutations in PBPs.

**Penicillinase-sensitive penicillins**

<b>MECHANISM</b>	Same as penicillin. Wider spectrum; penicillinase sensitive. Also combine with clavulanic acid to protect against destruction by $\beta$ -lactamase.	<b>Aminopenicillins</b> are <b>amped-up</b> penicillin. Amoxicillin has greater <b>oral bioavailability</b> than ampicillin.
<b>CLINICAL USE</b>	Extended-spectrum penicillin— <i>H influenzae</i> , <i>H pylori</i> , <i>E coli</i> , Enterococci, <i>Listeria monocytogenes</i> , <i>Proteus mirabilis</i> , <i>Salmonella</i> , <i>Shigella</i> .	Coverage: ampicillin/amoxicillin <b>HHEELPSS</b> kill enterococci.
<b>ADVERSE EFFECTS</b>	Hypersensitivity reactions, rash, pseudomembranous colitis.	
<b>MECHANISM OF RESISTANCE</b>	Penicillinase (a type of $\beta$ -lactamase) cleaves $\beta$ -lactam ring.	

**Penicillinase-resistant penicillins**

<b>MECHANISM</b>	Dicloxacillin, nafcillin, oxacillin.	
<b>CLINICAL USE</b>	Same as penicillin. Narrow spectrum; penicillinase resistant because bulky R group blocks access of $\beta$ -lactamase to $\beta$ -lactam ring.	
<b>ADVERSE EFFECTS</b>	<i>S aureus</i> (except MRSA).	“Use <b>naf</b> (nafcillin) for <b>staph</b> .”
<b>MECHANISM OF RESISTANCE</b>	Hypersensitivity reactions, interstitial nephritis.	

**Antipseudomonal penicillins**

<b>MECHANISM</b>	Piperacillin, ticarcillin.	
<b>CLINICAL USE</b>	Same as penicillin. Extended spectrum. Penicillinase sensitive; use with $\beta$ -lactamase inhibitors.	
<b>ADVERSE EFFECTS</b>	<i>Pseudomonas</i> spp. and gram $\ominus$ rods.	

## Cephalosporins

MECHANISM	<p>β-lactam drugs that inhibit cell wall synthesis but are less susceptible to penicillinases. Bactericidal.</p>	Organisms typically not covered by 1st–4th generation cephalosporins are <b>LAME: Listeria, Atypicals (Chlamydia, Mycoplasma), MRSA, and Enterococci.</b>
CLINICAL USE	<p>1st generation (cefazolin, cephalexin)—gram <math>\oplus</math> 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, cefotetan)—gram <math>\oplus</math> 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, cefpodoxime, ceftazidime, cefixime)—serious gram <math>\ominus</math> infections resistant to other β-lactams.</p> <p>4th generation (cefepime)—gram <math>\ominus</math> organisms, with ↑ activity against <i>Pseudomonas</i> and gram <math>\oplus</math> organisms.</p> <p>5th generation (ceftaroline)—broad gram <math>\oplus</math> and gram <math>\ominus</math> organism coverage; unlike 1st–4th generation cephalosporins, ceftaroline covers MRSA, and <i>Enterococcus faecalis</i>—does not cover <i>Pseudomonas</i>.</p>	<p>1st generation—<math>\oplus</math> PEcK.</p> <p>2nd graders wear <b>fake fox fur to tea parties.</b> 2nd generation—<math>\oplus</math> HENS PEcK.</p> <p>Can cross blood-brain barrier. Ceftriaxone—meningitis, gonorrhea, disseminated Lyme disease. Ceftazidime—<i>Pseudomonas</i>.</p>
ADVERSE EFFECTS	Hypersensitivity reactions, autoimmune hemolytic anemia, disulfiram-like reaction, vitamin K deficiency. Low rate of cross-reactivity even in penicillin-allergic patients. ↑ nephrotoxicity of aminoglycosides.	
MECHANISM OF RESISTANCE	Inactivated by cephalosporinases (a type of β-lactamase). Structural change in penicillin-binding proteins (transpeptidases).	

## β-lactamase inhibitors

Include Clavulanic acid, Avibactam, Sulbactam, Tazobactam. Often added to penicillin antibiotics to protect the antibiotic from destruction by β-lactamase.

**CAST** (eg, amoxicillin-clavulanate, ceftazidime-avibactam, ampicillin-sulbactam, piperacillin-tazobactam).

**Carbapenems**

Doripenem, imipenem, meropenem, ertapenem.

“Pens” (carbapenems) cost a **dime**.”

**MECHANISM**

Imipenem is a broad-spectrum,  $\beta$ -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 and 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, rash, and CNS toxicity (seizures) at high plasma levels.

**MECHANISM OF RESISTANCE**

Inactivated by carbapenemases produced by, eg, *K pneumoniae*, *E coli*, *E aerogenes*.

**Aztreonam****MECHANISM**

Less susceptible to  $\beta$ -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**

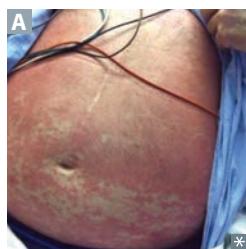
Inhibits cell wall peptidoglycan formation by binding D-Ala-D-Ala portion of cell wall precursors. Bactericidal against most bacteria (bacteriostatic against *C difficile*). Not susceptible to  $\beta$ -lactamases.

**CLINICAL USE**

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

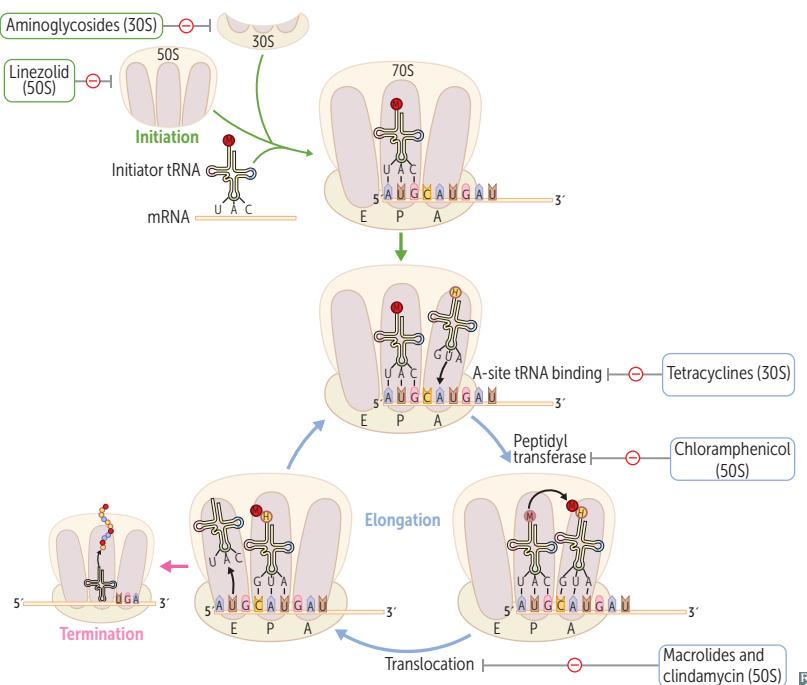
**ADVERSE EFFECTS**

Well tolerated in general but **not** trouble free: **nephrotoxicity**, **ototoxicity**, **thrombophlebitis**, diffuse **flushing** (**red man syndrome** **A**) idiopathic reaction largely preventable by pretreatment with antihistamines), DRESS syndrome.

**MECHANISM OF RESISTANCE**

Occurs in bacteria (eg, *Enterococcus*) via amino acid modification of D-Ala-D-Ala to **D-Ala-D-Lac**. “If you **Lack** a **D-Ala** (dollar), you can’t ride the **van** (vancomycin).”

## Protein synthesis inhibitors



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

All are bacteriostatic, except aminoglycosides (bactericidal) and linezolid (variable).

### 30S inhibitors

Aminoglycosides  
Tetracyclines

### 50S inhibitors

Chloramphenicol, clindamycin  
erythromycin (macrolides)  
linezolid

“Buy at 30, ccel (sell) at 50.”

## Aminoglycosides

Gentamicin, Neomycin, Amikacin,  
Tobramycin, Streptomycin.

“Mean” (aminoglycoside) **GNATS** cannot kill anaerobes.

### MECHANISM

Bactericidal; irreversible inhibition of initiation complex through binding of the 30S subunit. Can cause misreading of mRNA. Also block translocation. Require O<sub>2</sub> for uptake; therefore ineffective against anaerobes.

### CLINICAL USE

Severe gram ⊖ rod infections. Synergistic with β-lactam antibiotics.  
Neomycin for bowel surgery.

### ADVERSE EFFECTS

Nephrotoxicity, neuromuscular blockade (absolute contraindication with myasthenia gravis), ototoxicity (especially with loop diuretics), teratogenicity.

### MECHANISM OF RESISTANCE

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

**Tetracyclines**

MECHANISM	Tetracycline, doxycycline, minocycline. 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 ( $\text{Ca}^{2+}$ ), antacids (eg, $\text{Ca}^{2+}$ or $\text{Mg}^{2+}$ ), 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. Doxycycline effective against community-acquired MRSA.
ADVERSE EFFECTS	GI distress, discoloration of teeth and inhibition of bone growth in children, photosensitivity. “Teratocyclines” are teratogenic; generally avoided in pregnancy and in children (except doxycycline).
MECHANISM OF RESISTANCE	↓ uptake or ↑ efflux out of bacterial cells by plasmid-encoded transport pumps.

**Tigecycline**

MECHANISM	Tetracycline derivative. Binds to 30S, inhibiting protein synthesis. Generally bacteriostatic.
CLINICAL USE	Broad-spectrum anaerobic, gram $\ominus$ , and gram $\oplus$ coverage. Multidrug-resistant organisms (MRSA, VRE) or infections requiring deep tissue penetration.
ADVERSE EFFECTS	Nausea, vomiting.

**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 rickettsial diseases (eg, Rocky Mountain spotted fever [ <i>Rickettsia rickettsii</i> ]). Limited use due to toxicity 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-glucuronosyltransferase).
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.

**Linezolid**

MECHANISM	Inhibits protein synthesis by binding to 50S subunit and preventing formation of the initiation complex.
CLINICAL USE	Gram $\oplus$ species including MRSA and VRE.
ADVERSE EFFECTS	Bone marrow suppression (especially thrombocytopenia), peripheral neuropathy, serotonin syndrome (due to partial MAO inhibition).
MECHANISM OF RESISTANCE	Point mutation of ribosomal RNA.

**Macrolides**

MECHANISM	Inhibit protein synthesis by blocking translocation (“macrolides”); 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 $\oplus$ cocci (streptococcal infections in patients allergic to penicillin), and <i>B pertussis</i> .
ADVERSE EFFECTS	<b>MACRO:</b> Gastrointestinal Motility issues, Arrhythmia caused by prolonged QT interval, acute Cholestatic hepatitis, Rash, eosinophilia. Increases serum concentration of theophylline, oral anticoagulants. Clarithromycin and erythromycin inhibit cytochrome P-450.
MECHANISM OF RESISTANCE	Methylation of 23S rRNA-binding site prevents binding of drug.

**Polymyxins**

MECHANISM	Cation polypeptides that bind to phospholipids on cell membrane of gram $\ominus$ bacteria. Disrupt cell membrane integrity $\rightarrow$ leakage of cellular components $\rightarrow$ cell death.
CLINICAL USE	Salvage therapy for multidrug-resistant gram $\ominus$ bacteria (eg, <i>P aeruginosa</i> , <i>E coli</i> , <i>K pneumoniae</i> ). Polymyxin B is a component of a triple antibiotic ointment used for superficial skin infections.
ADVERSE EFFECTS	Nephrotoxicity, neurotoxicity (eg, slurred speech, weakness, paresthesias), respiratory failure.

**Sulfonamides**

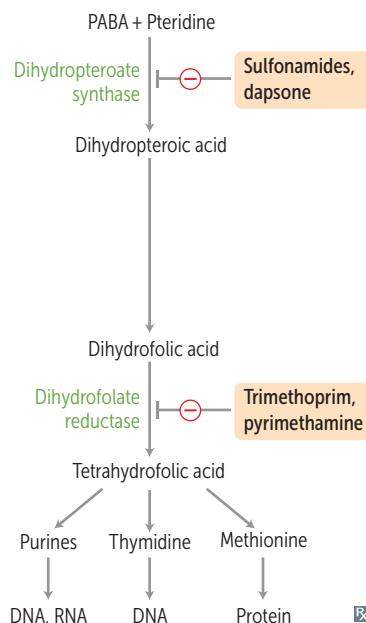
MECHANISM	Inhibit dihydropteroate synthase, thus inhibiting folate synthesis. Bacteriostatic (bactericidal when combined with trimethoprim).
CLINICAL USE	Gram $\oplus$ , gram $\ominus$ , <i>Nocardia</i> . TMP-SMX for simple UTI.
ADVERSE EFFECTS	Hypersensitivity reactions, hemolysis if G6PD deficient, nephrotoxicity (tubulointerstitial nephritis), photosensitivity, Stevens-Johnson syndrome, kernicterus in infants, displace other drugs from albumin (eg, warfarin).
MECHANISM OF RESISTANCE	Altered enzyme (bacterial dihydropteroate synthase), $\downarrow$ uptake, or $\uparrow$ PABA synthesis.

**Dapsone**

MECHANISM	Similar to sulfonamides, but structurally distinct agent.
CLINICAL USE	Leprosy (lepromatous and tuberculoid), <i>Pneumocystis jirovecii</i> prophylaxis, or treatment when used in combination with TMP.
ADVERSE EFFECTS	Hemolysis if G6PD deficient, methemoglobinemia, agranulocytosis.

**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	Hyperkalemia (high doses), megaloblastic anemia, leukopenia, granulocytopenia, which may be avoided with coadministration of leucovorin (folinic acid). <b>TMP Treats Marrow Poorly.</b>



**Fluoroquinolones**

Ciprofloxacin, enoxacin, norfloxacin, ofloxacin; respiratory fluoroquinolones: gemifloxacin, levofloxacin, moxifloxacin.

<b>MECHANISM</b>	Inhibit prokaryotic enzymes topoisomerase II (DNA gyrase) and topoisomerase IV. Bactericidal. Must not be taken with antacids.	
<b>CLINICAL USE</b>	Gram $\ominus$ rods of urinary and GI tracts (including <i>Pseudomonas</i> ), some gram $\oplus$ organisms, otitis externa.	
<b>ADVERSE EFFECTS</b>	GI upset, superinfections, skin rashes, headache, dizziness. Less commonly, can cause leg cramps and myalgias. Contraindicated during pregnancy or breastfeeding and in children $< 18$ years old due to possible damage to cartilage. Some may prolong QT interval.	May cause tendonitis or tendon rupture in people $> 60$ years old and in patients taking prednisone. Ciprofloxacin inhibits cytochrome P-450. <b>Fluoroquinolones</b> hurt attachments to your <b>bones</b> .
<b>MECHANISM OF RESISTANCE</b>	Chromosome-encoded mutation in DNA gyrase, plasmid-mediated resistance, efflux pumps.	

**Daptomycin**

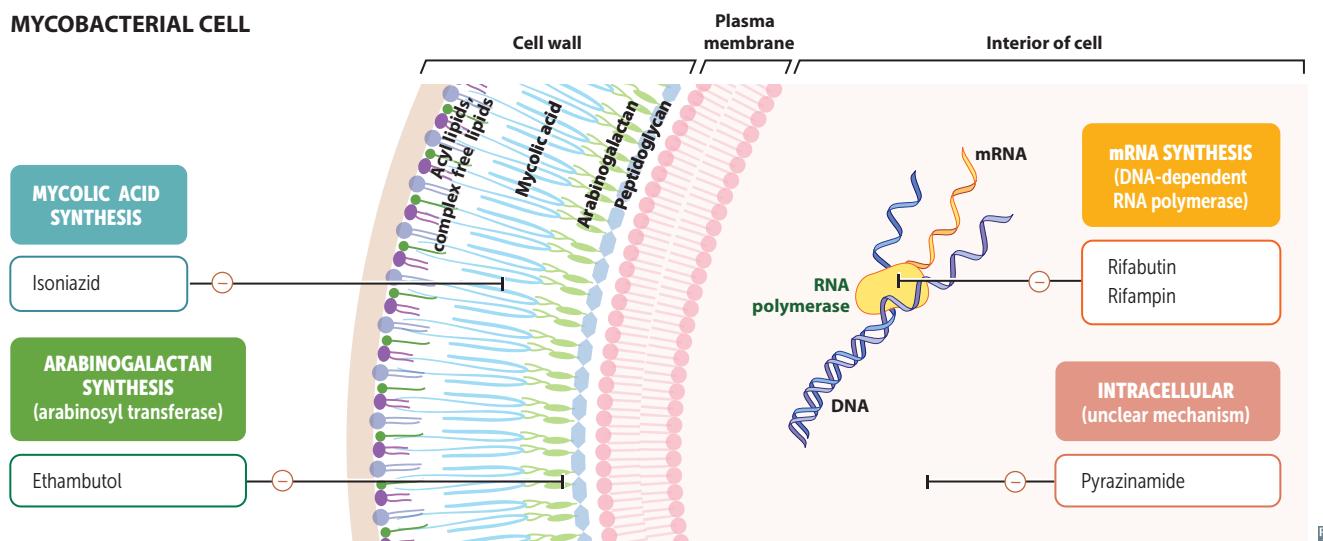
<b>MECHANISM</b>	Lipopeptide that disrupts cell membranes of gram $\oplus$ cocci by creating transmembrane channels.	
<b>CLINICAL USE</b>	<i>S aureus</i> skin infections (especially MRSA), bacteremia, endocarditis, VRE.	Not used for pneumonia (avidly binds to and is inactivated by surfactant). “Dapo-my-o-skin” is used for <b>skin</b> infections but can cause <b>myopathy</b> .
<b>ADVERSE EFFECTS</b>	Myopathy, rhabdomyolysis.	

**Metronidazole**

<b>MECHANISM</b>	Forms toxic free radical metabolites in the bacterial cell that damage DNA. Bactericidal, antiprotozoal.	
<b>CLINICAL USE</b>	Treats <i>Giardia</i> , <i>Entamoeba</i> , <i>Trichomonas</i> , <i>Gardnerella vaginalis</i> , Anaerobes ( <i>Bacteroides</i> , <i>C difficile</i> ). Can be used in place of amoxicillin in <i>H pylori</i> “triple therapy” in case of penicillin allergy.	<b>GET GAP</b> on the <b>Metro</b> with metronidazole! Treats anaerobic infection <b>below</b> the diaphragm vs clindamycin (anaerobic infections <b>above</b> diaphragm).
<b>ADVERSE EFFECTS</b>	Disulfiram-like reaction (severe flushing, tachycardia, hypotension) with alcohol; headache, metallic taste.	

**Antimycobacterial therapy**

BACTERIUM	PROPHYLAXIS	TREATMENT
<i>M tuberculosis</i>	Isoniazid	Rifampin, Isoniazid, Pyrazinamide, Ethambutol ( <b>RIPE</b> for treatment)
<i>M avium-intracellulare</i>	Azithromycin, rifabutin	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

**MYCOBACTERIAL CELL****Rifamycins**

MECHANISM	Rifampin, rifabutin, rifapentine.
CLINICAL USE	Inhibit DNA-dependent RNA polymerase. <i>Mycobacterium tuberculosis</i> ; delay resistance to dapsone when used for leprosy. Used for meningococcal prophylaxis and chemoprophylaxis in contacts of children with <i>H influenzae</i> type b.
ADVERSE EFFECTS	Minor hepatotoxicity and drug interactions ( $\uparrow$ 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.

**Rifampin's 4 R's:**

- RNA polymerase inhibitor
  - Ramps up microsomal cytochrome P-450
  - Red/orange body fluids
  - Rapid resistance if used alone
- Rifampin ramps up cytochrome P-450, but rifabutin does not.**

**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.
ADVERSE EFFECTS	Hepatotoxicity, cytochrome P-450 inhibition, drug-induced SLE, anion gap metabolic acidosis, vitamin B <sub>6</sub> deficiency (peripheral neuropathy, sideroblastic anemia), seizures (in high doses, refractory to benzodiazepines). Administer with pyridoxine (B <sub>6</sub> ).
MECHANISM OF RESISTANCE	Mutations leading to underexpression of KatG. <b>INH</b> Injures <b>N</b> eurons and <b>H</b> epatocytes.

**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	<b>Optic</b> neuropathy (red-green color blindness, usually reversible). Pronounce “ <b>eyethambutol</b> .”

**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
Exposure to meningococcal infection	Ceftriaxone, ciprofloxacin, or rifampin
High risk for endocarditis and undergoing surgical or dental procedures	Amoxicillin
History of recurrent UTIs	TMP-SMX
Malaria prophylaxis for travelers	Atovaquone-proguanil, mefloquine, doxycycline, primaquine, or chloroquine (for areas with sensitive species)
Pregnant patients 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; vancomycin if ⊕ for MRSA
Prophylaxis of strep pharyngitis in child with prior rheumatic fever	Benzathine penicillin G or oral penicillin V

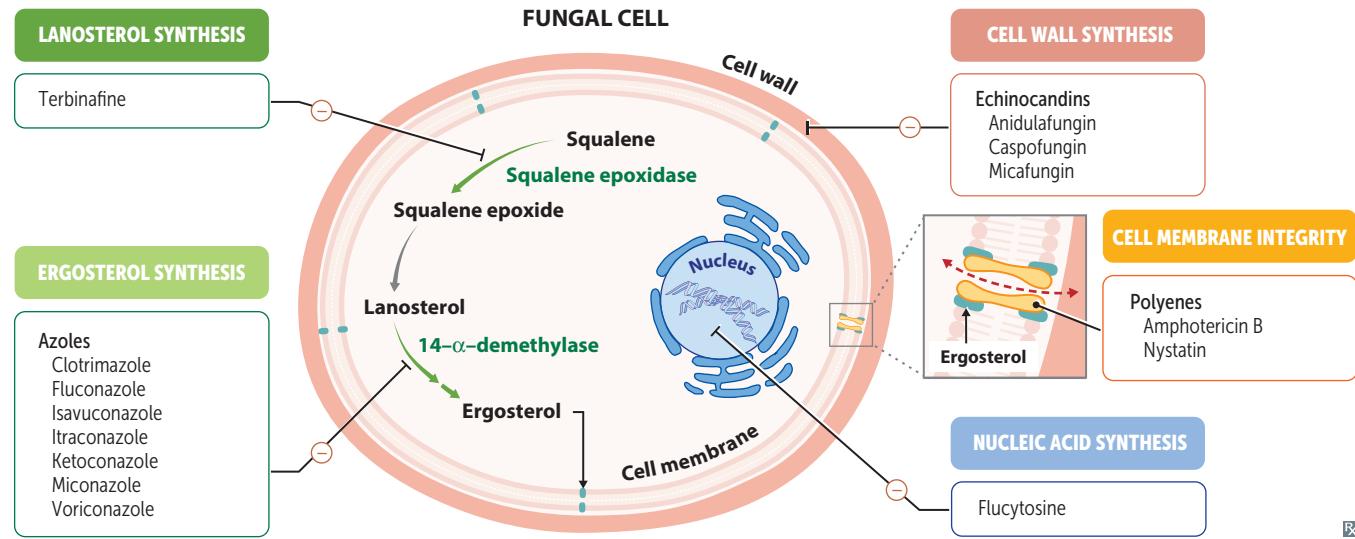
## Prophylaxis in HIV infection/AIDS

CELL COUNT	PROPHYLAXIS	INFECTION
CD4 < 200 cells/mm <sup>3</sup>	TMP-SMX	<i>Pneumocystis</i> pneumonia
CD4 < 100 cells/mm <sup>3</sup>	TMP-SMX	<i>Pneumocystis</i> pneumonia and toxoplasmosis

## Treatment of highly resistant bacteria

MRSA: vancomycin, daptomycin, linezolid, tigecycline, ceftaroline, doxycycline.  
VRE: daptomycin, linezolid, tigecycline, 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 +/- flucytosine for cryptococcal meningitis), <i>Blastomyces</i> , <i>Coccidioides</i> , <i>Histoplasma</i> , <i>Candida</i> , <i>Mucor</i> . Intrathecally for coccidioidal meningitis.	Supplement K <sup>+</sup> and Mg <sup>2+</sup> because of altered renal tubule permeability.
ADVERSE EFFECTS	Fever/chills (“shake and bake”), hypotension, nephrotoxicity, arrhythmias, anemia, IV phlebitis (“ <b>amphotericin B</b> ”).	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

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 people living with HIV and candidal infections of all types. Itraconazole may be used for <i>Blastomyces</i> , <i>Coccidioides</i> , <i>Histoplasma</i> , <i>Sporothrix schenckii</i> . Clotrimazole and miconazole for topical fungal infections. Voriconazole for <i>Aspergillus</i> and some <i>Candida</i> . Isavuconazole for serious <i>Aspergillus</i> and <i>Mucor</i> 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	Dermatophyoses (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  $\beta$ -glucan.

## CLINICAL USE

Invasive aspergillosis, *Candida*.

## ADVERSE EFFECTS

GI upset, flushing (by histamine release).

**Griseofulvin**

## MECHANISM

Interferes with microtubule function; disrupts mitosis. Deposits in keratin-containing tissues (eg, nails).

## CLINICAL USE

Oral treatment of superficial infections; inhibits growth of dermatophytes (tinea, ringworm).

## ADVERSE EFFECTS

Teratogenic, carcinogenic, confusion, headaches, disulfiram-like reaction, ↑ cytochrome P-450 and warfarin metabolism.

**Antiprotozoal therapy**

Pyrimethamine (toxoplasmosis), suramin and melarsoprol (*Trypanosoma brucei*), nifurtimox (*T cruzi*), sodium stibogluconate (leishmaniasis).

**Anti-mite/louse therapy**

Permethrin, malathion (acetylcholinesterase inhibitor), topical or oral ivermectin. Used to treat scabies (*Sarcoptes scabiei*) and lice (*Pediculus* and *Pthirus*).

**Chloroquine**

## MECHANISM

Blocks detoxification of heme into hemozoin. Heme accumulates and is toxic to plasmodia.

## CLINICAL USE

Treatment of plasmodial species other than *P falciparum* (frequency of resistance in *P falciparum* is too high). Resistance due to membrane pump that ↓ intracellular concentration of drug. Treat *P falciparum* with artemether/lumefantrine or atovaquone/proguanil. For life-threatening malaria, use quinidine in US (quinine elsewhere) or artesunate.

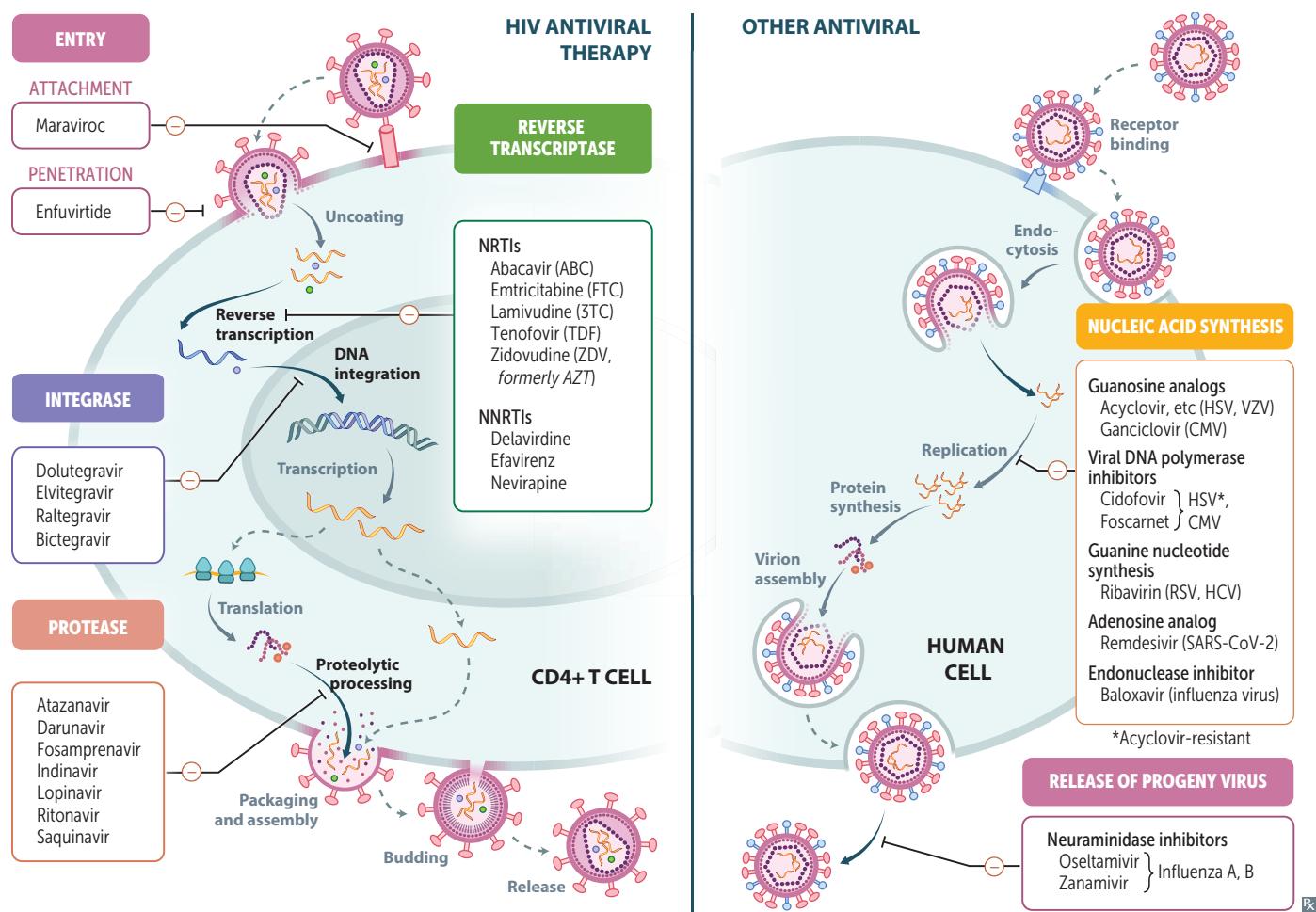
## ADVERSE EFFECTS

Retinopathy; pruritus (especially in dark-skinned individuals).

**Antihelminthic therapy**

Pyrantel pamoate, ivermectin, me**bendazole** (microtubule inhibitor to treat “**bendy** worms”), praziquantel (↑  $\text{Ca}^{2+}$  permeability, ↑ vacuolization), diethylcarbamazine.

## Antiviral therapy



## Oseltamivir, zanamivir

MECHANISM	Inhibit influenza neuraminidase → ↓ release of progeny virus.
CLINICAL USE	Treatment and prevention of influenza A and B. Beginning therapy within 48 hours of symptom onset may shorten duration of illness.

## Baloxavir

MECHANISM	Inhibits the “cap snatching” endonuclease activity of the influenza virus RNA polymerase → ↓ viral replication.
CLINICAL USE	Treatment within 48 hours of symptom onset shortens duration of illness.

## Remdesivir

MECHANISM	Prodrug of an ATP analog. The active metabolite inhibits viral RNA-dependent RNA polymerase and evades proofreading by viral exoribonuclease (ExoN) → ↓ viral RNA production.
CLINICAL USE	Recently approved for treatment of COVID-19 requiring hospitalization.

**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 patients who are immunocompromised. No effect on latent forms of HSV and VZV. Valacyclovir, a prodrug of acyclovir, has better oral bioavailability.
	For herpes zoster, use famciclovir.
ADVERSE EFFECTS	Obstructive crystalline nephropathy and acute kidney injury if not adequately hydrated.
MECHANISM OF RESISTANCE	Mutated viral thymidine kinase.

**Ganciclovir**

MECHANISM	Guanosine analog. 5'-monophosphate formed by a CMV viral kinase. Triphosphate formed by cellular kinases. Preferentially inhibits viral DNA polymerase.
CLINICAL USE	CMV, especially in patients who are immunocompromised. 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.	<b>Foscarnet</b> = pyrofosphate analog.
CLINICAL USE	CMV retinitis in immunocompromised patients when ganciclovir fails; acyclovir-resistant HSV.	
ADVERSE EFFECTS	Nephrotoxicity, electrolyte abnormalities (hypo- or hypercalcemia, hypo- or hyperphosphatemia, hypokalemia, hypomagnesemia) can lead to seizures.	
MECHANISM OF RESISTANCE	Mutated DNA polymerase.	

**Cidofovir**

MECHANISM	Preferentially inhibits viral DNA polymerase. Does not require phosphorylation by viral kinase.
CLINICAL USE	CMV retinitis in immunocompromised patients; acyclovir-resistant HSV. Long half-life.
ADVERSE EFFECTS	Nephrotoxicity (coadminister with probenecid and IV saline to ↓ toxicity).

**HIV therapy**

Antiretroviral therapy (ART): often initiated at the time of HIV diagnosis. Strongest indication for use with patients presenting with AIDS-defining illness, low CD4+ cell counts ( $< 500 \text{ cells/mm}^3$ ), or high viral load. Regimen consists of 3 drugs to prevent resistance: 2 NRTIs and preferably an integrase inhibitor. Most ARTs are active against both HIV-1 and HIV-2 (exceptions: NNRTIs and enfuvirtide not effective against HIV-2).

DRUG	MECHANISM	TOXICITY
<b>NRTIs</b>		
Abacavir (ABC)	Competitively inhibit nucleotide binding to reverse transcriptase and terminate the DNA chain (lack a 3' OH group). Tenofovir is a nucleoTide; the others are nucleosides. All need to be phosphorylated to be active.	Bone marrow suppression (can be reversed with granulocyte colony-stimulating factor [G-CSF] and erythropoietin), peripheral neuropathy, lactic acidosis (nucleosides), anemia (ZDV).
Emtricitabine (FTC)	ZDV can be used for general prophylaxis and during pregnancy to ↓ risk of fetal transmission.	Abacavir contraindicated if patient has HLA-B*5701 mutation due to ↑ risk of hypersensitivity.
Lamivudine (3TC)		
Tenofovir (TDF)		
Zidovudine (ZDV, formerly AZT)	Have you dined (vudine) with my nuclear (nucleosides) family?	
<b>NNRTIs</b>		
Delavirdine	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.
Efavirenz		
Nevirapine		
<b>Integrase inhibitors</b>		
Bictegravir	Inhibits HIV genome integration into host cell chromosome by reversibly inhibiting HIV integrase.	↑ creatine kinase.
Dolutegravir		
Elvitegravir		
Raltegravir		
<b>Protease inhibitors</b>		
Atazanavir	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.	Hyperglycemia, GI intolerance (nausea, diarrhea), lipodystrophy (Cushing-like syndrome).
Darunavir		
Lopinavir		
Ritonavir	Ritonavir can “boost” other drug concentrations by inhibiting cytochrome P-450. Navir (never) tease a protease.	Rifampin (potent CYP/UGT inducer) reduces protease inhibitor concentrations; use rifabutin instead.
<b>Entry inhibitors</b>		
Enfuvirtide	Binds gp41, inhibiting viral entry.	Skin reaction at injection sites. Enfuvirtide inhibits fusion.
Maraviroc	Binds CCR-5 on surface of T cells/monocytes, inhibiting interaction with gp120.	Maraviroc inhibits docking.

**Hepatitis C therapy**

Chronic HCV infection treated with multidrug therapy that targets specific steps within HCV replication cycle (HCV-encoded proteins). Examples of drugs are provided.

DRUG	MECHANISM	TOXICITY
<b>NS5A inhibitors</b>		
Ledipasvir	Inhibits NS5A, a viral phosphoprotein that plays a key role in RNA replication	Headache, diarrhea
Ombitasvir		
Velpatasvir	Exact mechanism unknown	
<b>NS5B inhibitors</b>		
Sofosbuvir	Inhibits NS5B, an RNA-dependent RNA polymerase acting as a chain terminator	Fatigue, headache
Dasabuvir	Prevents viral RNA replication	
<b>NS3/4A inhibitors</b>		
Grazoprevir	Inhibits NS3/4A, a viral protease, preventing viral replication	Grazoprevir: headache, fatigue
Simeprevir		Simeprevir: photosensitivity reactions, rash
<b>Alternative drugs</b>		
Ribavirin	Inhibits synthesis of guanine nucleotides by competitively inhibiting IMP dehydrogenase Used as adjunct in cases refractory to newer medications	Hemolytic anemia, severe teratogen

**Disinfection and sterilization**

Goals include the reduction of pathogenic organism counts to safe levels (disinfection) and the inactivation of all microbes including spores (sterilization).

**Chlorine and heat** are sporicidal.

<b>Autoclave</b>	Pressurized steam at > 120°C. Sporicidal. May not reliably inactivate prions.
<b>Alcohols</b>	Denature proteins and disrupt cell membranes. Not sporicidal.
<b>Chlorhexidine</b>	Disrupts cell membranes and coagulates intracellular components.
<b>Chlorine</b>	Oxidizes and denatures proteins. Sporicidal.
<b>Ethylene oxide</b>	Alkylating agent. Sporicidal.
<b>Hydrogen peroxide</b>	Free radical oxidation. Sporicidal.
<b>Iodine and iodophors</b>	Halogenation of DNA, RNA, and proteins. May be sporicidal.
<b>Quaternary amines</b>	Impair permeability of cell membranes. Not 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 take really good care.**

# Pathology

*“Digressions, objections, delight in mockery, carefree mistrust are signs of health; everything unconditional belongs in pathology.”*

—Friedrich Nietzsche

*“You cannot separate passion from pathology any more than you can separate a person’s spirit from his body.”*

—Richard Selzer

*“My business is not prognosis, but diagnosis. I am not engaged in therapeutics, but in pathology.”*

—H.L. Mencken

The fundamental principles of pathology are key to understanding diseases in all organ systems. Major topics such as inflammation and neoplasia appear frequently in questions across different organ systems, and such topics are definitely high yield. For example, the concepts of cell injury and inflammation are key to understanding the inflammatory response that follows myocardial infarction, a very common subject of board questions. Similarly, a familiarity with the early cellular changes that culminate in the development of neoplasias—for example, esophageal or colon cancer—is critical. Finally, make sure you recognize the major tumor-associated genes and are comfortable with key cancer concepts such as tumor staging and metastasis.

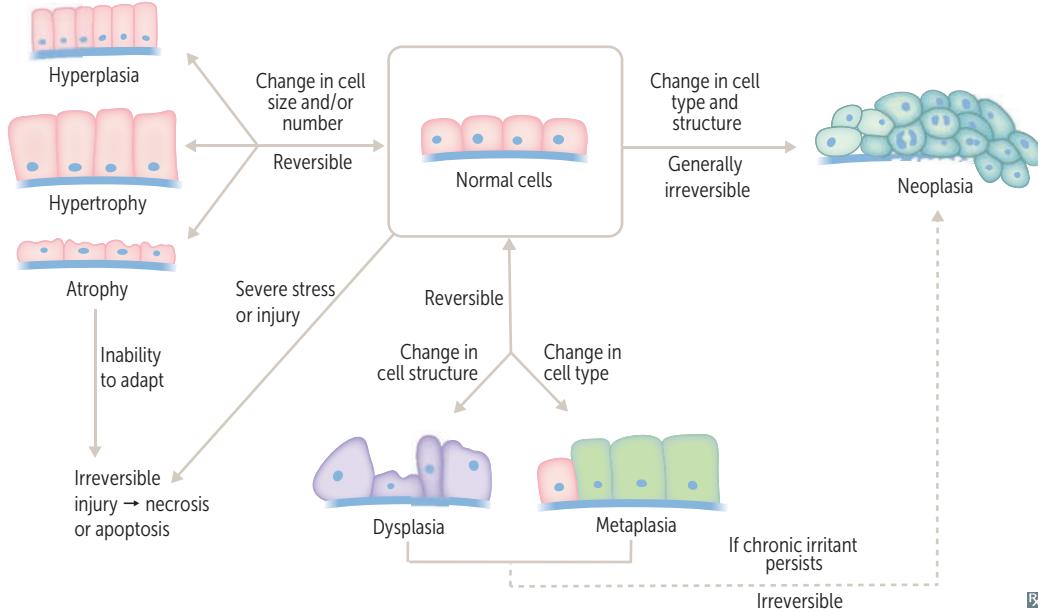
► Cellular Injury 206

► Inflammation 214

► Neoplasia 220

## ► PATHOLOGY—CELLULAR INJURY

<b>Cellular adaptations</b>	Reversible changes that can be physiologic (eg, uterine enlargement during pregnancy) or pathologic (eg, myocardial hypertrophy 2° to systemic HTN). If stress is excessive or persistent, adaptations can progress to cell injury (eg, significant LV hypertrophy → injury to myofibrils → HF).
<b>Hypertrophy</b>	↑ structural proteins and organelles → ↑ in size of cells. Example: cardiac hypertrophy.
<b>Hyperplasia</b>	Controlled proliferation of stem cells and differentiated cells → ↑ in number of cells (eg, benign prostatic hyperplasia). Excessive stimulation → pathologic hyperplasia (eg, endometrial hyperplasia), which may progress to dysplasia and cancer.
<b>Atrophy</b>	↓ in tissue mass due to ↓ in size (↑ cytoskeleton degradation via ubiquitin-proteasome pathway and autophagy; ↓ protein synthesis) and/or number of cells (apoptosis). Causes include disuse, denervation, loss of blood supply, loss of hormonal stimulation, poor nutrition.
<b>Metaplasia</b>	Reprogramming of stem cells → replacement of one cell type by another that can adapt to a new stress. Usually due to exposure to an irritant, such as gastric acid (→ Barrett esophagus) or tobacco smoke (→ respiratory ciliated columnar epithelium replaced by stratified squamous epithelium). May progress to dysplasia → malignant transformation with persistent insult (eg, Barrett esophagus → esophageal adenocarcinoma). Metaplasia of connective tissue can also occur (eg, myositis ossificans, the formation of bone within muscle after trauma).
<b>Dysplasia</b>	Disordered, precancerous epithelial cell growth; not considered a true adaptive response. Characterized by loss of uniformity of cell size and shape (pleomorphism); loss of tissue orientation; nuclear changes (eg, ↑ nuclear:cytoplasmic ratio and clumped chromatin). Mild and moderate dysplasias (ie, do not involve entire thickness of epithelium) may regress with alleviation of inciting cause. Severe dysplasia often becomes irreversible and progresses to carcinoma in situ. Usually preceded by persistent metaplasia or pathologic hyperplasia.



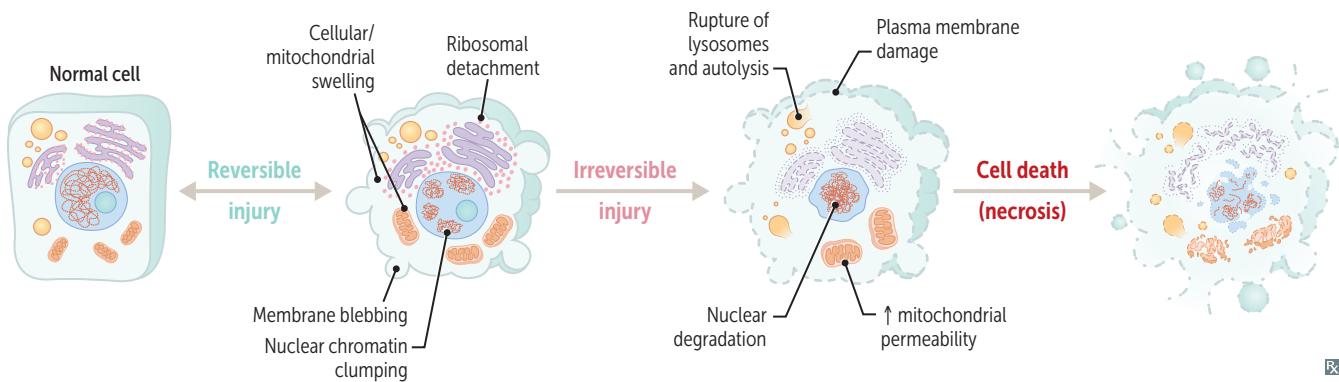
## Cell injury

### Reversible cell injury

- ↓ ATP → ↓ activity of  $\text{Ca}^{2+}$  and  $\text{Na}^+/\text{K}^+$  pumps → cellular swelling (earliest morphologic manifestation), mitochondrial swelling
- Ribosomal/polysomal detachment → ↓ protein synthesis
- Plasma membrane changes (eg, blebbing)
- Nuclear changes (eg, chromatin clumping)
- Rapid loss of function (eg, myocardial cells are noncontractile after 1-2 minutes of ischemia)
- Myelin figures (aggregation of peroxidized lipids)

### Irreversible cell injury

- Breakdown of plasma membrane → cytosolic enzymes (eg, troponin) leak outside of cell, influx of  $\text{Ca}^{2+}$  → activation of degradative enzymes
- Mitochondrial damage/dysfunction → loss of electron transport chain → ↓ ATP
- Rupture of lysosomes → autolysis
- Nuclear degradation: pyknosis (nuclear condensation) → karyorrhexis (nuclear fragmentation caused by endonuclease-mediated cleavage) → karyolysis (nuclear dissolution)
- Amorphous densities/inclusions in mitochondria



**Apoptosis**

ATP-dependent programmed cell death.

Intrinsic and extrinsic pathways; both pathways activate caspases (cytosolic proteases) → cellular breakdown including cell shrinkage, chromatin condensation, membrane blebbing, and formation of apoptotic bodies, which are then phagocytosed.

Characterized by deeply eosinophilic cytoplasm and basophilic nucleus, pyknosis, and karyorrhexis. Cell membrane typically remains intact without significant inflammation (unlike necrosis).

DNA laddering (fragments in multiples of 180 bp) is a sensitive indicator of apoptosis.

**Intrinsic (mitochondrial) pathway**

Involved in tissue remodeling in embryogenesis. Occurs when a regulating factor is withdrawn from a proliferating cell population (eg, ↓ IL-2 after a completed immunologic reaction → apoptosis of proliferating effector cells). Also occurs after exposure to injurious stimuli (eg, radiation, toxins, hypoxia).

Regulated by Bcl-2 family of proteins. **BAX** and **BAK** are proapoptotic (**BAd** for survival), while **Bcl-2** and **Bcl-xL** are antiapoptotic (**Be clever, live**).

BAX and BAK form pores in the mitochondrial membrane → release of cytochrome C from inner mitochondrial membrane into the cytoplasm → activation of caspases.

Bcl-2 keeps the mitochondrial membrane impermeable, thereby preventing cytochrome C release. Bcl-2 overexpression (eg, follicular lymphoma t[14;18]) → ↓ caspase activation → tumorigenesis.

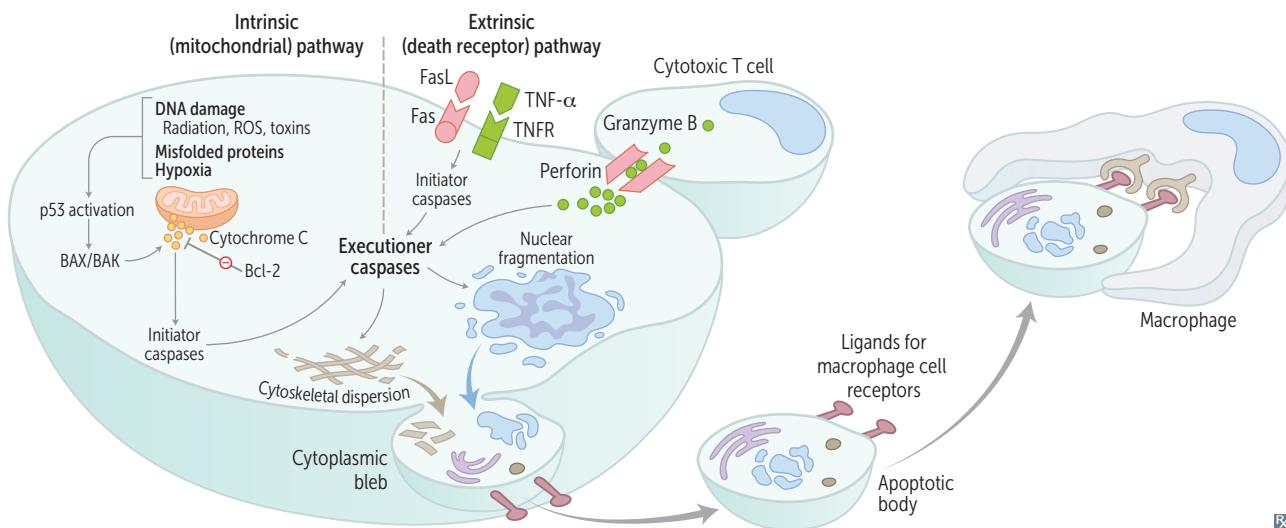
**Extrinsic (death receptor) pathway**

2 pathways:

- Ligand receptor interactions (FasL binding to Fas [CD95] or TNF- $\alpha$  binding to its receptor)
- Immune cell (cytotoxic T-cell release of perforin and granzyme B)

Fas-FasL interaction is necessary in thymic medullary negative selection.

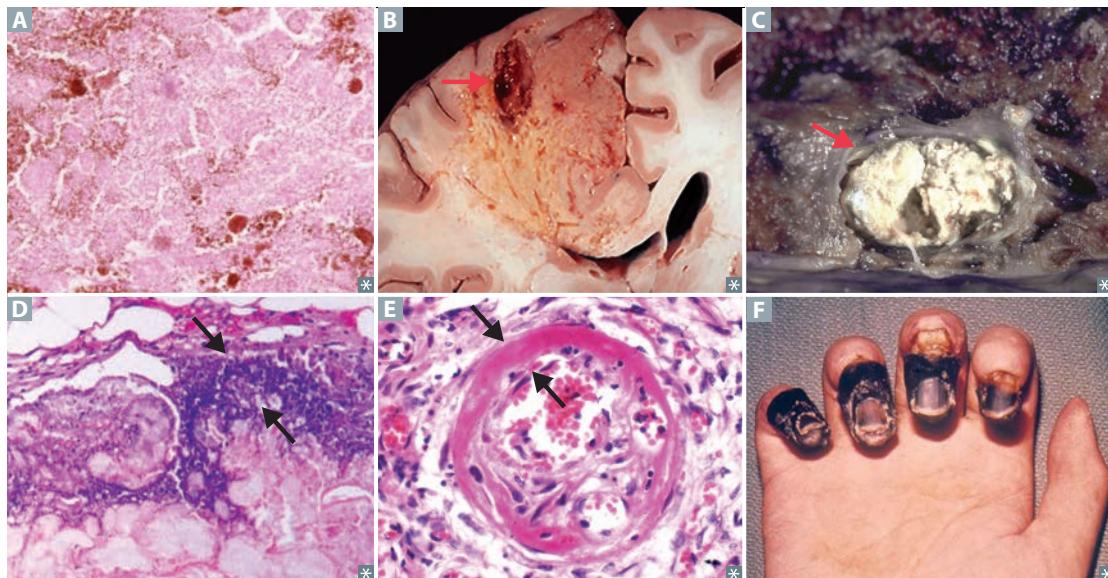
Defective Fas-FasL interactions → failure of clonal deletion → ↑ numbers of self-reacting lymphocytes → autoimmune lymphoproliferative syndrome.



**Necrosis**

Exogenous injury → plasma membrane damage → cell undergoes enzymatic degradation and protein denaturation, intracellular components leak → local inflammatory reaction (unlike apoptosis).

TYPE	SEEN IN	DUE TO	HISTOLOGY
<b>Coagulative</b>	Ischemia/infarcts in most tissues (except brain)	Ischemia or infarction; injury denatures enzymes → proteolysis blocked	Preserved cellular architecture (cell outlines seen), but nuclei disappear; ↑ cytoplasmic binding of eosin stain (→ ↑ eosinophilia; red/pink color) <b>A</b>
<b>Liquefactive</b>	Bacterial abscesses, brain infarcts	Neutrophils release lysosomal enzymes that digest the tissue <b>B</b>	Early: cellular debris and macrophages Late: cystic spaces and cavitation (brain) Neutrophils and cell debris seen with bacterial infection
<b>Caseous</b>	TB, systemic fungi (eg, <i>Histoplasma capsulatum</i> ), <i>Nocardia</i>	Macrophages wall off the infecting microorganism → granular debris	Cheese-like gross appearance <b>C</b> Fragmented cells and debris surrounded by lymphocytes and macrophages (granuloma)
<b>Fat</b>	Enzymatic: acute pancreatitis (saponification of peripancreatic fat) Nonenzymatic: traumatic (eg, injury to breast tissue)	Damaged pancreatic cells release lipase, which breaks down triglycerides; liberated fatty acids bind calcium → saponification (chalky-white appearance)	Outlines of dead fat cells without peripheral nuclei; saponification of fat (combined with $\text{Ca}^{2+}$ ) appears dark blue on H&E stain <b>D</b>
<b>Fibrinoid</b>	Immune vascular reactions (eg, PAN) Nonimmune vascular reactions (eg, hypertensive emergency, preeclampsia)	Immune complex deposition (type III hypersensitivity reaction) and/or plasma protein (eg, fibrin) leakage from damaged vessel	Vessel walls contain eosinophilic layer of proteinaceous material <b>E</b>
<b>Gangrenous</b>	Distal extremity and GI tract, after chronic ischemia	Dry: ischemia <b>F</b> Wet: superinfection	Coagulative Liquefactive superimposed on coagulative



**Ischemia**

Inadequate blood supply to meet demand. Mechanisms include ↓ arterial perfusion (eg, atherosclerosis), ↓ venous drainage (eg, testicular torsion, Budd-Chiari syndrome), shock. Regions most vulnerable to hypoxia/ischemia and subsequent infarction:

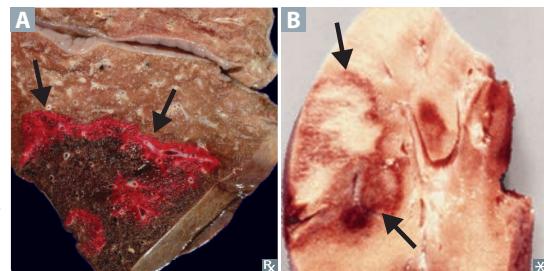
ORGAN	REGION
Brain	ACA/MCA/PCA boundary areas <sup>a,b</sup>
Heart	Subendocardium of LV (yellow lines in A outline a subendocardial infarction)
Kidney	Straight segment of proximal tubule (medulla) Thick ascending limb (medulla)
Liver	Area around central vein (zone III)
Colon	Splenic flexure (Griffith point), <sup>a</sup> rectosigmoid junction (Sudeck point) <sup>a</sup>

<sup>a</sup>Watershed areas (border zones) receive blood supply from most distal branches of 2 arteries with limited collateral vascularity. These areas are susceptible to ischemia from hypoperfusion.

<sup>b</sup>Neurons most vulnerable to hypoxic-ischemic insults include Purkinje cells of the cerebellum and pyramidal cells of the hippocampus and neocortex (zones 3, 5, 6).

**Types of infarcts****Red infarct**

Occurs in venous occlusion and tissues with multiple blood supplies (eg, liver, lung **A**, intestine, testes), and with reperfusion (eg, after angioplasty). **Reperfusion** injury is due to damage by free radicals.

**Pale infarct**

Occurs in solid organs with a single (end-arterial) blood supply (eg, heart, kidney **B**).

**Free radical injury**

Free radicals damage cells via membrane lipid peroxidation, protein modification, DNA breakage. Initiated via radiation exposure (eg, cancer therapy), metabolism of drugs (phase I), redox reactions, nitric oxide (eg, inflammation), transition metals, WBC (eg, neutrophils, macrophages) oxidative burst.

Free radicals can be eliminated by scavenging enzymes (eg, catalase, superoxide dismutase, glutathione peroxidase), spontaneous decay, antioxidants (eg, vitamins A, C, E), and certain metal carrier proteins (eg, transferrin, ceruloplasmin).

Examples:

- Oxygen toxicity: retinopathy of prematurity (abnormal vascularization), bronchopulmonary dysplasia, reperfusion injury after thrombolytic therapy
- Drug/chemical toxicity: acetaminophen overdose (hepatotoxicity), carbon tetrachloride (converted by cytochrome P-450 into  $\text{CCl}_3$  free radical → fatty liver [cell injury  
→ ↓ apolipoprotein synthesis → fatty change], centrilobular necrosis)
- Metal storage diseases: hemochromatosis (iron) and Wilson disease (copper)

**Ionizing radiation toxicity**

Ionization radiation induces cellular and DNA damage directly (via photons or particles) and indirectly (via generation of reactive oxygen species) → progressive inflammation and tissue damage. Rapidly regenerating tissues (eg, skin epithelia, bone marrow, GI tract, GU tract, gonads) more susceptible to injury. Can cause both acute and delayed (late) toxicities.

RADIATION TOXICITY	SYSTEM	DISEASE/CLINICAL MANIFESTATION
<b>Full exposure</b>		
<b>Acute radiation syndrome</b>	Skin	Hair loss, erythema, desquamation, ulcers/necrosis
	Hematopoietic	Myelosuppression
	Gastrointestinal	Mucosal denudation, inflammation, edema → abdominal pain, diarrhea, GI bleeding, nausea, vomiting, stomatitis
	Neurovascular	Papilledema, seizures, ataxia, impaired reflexes, cognitive deficits
<b>Partial exposure</b>		
<b>Acute local toxicity</b>	Skin, gonads, eye	Blisters, sterility, ↓ spermatogenesis, cataracts
<b>Late complication</b>		
<b>Radiation-induced fibrosis</b>	Skin, subcutaneous tissue	Induration, thickening, loss of elasticity, shrinkage, lymphedema
	Lung	Pulmonary fibrosis
	Head and neck	Trismus, mucosal fibrosis, ulceration, fistulae
	Gastrointestinal	Obstruction, ulcerations, fistulae
	Genitourinary	Ureteral and urethral stenosis, fibrotic bladder constriction → obstructive uropathy; fibrosis of ovaries, vulva, vagina; azoospermia
<b>Radiation-related malignancies</b>		
	Thyroid	Papillary thyroid carcinoma
	Hematopoietic	Myelodysplastic syndromes, lymphomas, leukemias (eg, CML, AML, ALL)
	Skin	Angiosarcoma
	Bone	Osteosarcoma
	Others	Solid tumors (eg, breast, ovarian, lung)

**Types of calcification**

Calcium deposits appear deeply basophilic (arrow in A) on H&E stain.

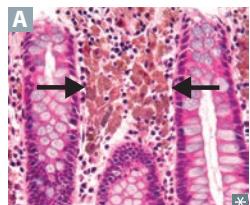
	Dystrophic calcification	Metastatic calcification
Ca <sup>2+</sup> DEPOSITION	In abnormal (diseased) tissues	In normal tissues
EXTENT	Tends to be localized (eg, calcific aortic stenosis)	Widespread (ie, diffuse, metastatic)
ASSOCIATED CONDITIONS	TB (lung and pericardium) and other granulomatous infections, liquefactive necrosis of chronic abscesses, fat necrosis, infarcts, thrombi, schistosomiasis, congenital CMV, toxoplasmosis, rubella, psammoma bodies, CREST syndrome, atherosclerotic plaques can become calcified	Predominantly in interstitial tissues of kidney, lung, and gastric mucosa (these tissues lose acid quickly; ↑ pH favors Ca <sup>2+</sup> deposition) Nephrocalcinosis of collecting ducts may lead to nephrogenic diabetes insipidus and renal failure
ETIOLOGY	2° to injury or necrosis	2° to hypercalcemia (eg, 1° hyperparathyroidism, sarcoidosis, hypervitaminosis D) or high calcium-phosphate product levels (eg, chronic kidney disease with 2° hyperparathyroidism, long-term dialysis, calciphylaxis, multiple myeloma)
SERUM Ca <sup>2+</sup> LEVELS	Normal	Usually abnormal

**Lipofuscin**

A yellow-brown “wear and tear” pigment A associated with normal aging.

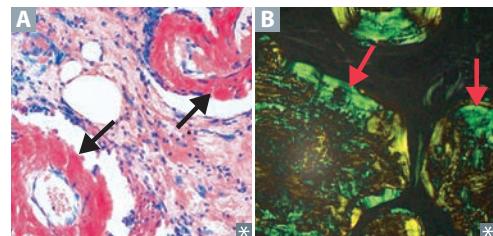
Composed of polymers of lipids and phospholipids complexed with protein. May be derived through lipid peroxidation of polyunsaturated lipids of subcellular membranes.

Autopsy of elderly person will reveal deposits in heart, colon, liver, kidney, eye, and other organs.



**Amyloidosis**

Abnormal aggregation of proteins (or their fragments) into  $\beta$ -pleated linear sheets  
 → insoluble fibrils → cellular damage and apoptosis. Amyloid deposits visualized by Congo red stain (red/orange on nonpolarized light [arrows in A]), (apple-green birefringence on polarized light [arrows in B]), and H&E stain (shows deposits in glomerular mesangial areas). Tubular basement membranes are enlarged on light microscopy.



COMMON TYPES	FIBRIL PROTEIN	DESCRIPTION	
<b>Systemic</b>			
<b>Primary amyloidosis</b>	AL (from Ig Light chains)	Seen in plasma cell disorders (eg, multiple myeloma)	Manifestations include:
<b>Secondary amyloidosis</b>	Serum Amyloid A (AA)	Seen in chronic inflammatory conditions, (eg, rheumatoid arthritis, IBD, familial Mediterranean fever, protracted infection)	<ul style="list-style-type: none"> <li>▪ Cardiac (eg, restrictive cardiomyopathy)</li> <li>▪ GI (eg, macroglossia, hepatomegaly)</li> <li>▪ Renal (eg, nephrotic syndrome)</li> <li>▪ Hematologic (eg, easy bruising, splenomegaly)</li> <li>▪ Neurologic (eg, neuropathy)</li> <li>▪ Musculoskeletal (eg, carpal tunnel syndrome)</li> </ul>
<b>Dialysis-related amyloidosis</b>	$\beta_2$ -microglobulin	Seen in patients with ESRD and/or on long-term dialysis	
<b>Localized</b>			
<b>Alzheimer disease</b>	$\beta$ -amyloid protein	Cleaved from amyloid precursor protein (APP)	
<b>Type 2 diabetes mellitus</b>	Islet amyloid polypeptide (IAPP)	Caused by deposition of amylin in pancreatic islets	
<b>Medullary thyroid cancer</b>	Calcitonin		
<b>Isolated atrial amyloidosis</b>	ANP	Common in normal aging ↑ risk of atrial fibrillation	
<b>Systemic senile (age-related) amyloidosis</b>	Normal (wild-type) transthyretin (TTR)	Seen predominantly in cardiac ventricles	Cardiac dysfunction more insidious than in AL amyloidosis
<b>Hereditary</b>			
<b>Familial amyloid cardiomyopathy</b>	Mutated transthyretin (ATTR)	Ventricular endomyocardium deposition → restrictive cardiomyopathy, arrhythmias	3–4% of African-Americans are carriers of a mutated allele
<b>Familial amyloid polyneuropathies</b>	Mutated transthyretin (ATTR)	Due to transthyretin gene mutation	

## ► PATHOLOGY—INFLAMMATION

**Inflammation**

Response to eliminate initial cause of cell injury, to remove necrotic cells resulting from the original insult, and to initiate tissue repair. Divided into acute and chronic. The inflammatory response itself can be harmful to the host if the reaction is excessive (eg, septic shock), prolonged (eg, persistent infections such as TB), or inappropriate (eg, autoimmune diseases such as SLE).

SIGN	MECHANISM	MEDIATORS
<b>Cardinal signs</b>		
<b>Rubor and calor</b>	Redness and warmth. Vasodilation (relaxation of arteriolar smooth muscle) → ↑ blood flow.	Histamine, prostaglandins, bradykinin, NO.
<b>Tumor</b>	Swelling. Endothelial contraction/disruption (eg, from tissue damage) → ↑ vascular permeability → leakage of protein-rich fluid from postcapillary venules into interstitial space (exudate) → ↑ interstitial oncotic pressure.	Endothelial contraction: leukotrienes (C <sub>4</sub> , D <sub>4</sub> , E <sub>4</sub> ), histamine, serotonin.
<b>Dolor</b>	Pain. Sensitization of sensory nerve endings.	Bradykinin, PGE <sub>2</sub> , histamine.
<b>Functio laesa</b>	Loss of function. Inflammation impairs function (eg, inability to make fist due to hand cellulitis).	

**Systemic manifestations (acute-phase reaction)**

<b>Fever</b>	Pyrogens (eg, LPS) induce macrophages to release IL-1 and TNF → ↑ COX activity in perivascular cells of anterior hypothalamus → ↑ PGE <sub>2</sub> → ↑ temperature set point.	
<b>Leukocytosis</b>	↑ WBC count; type of predominant cell depends on inciting agent or injury (eg, bacteria → ↑ neutrophils).	
<b>↑ plasma acute-phase reactants</b>	Serum concentrations significantly change in response to acute and chronic inflammation. Produced by liver.	Notably induced by IL-6.

**Acute phase reactants**

More FFISHH Pee in the C (sea).

## POSITIVE (UPREGULATED)

<b>Ferritin</b>	Binds and sequesters iron to inhibit microbial iron scavenging.
<b>Fibrinogen</b>	Coagulation factor; promotes endothelial repair; correlates with ESR.
<b>Serum amyloid A</b>	Prolonged elevation can lead to amyloidosis.
<b>Hepcidin</b>	↓ iron absorption (by degrading ferroportin) and ↓ iron release (from macrophages) → anemia of chronic disease.
<b>Haptoglobin</b>	Binds extracellular hemoglobin, protects against oxidative stress.
<b>Procalcitonin</b>	Rises in bacterial infections.
<b>C-reactive protein</b>	Opsonin; fixes complement and facilitates phagocytosis. Measured clinically as a nonspecific sign of ongoing inflammation.

## NEGATIVE (DOWNREGULATED)

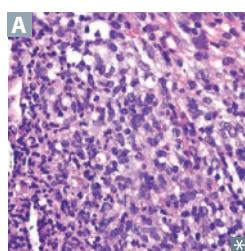
<b>Albumin</b>	Reduction conserves amino acids for positive reactants.
<b>Transferrin</b>	Internalized by macrophages to sequester iron.

### Erythrocyte sedimentation rate

RBCs normally remain separated via  $\ominus$  charges. Products of inflammation (eg, fibrinogen) coat RBCs  $\rightarrow$   $\downarrow \ominus$  charge  $\rightarrow$   $\uparrow$  RBC aggregation. Denser RBC aggregates fall at a faster rate within a pipette tube  $\rightarrow$   $\uparrow$  ESR. Often co-tested with CRP (more specific marker of inflammation).

$\uparrow$ ESR	$\downarrow$ ESR
Most anemias	Sickle cell anemia (altered shape)
Infections	Polycythemia ( $\uparrow$ RBCs “dilute” aggregation factors)
Inflammation (eg, giant cell [temporal] arteritis, polymyalgia rheumatica)	HF
Cancer (eg, metastases, multiple myeloma)	Microcytosis
Renal disease (end-stage or nephrotic syndrome)	Hypofibrinogenemia
Pregnancy	

### Acute inflammation



Transient and early response to injury or infection. Characterized by neutrophils in tissue **A**, often with associated edema. Rapid onset (seconds to minutes) and short duration (minutes to days). Represents a reaction of the innate immune system (ie, less specific response than chronic inflammation).

#### STIMULI

Infections, trauma, necrosis, foreign bodies.

#### MEDIATORS

Toll-like receptors, arachidonic acid metabolites, neutrophils, eosinophils, antibodies (pre-existing), mast cells, basophils, complement, Hageman factor (factor XII).

**Inflammasome**—Cytoplasmic protein complex that recognizes products of dead cells, microbial products, and crystals (eg, uric acid crystals)  $\rightarrow$  activation of IL-1 and inflammatory response.

#### COMPONENTS

- Vascular: vasodilation ( $\rightarrow$   $\uparrow$  blood flow and stasis) and  $\uparrow$  endothelial permeability (contraction of endothelial cells opens interendothelial junctions)
- Cellular: extravasation of leukocytes (mainly neutrophils) from postcapillary venules and accumulation in the focus of injury followed by leukocyte activation

To bring cells and proteins to site of injury or infection.

Leukocyte extravasation has 4 steps: margination and rolling, adhesion, transmigration, and migration (chemoattraction).

#### OUTCOMES

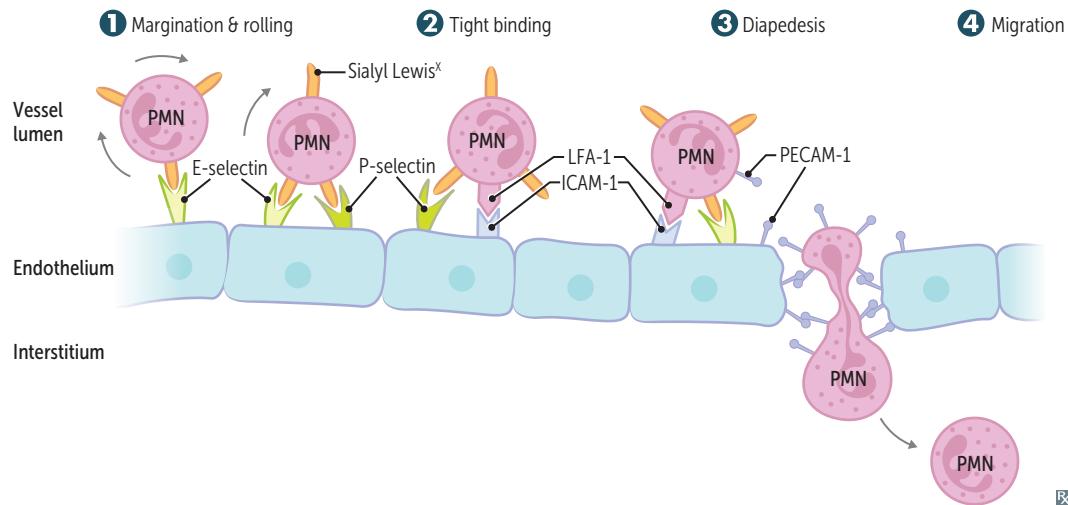
- Resolution and healing (IL-10, TGF- $\beta$ )
- Persistent acute inflammation (IL-8)
- Abscess (acute inflammation walled off by fibrosis)
- Chronic inflammation (antigen presentation by macrophages and other APCs  $\rightarrow$  activation of CD4 $^+$  Th cells)
- Scarring

Macrophages predominate in the late stages of acute inflammation (peak 2–3 days after onset) and influence outcome by secreting cytokines.

## Leukocyte extravasation

Extravasation predominantly occurs at postcapillary venules.

STEP	VASCULATURE/STROMA	LEUKOCYTE
❶ Margination and rolling—defective in leukocyte adhesion deficiency type 2 ( $\downarrow$ Sialyl Lewis <sup>X</sup> )	E-selectin (upregulated by TNF and IL-1) P-selectin (released from Weibel-palade bodies) GlyCAM-1, CD34	Sialyl Lewis <sup>X</sup> Sialyl Lewis <sup>X</sup> L-selectin
❷ Tight binding (adhesion)—defective in leukocyte adhesion deficiency type 1 ( $\downarrow$ CD18 integrin subunit)	ICAM-1 (CD54) VCAM-1 (CD106)	CD11/18 integrins (LFA-1, Mac-1) VLA-4 integrin
❸ Diapedesis (transmigration)—WBC travels between endothelial cells and exits blood vessel	PECAM-1 (CD31)	PECAM-1 (CD31)
❹ Migration—WBC travels through interstitium to site of injury or infection guided by chemotactic signals	Chemotactic factors: C5a, IL-8, LTB <sub>4</sub> , kallikrein, platelet-activating factor, N-formylmethionyl peptides	Various



<b>Chronic inflammation</b>	Prolonged inflammation characterized by mononuclear infiltration (macrophages, lymphocytes, plasma cells), which leads to simultaneous tissue destruction and repair (including angiogenesis and fibrosis). May be preceded by acute inflammation.
<b>STIMULI</b>	Persistent infections (eg, TB, <i>T pallidum</i> , certain fungi and viruses) → type IV hypersensitivity, autoimmune diseases, prolonged exposure to toxic agents (eg, silica) and foreign material.
<b>MEDIATORS</b>	Macrophages are the dominant cells. Interaction of macrophages and T lymphocytes → chronic inflammation. ▪ Th1 cells secrete IFN-γ → macrophage classical activation (proinflammatory) ▪ Th2 cells secrete IL-4 and IL-13 → macrophage alternative activation (repair and anti-inflammatory)
<b>OUTCOMES</b>	Scarring, amyloidosis, and neoplastic transformation (eg, chronic HCV infection → chronic inflammation → hepatocellular carcinoma; <i>Helicobacter pylori</i> infection → chronic gastritis → gastric adenocarcinoma).

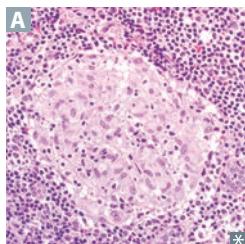
### Wound healing

Tissue mediators	MEDIATOR	ROLE
	FGF	Stimulates angiogenesis
	TGF-β	Angiogenesis, fibrosis
	VEGF	Stimulates angiogenesis
	PDGF	Secreted by activated platelets and macrophages Induces vascular remodeling and smooth muscle cell migration Stimulates fibroblast growth for collagen synthesis
	Metalloproteinases	Tissue remodeling
	EGF	Stimulates cell growth via tyrosine kinases (eg, EGFR/ErbB1)
PHASE OF WOUND HEALING	EFFECTOR CELLS	CHARACTERISTICS
<b>Inflammatory (up to 3 days after wound)</b>	Platelets, neutrophils, macrophages	Clot formation, ↑ vessel permeability and neutrophil migration into tissue; macrophages clear debris 2 days later
<b>Proliferative (day 3–weeks after wound)</b>	Fibroblasts, myofibroblasts, endothelial cells, keratinocytes, macrophages	Deposition of granulation tissue and type III collagen, angiogenesis, epithelial cell proliferation, dissolution of clot, and wound contraction (mediated by myofibroblasts) Delayed second phase of wound healing in vitamin C and copper deficiency
<b>Remodeling (1 week–6+ months after wound)</b>	Fibroblasts	Type III collagen replaced by type I collagen, ↑ tensile strength of tissue Collagenases (require zinc to function) break down type III collagen Zinc deficiency → delayed wound healing

## Granulomatous inflammation

A pattern of chronic inflammation. Can be induced by persistent T-cell response to certain infections (eg, TB), immune-mediated diseases, and foreign bodies. Granulomas “wall off” a resistant stimulus without completely eradicating or degrading it → persistent inflammation → fibrosis, organ damage.

### HISTOLOGY



Focus of epithelioid cells (activated macrophages with abundant pink cytoplasm) surrounded by lymphocytes and multinucleated giant cells (formed by fusion of several activated macrophages).

Two types:

**Caseating:** associated with central necrosis. Seen with infectious etiologies (eg, TB, fungal).

**Noncaseating A:** no central necrosis. Seen with autoimmune diseases (eg, sarcoidosis, Crohn disease).

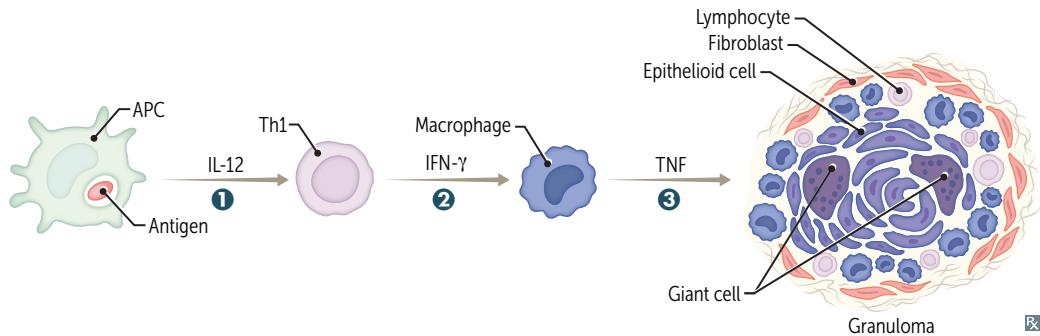
### MECHANISM

- ① APCs present antigens to CD4+ Th cells and secrete IL-12 → CD4+ Th cells differentiate into Th1 cells
- ② Th1 secretes IFN- $\gamma$  → macrophage activation
- ③ Macrophages ↑ cytokine secretion (eg, TNF) → formation of epithelioid macrophages and giant cells

Anti-TNF therapy can cause sequestering granulomas to break down → disseminated disease.

Always test for latent TB before starting anti-TNF therapy.

Associated with hypercalcemia due to ↑ 1 $\alpha$ -hydroxylase activity in activated macrophages, resulting in ↑ vitamin D activity.



### ETIOLOGIES

#### INFECTIOUS

Bacterial: *Mycobacteria* (tuberculosis, leprosy), *Bartonella henselae* (cat scratch disease; stellate necrotizing granulomas), *Listeria monocytogenes* (granulomatosis infantiseptica), *Treponema pallidum* (3° syphilis)  
Fungal: endemic mycoses (eg, histoplasmosis)  
Parasitic: schistosomiasis

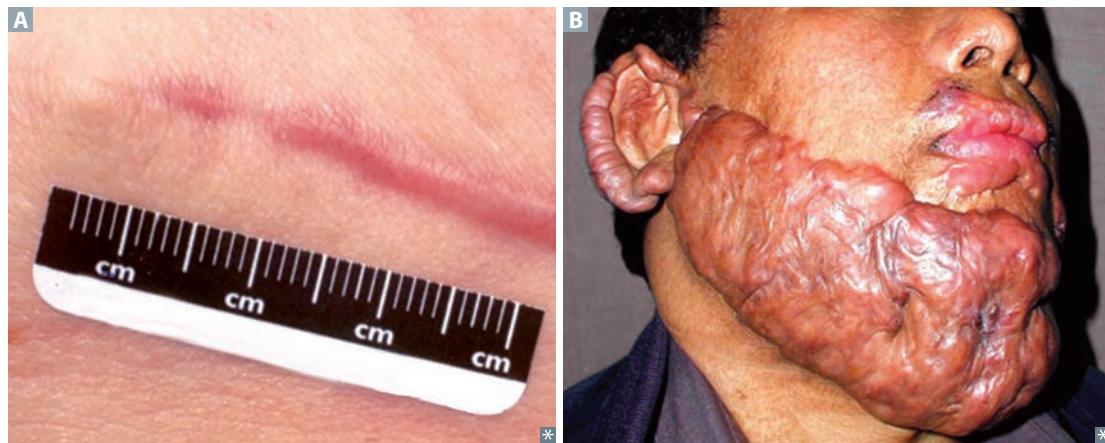
#### NONINFECTIOUS

Immune-mediated: sarcoidosis, Crohn disease, 1° biliary cholangitis, subacute (de Quervain/granulomatous) thyroiditis  
Vasculitis: granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis, giant cell (temporal) arteritis, Takayasu arteritis  
Foreign bodies: berylliosis, talcosis, hypersensitivity pneumonitis  
Chronic granulomatous disease

**Scar formation**

Occurs when repair cannot be accomplished by cell regeneration alone. Nonregenerated cells ( $2^{\circ}$  to severe acute or chronic injury) are replaced by connective tissue. 70–80% of tensile strength regained at 3 months; little tensile strength regained thereafter. Associated with excess TGF- $\beta$ .

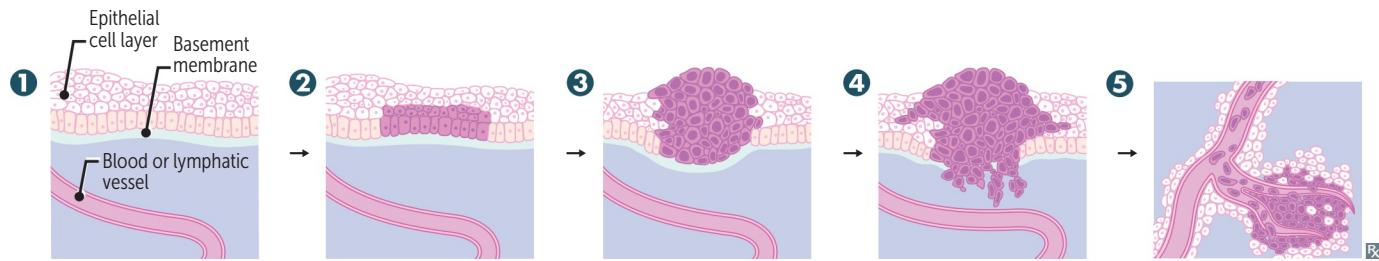
SCAR TYPE	Hypertrophic A	Keloid B
COLLAGEN SYNTHESIS	↑ (type III collagen)	↑↑ (types I and III collagen)
COLLAGEN ORGANIZATION	Parallel	Disorganized
EXTENT OF SCAR	Confined to borders of original wound	Extends beyond borders of original wound with “claw-like” projections typically on earlobes, face, upper extremities
RECURRENCE	Infrequent	Frequent
PREDISPOSITION	None	↑ incidence in people with darker skin



## ▶ PATHOLOGY—NEOPLASIA

**Neoplasia and neoplastic progression**

Uncontrolled, monoclonal proliferation of cells. Can be benign or malignant. Any neoplastic growth has two components: parenchyma (neoplastic cells) and supporting stroma (non-neoplastic; eg, blood vessels, connective tissue).

**Normal cells**

**①** Normal cells with basal → apical polarity. See cervical example **A**, which shows normal cells and spectrum of dysplasia, as discussed below.

**Dysplasia**

**②** Loss of uniformity in cell size and shape (pleomorphism); loss of tissue orientation; nuclear changes (eg, ↑ nuclear:cytoplasmic ratio) **A**; often reversible.

**Carcinoma in situ/ preinvasive**

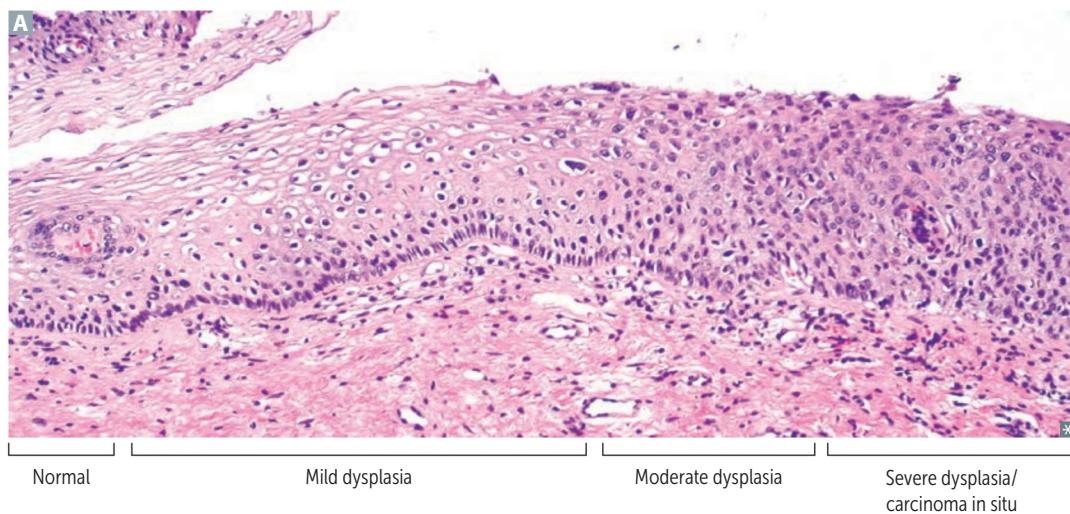
**③** Irreversible severe dysplasia that involves the entire thickness of epithelium but does not penetrate the intact basement membrane **A**.

**Invasive carcinoma**

**④** Cells have invaded basement membrane using collagenases and hydrolases (metalloproteinases). Cell-cell contacts lost by inactivation of E-cadherin.

**Metastasis**

**⑤** Spread to distant organ(s) via lymphatics or blood.



**Tumor nomenclature**

**Carcinoma** implies epithelial origin, whereas **sarcoma** denotes mesenchymal origin. Both terms generally imply malignancy.

**Benign** tumors are usually well-differentiated and well-demarcated, with low mitotic activity, no metastases, and no necrosis.

**Malignant** tumors (cancers) may show poor differentiation, erratic growth, local invasion, metastasis, and ↓ apoptosis.

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).

CELL TYPE	BENIGN	MALIGNANT
<b>Epithelium</b>	Adenoma, papilloma	Adenocarcinoma, papillary carcinoma
<b>Mesenchyme</b>		
Blood cells		Leukemia, lymphoma
Blood vessels	Hemangioma	Angiosarcoma
Smooth muscle	Leiomyoma	Leiomyosarcoma
Striated muscle	Rhabdomyoma	Rhabdomyosarcoma
Connective tissue	Fibroma	Fibrosarcoma
Bone	Osteoma	Osteosarcoma
Fat	Lipoma	Liposarcoma
Melanocyte	Nevus/mole	Melanoma

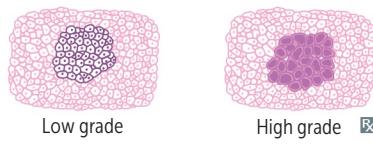
**Tumor grade vs stage**

**Differentiation**—degree to which a tumor resembles its tissue of origin. Well-differentiated tumors (often less aggressive) closely resemble their tissue of origin, whereas poorly differentiated tumors (often more aggressive) do not.

**Anaplasia**—complete lack of differentiation of cells in a malignant neoplasm.

**Grade**

Degree of cellular differentiation and mitotic activity on histology. Ranges from low grade (well-differentiated) to high grade (poorly differentiated, undifferentiated, or anaplastic).

**Stage**

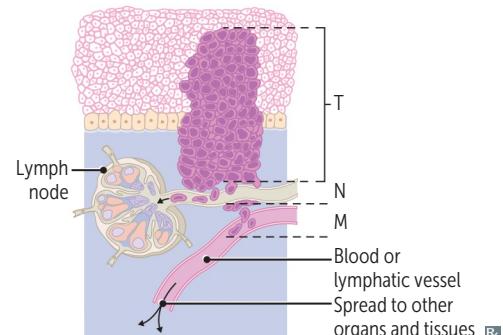
Degree of localization/spread based on site and size of 1° lesion, spread to regional lymph nodes, presence of metastases. Based on clinical (c) or pathologic (p) findings. Stage generally has more prognostic value than grade (eg, a high-stage yet low-grade tumor is usually worse than a low-stage yet high-grade tumor). **Stage determines Survival.**

TNM staging system (**Stage = Spread**):

**T** = **Tumor size/invasiveness**, **N** = **Node**

involvement, **M** = **Metastases**, eg, cT3N1M0.

Each TNM factor has independent prognostic value; N and M are often most important.



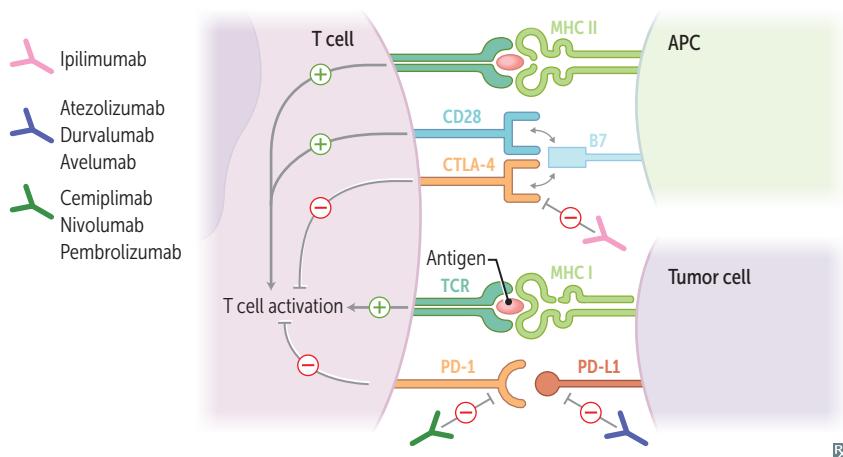
<b>Hallmarks of cancer</b>	Cancer is caused by (mostly acquired) DNA mutations that affect fundamental cellular processes (eg, growth, DNA repair, survival).
HALLMARK	MECHANISM
<b>Growth signal self-sufficiency</b>	Mutations in genes encoding: <ul style="list-style-type: none"> <li>▪ Proto-oncogenes → ↑ growth factors → autocrine loop (eg, ↑ PDGF in brain tumors)</li> <li>▪ Growth factor receptors → constitutive signaling (eg, <i>HER2/neu</i> in breast cancer)</li> <li>▪ Signaling molecules (eg, RAS)</li> <li>▪ Transcription factors (eg, MYC)</li> <li>▪ Cell cycle regulators (eg, cyclins, CDKs)</li> </ul>
<b>Anti-growth signal insensitivity</b>	<ul style="list-style-type: none"> <li>▪ Mutations in tumor suppressor genes (eg, <i>Rb</i>)</li> <li>▪ Loss of E-cadherin function → loss of contact inhibition (eg, <i>NF2</i> mutations)</li> </ul>
<b>Evasion of apoptosis</b>	Mutations in genes that regulate apoptosis (eg, <i>TP53</i> , <i>BCL2</i> → follicular B cell lymphoma).
<b>Limitless replicative potential</b>	Reactivation of telomerase → maintenance and lengthening of telomeres → prevention of chromosome shortening and cell aging.
<b>Sustained angiogenesis</b>	↑ pro-angiogenic factors (eg, VEGF) or ↓ inhibitory factors. Factors may be produced by tumor or stromal cells. Vessels can sprout from existing capillaries (neoangiogenesis) or endothelial cells are recruited from bone marrow (vasculogenesis). Vessels may be leaky and/or dilated.
<b>Tissue invasion</b>	Loss of E-cadherin function → loosening of intercellular junctions → metalloproteinases degrade basement membrane and ECM → cells attach to ECM proteins (eg, laminin, fibronectin) → cells migrate through degraded ECM (“locomotion”) → vascular dissemination.
<b>Metastasis</b>	Tumor cells or emboli spread via lymphatics or blood → adhesion to endothelium → extravasation and homing. Site of metastasis can be predicted by site of 1° tumor, as the target organ is often the first-encountered capillary bed. Some cancers show organ tropism (eg, lung cancers commonly metastasize to adrenals).
<b>Warburg effect</b>	Shift of glucose metabolism away from mitochondrial oxidative phosphorylation toward glycolysis. Glycolysis provides rapidly dividing cancer cells with the carbon needed for synthesis of cellular structures.
<b>Immune evasion in cancer</b>	Normally, immune cells can recognize and attack tumor cells. For successful tumorigenesis, tumor cells must evade the immune system. Multiple escape mechanisms exist: <ul style="list-style-type: none"> <li>▪ ↓ MHC class I expression by tumor cells → cytotoxic T cells are unable to recognize tumor cells.</li> <li>▪ Tumor cells secrete immunosuppressive factors (eg, TGF-β) and recruit regulatory T cells to down regulate immune response.</li> <li>▪ Tumor cells up regulate immune checkpoint molecules, which inhibit immune response.</li> </ul>

### Immune checkpoint interactions

Signals that modulate T cell activation and function → ↓ immune response against tumor cells.

Targeted by several cancer immunotherapies. Examples:

- Interaction between PD-1 (on T cells) and PD-L1/2 (on tumor cells or immune cells in tumor microenvironment) → T cell dysfunction (exhaustion). Inhibited by antibodies against PD-1 (eg, pembrolizumab, nivolumab, cemiplimab) or PD-L1 (eg, atezolizumab, durvalumab, avelumab).
- CTLA-4 on T cells outcompetes CD28 for B7 on APCs → loss of T cell costimulatory signal. Inhibited by ipilimumab (anti-CTLA-4 antibody).



### Cancer epidemiology

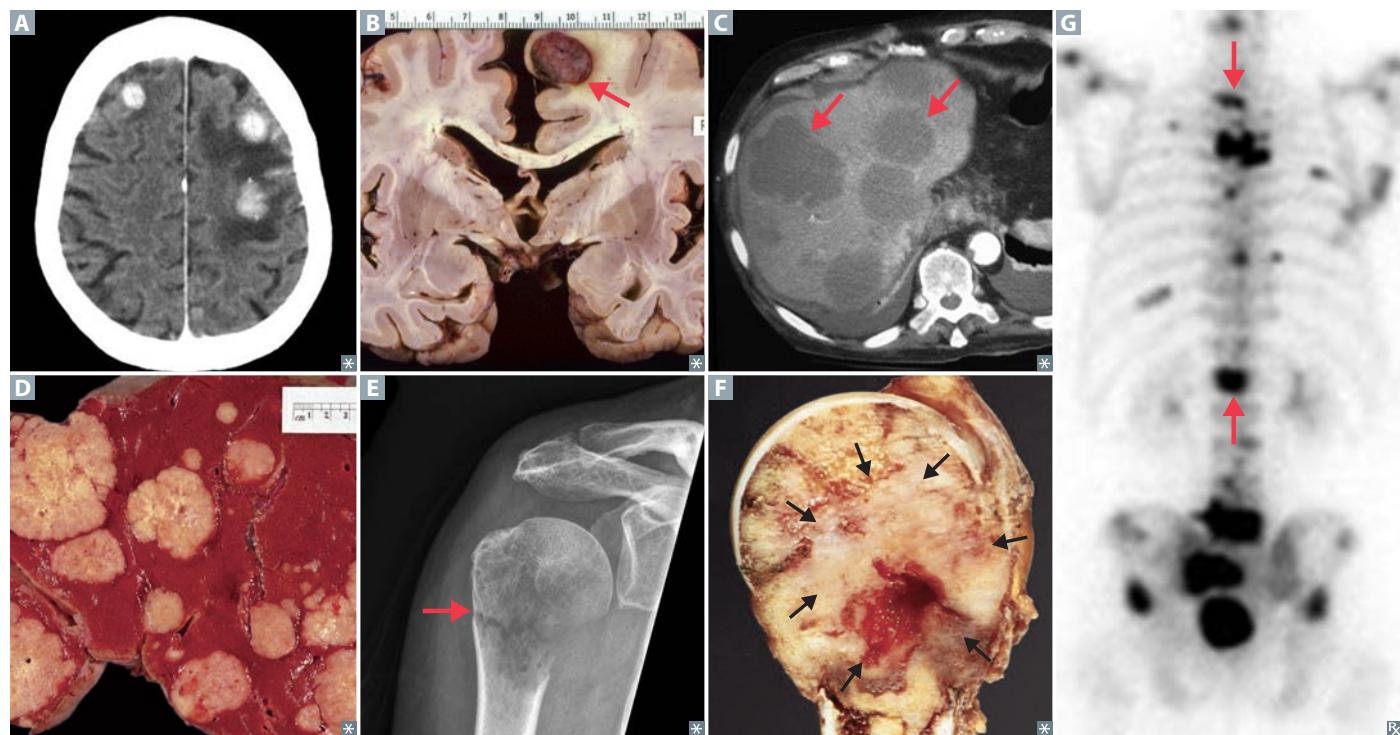
Skin cancer (basal > squamous >> melanoma) is the most common cancer (not included below).

	MALES	FEMALES	CHILDREN (AGE 0–14)	NOTES
<b>Cancer incidence</b>	1. Prostate 2. Lung 3. Colon/rectum	1. Breast 2. Lung 3. Colon/rectum	1. Leukemia 2. CNS 3. Neuroblastoma	Lung cancer incidence has ↓ in males, but has not changed significantly in females.
<b>Cancer mortality</b>	1. Lung 2. Prostate 3. Colon/rectum	1. Lung 2. Breast 3. Colon/rectum	1. Leukemia 2. CNS 3. Neuroblastoma	Cancer is the 2nd leading cause of death in the United States (heart disease is 1st).

**Common metastases**

Most sarcomas spread hematogenously; most carcinomas spread via lymphatics. However, four carcinomas route hematogenously: follicular thyroid carcinoma, choriocarcinoma, renal cell carcinoma, and hepatocellular carcinoma.

SITE OF METASTASIS	1 <sup>o</sup> TUMOR	NOTES
<b>Brain</b>	Lung > breast > melanoma, colon, kidney (lots of brain metastases can kill)	50% of brain tumors are from metastases Commonly seen as multiple well-circumscribed tumors at gray/white matter junction <b>A B</b>
<b>Liver</b>	Colon >> stomach > pancreas (cancer sometimes penetrates liver)	Liver <b>C D</b> and lung are the most common sites of metastasis after the regional lymph nodes
<b>Bone</b>	Prostate, breast > kidney, thyroid, lung (painful bones kill the lungs)	Bone metastasis <b>E F</b> >> 1 <sup>o</sup> bone tumors (eg, multiple myeloma) Predilection for axial skeleton <b>G</b> Bone metastasis can be: <ul style="list-style-type: none"> <li>▪ Lytic (eg, thyroid, kidney, non-small cell lung cancer)</li> <li>▪ Blastic (eg, prostate, small cell lung cancer)</li> <li>▪ Mixed (eg, breast cancer)</li> </ul>



**Oncogenes**

Gain of function mutation converts proto-oncogene (normal gene) to oncogene → ↑ cancer risk.  
Requires damage to only one allele of a proto-oncogene.

GENE	GENE PRODUCT	ASSOCIATED NEOPLASM
<b>ALK</b>	Receptor tyrosine kinase	Lung adenocarcinoma
<b>HER2/neu (ERBB2)</b>	Receptor tyrosine kinase	Breast and gastric carcinomas
<b>RET</b>	REceptor Tyrosine kinase	MEN 2A and 2B, medullary and papillary thyroid carcinoma, pheochromocytoma
<b>BCR-ABL</b>	Non-receptor tyrosine kinase	CML, ALL
<b>JAK2</b>	Non-receptor tyrosine kinase	Myeloproliferative neoplasms
<b>BRAF</b>	Serine/threonine kinase	Melanoma, non-Hodgkin lymphoma, colorectal carcinoma, papillary thyroid carcinoma, hairy cell leukemia
<b>c-KIT</b>	CytoKine receptor	Gastrointestinal stromal tumor (GIST), mastocytosis
<b>c-MYC</b>	Transcription factor	Burkitt lymphoma
<b>MYCL1</b>	Transcription factor	Lung cancer
<b>MYCN (N-myc)</b>	Transcription factor	Neuroblastoma
<b>KRAS</b>	RAS GTPase	Colorectal, lung, pancreatic cancers
<b>BCL-2</b>	Antia apoptotic molecule (inhibits apoptosis)	Follicular and diffuse large B-Cell Lymphomas

**Tumor suppressor genes**

Loss of function → ↑ cancer risk; both (two) alleles of a tumor suppressor gene must be lost for expression of disease (Knudson's 2-hit hypothesis).

GENE	GENE PRODUCT	ASSOCIATED CONDITION
<b>APC</b>	Negative regulator of β-catenin/WNT pathway	Colorectal cancer (associated with FAP)
<b>BRCA1/BRCA2</b>	BRCA1/BRCA2 proteins	BReast, ovarian, prostate, pancreatic CAncers
<b>CDKN2A</b>	p16, blocks G <sub>1</sub> → S phase	Many cancers (eg, melanoma, lung)
<b>DCC</b>	<b>DCC</b> —Deleted in Colorectal Cancer	Colorectal cancer
<b>SMAD4 (DPC4)</b>	<b>DPC</b> —Deleted in Pancreatic Cancer	Pancreatic cancer, colorectal cancer
<b>MEN1</b>	<b>MEN</b> in	Multiple Endocrine Neoplasia type 1
<b>NF1</b>	Neurofibromin (Ras GTPase activating protein)	NeuroFibromatosis type 1
<b>NF2</b>	Merlin (schwannomin) protein	NeuroFibromatosis type 2
<b>PTEN</b>	Negative regulator of PI3k/AKT pathway	Prostate, breast, and ENdometrial cancers
<b>RB1</b>	Inhibits E2F; blocks G <sub>1</sub> → S phase	Retinoblastoma, osteosarcoma (bone cancer)
<b>TP53</b>	p53, activates p21, blocks G <sub>1</sub> → S phase	Most cancers, Li-Fraumeni syndrome (multiple malignancies at early age, aka, SBLA syndrome: Sarcoma, Breast, Leukemia, Adrenal gland)
<b>TSC1</b>	Hamartin protein	Tuberous sclerosis
<b>TSC2</b>	Tuberin (“2berin”)	Tuberous sclerosis
<b>VHL</b>	Inhibits hypoxia-inducible factor 1α	von Hippel-Lindau disease
<b>WT1</b>	Urogenital development transcription factor	Wilms Tumor (nephroblastoma)

**Carcinogens**

TOXIN	EXPOSURE	ORGAN	IMPACT
Aflatoxins ( <i>Aspergillus</i> )	Stored grains and nuts	Liver	Hepatocellular carcinoma
Alkylating agents	Oncologic chemotherapy	Blood	Leukemia/lymphoma
Aromatic amines (eg, benzidine, 2-naphthylamine)	Textile industry (dyes), tobacco smoke (2-naphthylamine)	Bladder	Transitional cell carcinoma
Arsenic	Herbicides (vineyard workers), metal smelting, wood preservation	Liver Lung Skin	Hepatic angiosarcoma Lung cancer Squamous cell carcinoma
Asbestos	Old roofing material, shipyard workers	Lung	Bronchogenic carcinoma > mesothelioma
Tobacco smoke		Bladder Cervix Esophagus  Kidney Larynx Lung  Oropharynx Pancreas	Transitional cell carcinoma Squamous cell carcinoma Squamous cell carcinoma/ adenocarcinoma Renal cell carcinoma Squamous cell carcinoma Squamous cell and small cell carcinoma Oropharyngeal cancer Pancreatic adenocarcinoma
Ethanol		Esophagus Liver Breast	Squamous cell carcinoma Hepatocellular carcinoma Breast cancer
Ionizing radiation		Thyroid	Papillary thyroid carcinoma, leukemias
Nickel, chromium, beryllium, silica	Occupational exposure	Lung	Lung cancer
Nitrosamines	Smoked foods	Stomach	Gastric cancer (intestinal type)
Radon	Byproduct of uranium decay, accumulates in basements	Lung	Lung cancer (2nd leading cause after tobacco smoke)
Vinyl chloride	Used to make PVC pipes (plumbers)	Liver	Hepatic angiosarcoma

**Oncogenic microbes**

Microbe	Associated cancer
EBV	Burkitt lymphoma, Hodgkin lymphoma, nasopharyngeal carcinoma, 1° CNS lymphoma (in immunocompromised patients)
HBV, HCV	Hepatocellular carcinoma
HHV-8	Kaposi sarcoma
HPV (usually types 16, 18)	Cervical and penile/anal carcinoma, 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>	Squamous cell bladder cancer

**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 made via biopsy. Some can be associated with non-neoplastic conditions.

MARKER	IMPORTANT ASSOCIATIONS	NOTES
<b>Alkaline phosphatase</b>	Metastases to bone or liver, Paget disease of bone, seminoma (placental ALP).	Exclude hepatic origin by checking LFTs and GGT levels.
<b>α-fetoprotein</b>	Hepatocellular carcinoma, endodermal sinus (yolk sac) tumor, mixed germ cell tumor, ataxia-telangiectasia, neural tube defects.	Normally made by fetus. Transiently elevated in pregnancy. High levels associated with neural tube and abdominal wall defects, low levels associated with Down syndrome.
<b>hCG</b>	Hydatidiform moles and Choriocarcinomas (Gestational trophoblastic disease), testicular cancer, mixed germ cell tumor.	Produced by syncytiotrophoblasts of the placenta.
<b>CA 15-3/CA 27-29</b>	Breast cancer.	
<b>CA 19-9</b>	Pancreatic adenocarcinoma.	
<b>CA 125</b>	Ovarian cancer.	
<b>Calcitonin</b>	Medullary thyroid carcinoma (alone and in MEN2A, MEN2B).	Calci2nin.
<b>CEA</b>	Colorectal and pancreatic cancers. Minor associations: gastric, breast, and medullary thyroid carcinomas.	CarcinoEEmbryonic Antigen. Very nonspecific.
<b>Chromogranin</b>	Neuroendocrine tumors.	
<b>LDH</b>	Testicular germ cell tumors, ovarian dysgerminoma, other cancers.	Can be used as an indicator of tumor burden.
<b>Neuron-specific enolase</b>	Neuroendocrine tumors (eg, small cell lung cancer, carcinoid tumor, neuroblastoma).	
<b>PSA</b>	Prostate cancer.	Prostate-Specific Antigen. Also elevated in BPH and prostatitis. Questionable risk/benefit for screening. Marker for recurrence after treatment.

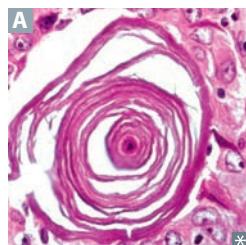
**Important****immunohistochemical stains**

Determine primary site of origin for metastatic tumors and characterize tumors that are difficult to classify. Can have prognostic and predictive value.

STAIN	TARGET	TUMORS IDENTIFIED
<b>Chromogranin and synaptophysin</b>	Neuroendocrine cells	Small cell carcinoma of the lung, carcinoid tumor, neuroblastoma
<b>Cytokeratin</b>	Epithelial cells	Epithelial tumors (eg, squamous cell carcinoma)
<b>Desmin</b>	Muscle	Muscle tumors (eg, rhabdomyosarcoma)
<b>GFAP</b>	NeuroGlia (eg, astrocytes, Schwann cells, oligodendrocytes)	Astrocytoma, Glioblastoma
<b>Neurofilament</b>	Neurons	Neuronal tumors (eg, neuroblastoma)
<b>PSA</b>	Prostatic epithelium	Prostate cancer
<b>S-100</b>	Neural crest cells	Melanoma, schwannoma, Langerhans cell histiocytosis
<b>TRAP</b>	Tartrate-resistant acid phosphatase	Hairy cell leukemia
<b>Vimentin</b>	Mesenchymal tissue (eg, fibroblasts, endothelial cells, macrophages)	Mesenchymal tumors (eg, sarcoma), but also many other tumors (eg, endometrial carcinoma, renal cell carcinoma, meningioma)

**P-glycoprotein**

ATP-dependent efflux pump also known as multidrug resistance protein 1 (MDR1). Classically seen in adrenocortical carcinoma but also expressed by other cancer cells (eg, colon, liver). Used to pump out toxins, including chemotherapeutic agents (one mechanism of ↓ responsiveness or resistance to chemotherapy over time).

**Psammoma bodies**

Laminated, concentric spherules with dystrophic calcification **A**, **PSAMMOMAs** bodies are seen in:

- Papillary carcinoma of thyroid
- Somatostatinoma
- Adrenals (calcifying fibrous pseudotumor)
- Meningioma
- Malignant Mesothelioma
- Ovarian serous carcinoma
- Prolactinoma (**Milk**)
- Serous endometrial carcinoma

**Cachexia**

Weight loss, muscle atrophy, and fatigue that occur in chronic disease (eg, cancer, AIDS, heart failure, COPD). Mediated by TNF- $\alpha$ , IFN- $\gamma$ , IL-1, and IL-6.

### Paraneoplastic syndromes

MANIFESTATION	DESCRIPTION/MECHANISM	MOST COMMONLY ASSOCIATED TUMOR(S)
<b>Musculoskeletal and cutaneous</b>		
<b>Dermatomyositis</b>	Progressive proximal muscle weakness, Gottron papules, heliotrope rash	Adenocarcinomas, especially ovarian
<b>Acanthosis nigricans</b>	Hyperpigmented velvety plaques in axilla and neck	Gastric adenocarcinoma and other visceral malignancies
<b>Sign of Leser-Trélat</b>	Sudden onset of multiple seborrheic keratoses	GI adenocarcinomas and other visceral malignancies
<b>Hypertrophic osteoarthropathy</b>	Abnormal proliferation of skin and bone at distal extremities → clubbing, arthralgia, joint effusions, periostosis of tubular bones	Adenocarcinoma of the lung
<b>Endocrine</b>		
<b>Hypercalcemia</b>	PTHrP	SCa <sup>2+</sup> mous cell carcinomas of lung, head, and neck; renal, bladder, breast, and ovarian carcinomas
	↑ 1,25-(OH) <sub>2</sub> vitamin D <sub>3</sub> (calcitriol)	Lymphoma
<b>Cushing syndrome</b>	↑ ACTH	Small cell lung cancer
<b>Hyponatremia (SIADH)</b>	↑ ADH	
<b>Hematologic</b>		
<b>Polycythemia</b>	↑ Erythropoietin Paraneoplastic rise to High hematocrit levels	Pheochromocytoma, renal cell carcinoma, HCC, hemangioblastoma, leiomyoma
<b>Pure red cell aplasia</b>	Anemia with low reticulocytes	
<b>Good syndrome</b>	Hypogammaglobulinemia	Thymoma
<b>Trousseau syndrome</b>	Migratory superficial thrombophlebitis	
<b>Nonbacterial thrombotic (marantic) endocarditis</b>	Deposition of sterile platelet thrombi on heart valves	Adenocarcinomas, especially pancreatic
<b>Neuromuscular</b>		
<b>Anti-NMDA receptor encephalitis</b>	Psychiatric disturbance, memory deficits, seizures, dyskinesias, autonomic instability, language dysfunction	Ovarian teratoma
<b>Opsoclonus-myoclonus ataxia syndrome</b>	“Dancing eyes, dancing feet”	Neuroblastoma (children), small cell lung cancer (adults)
<b>Paraneoplastic cerebellar degeneration</b>	Antibodies against antigens in Purkinje cells	Small cell lung cancer (anti-Hu), gynecologic and breast cancers (anti-Yo), and Hodgkin lymphoma (anti-Tr)
<b>Paraneoplastic encephalomyelitis</b>	Antibodies against Hu antigens in neurons	
<b>Lambert-Eaton myasthenic syndrome</b>	Antibodies against presynaptic (P/Q-type) Ca <sup>2+</sup> channels at NMJ	Small cell lung cancer
<b>Myasthenia gravis</b>	Antibodies against postsynaptic ACh receptors at NMJ	Thymoma

▶ NOTES

# Pharmacology

*“Cure sometimes, treat often, and comfort always.”*

—Hippocrates

*“One pill makes you larger, and one pill makes you small.”*

—Jefferson Airplane, *White Rabbit*

*“For the chemistry that works on one patient may not work for the next, because even medicine has its own conditions.”*

—Suzy Kassem

*“I wondher why ye can always read a doctor’s bill an’ ye niver can read his purscription.”*

—Finley Peter Dunne

*“Love is the drug I’m thinking of.”*

—The Bryan Ferry Orchestra

Preparation for pharmacology questions is not as straightforward as in years past. The big change is that the USMLE Step 1 is moving away from pharmacotherapeutics. That means you will generally not be required to identify medications indicated for a specific condition. You still need to know all the mechanisms and important adverse effects of key drugs and their major variants. Obscure derivatives are low-yield. Learn their classic and distinguishing toxicities as well as major drug-drug interactions.

Reviewing associated biochemistry, physiology, and microbiology concepts can be useful while studying pharmacology. The exam has a strong emphasis on ANS, CNS, antimicrobial, and cardiovascular agents as well as on NSAIDs, which are covered throughout the text. Specific drug dosages or trade names are generally not testable. The exam may use graphs to test various pharmacology content, so make sure you are comfortable interpreting them.

► Pharmacokinetics and Pharmacodynamics 232

► Autonomic Drugs 239

► Toxicities and Side Effects 250

► Miscellaneous 256

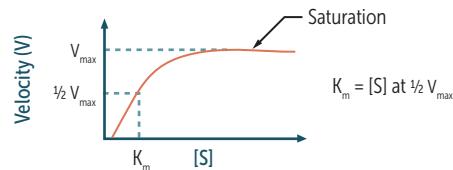
## ► PHARMACOLOGY—PHARMACOKINETICS AND PHARMACODYNAMICS

### Enzyme kinetics

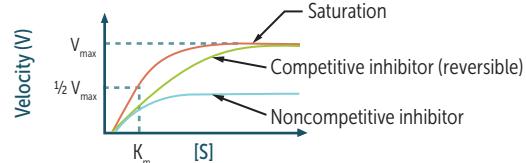
#### Michaelis-Menten kinetics

$K_m$  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.

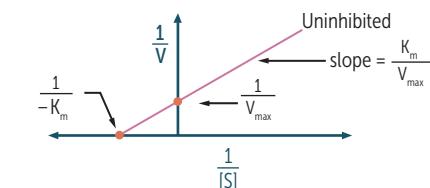


#### Effects of enzyme inhibition

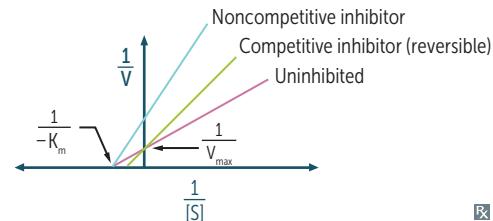


#### Lineweaver-Burk plot

The closer to 0 on the Y-axis, the higher the  $V_{max}$ .  
 The closer to 0 on the X-axis, the higher the  $K_m$ .  
 The higher the  $K_m$ , the lower the affinity.  
**Competitive inhibitors** cross each other, whereas **noncompetitive inhibitors** do **not**.  
**Kompetitive inhibitors increase  $K_m$ .**



#### Effects of enzyme inhibition

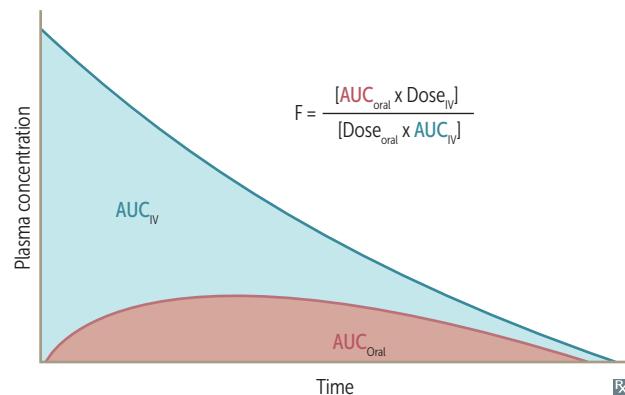


	Competitive inhibitors, reversible	Competitive inhibitors, irreversible	Noncompetitive inhibitors
Resemble substrate	Yes	Yes	No
Overcome by ↑ [S]	Yes	No	No
Bind active site	Yes	Yes	No
Effect on $V_{max}$	Unchanged	↓	↓
Effect on $K_m$	↑	Unchanged	Unchanged
Pharmacodynamics	↓ potency	↓ efficacy	↓ efficacy

## 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. Can be calculated from the area under the curve in a plot of plasma concentration over time.



### 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 ( $\downarrow$  protein binding,  $\uparrow V_d$ ). Drugs may distribute in more than one compartment. Hemodialysis is most effective for drugs with a low  $V_d$ .

$$V_d = \frac{\text{amount of drug in the body}}{\text{plasma drug concentration}}$$

$V_d$	COMPARTMENT	DRUG TYPES
Low	Intravascular	Large/charged molecules; plasma protein bound
Medium	ECF	Small hydrophilic molecules
High	All tissues including fat	Small lipophilic molecules, especially if bound to tissue protein

### Clearance (CL)

The volume of plasma cleared of drug per unit time. Clearance may be impaired with defects in cardiac, hepatic, or renal function.

$$CL = \frac{\text{rate of elimination of drug}}{\text{plasma drug concentration}} = V_d \times K_e \text{ (elimination constant)}$$

### Half-life ( $t_{1/2}$ )

The time required to change the amount of drug in the body by  $\frac{1}{2}$  during elimination. Steady state is a dynamic equilibrium in which drug concentration stays constant (ie, rate of drug elimination = rate of drug ingestion). In first-order kinetics, a drug infused at a constant rate takes 4–5 half-lives to reach steady state. It takes 3.3 half-lives to reach 90% of the steady-state level.

$$t_{1/2} = \frac{0.7 \times V_d}{CL} \text{ in first-order elimination}$$

# of half-lives	1	2	3	4
% remaining	50%	25%	12.5%	6.25%

### Dosage calculations

$$\text{Loading dose} = \frac{C_p \times V_d}{F}$$

$$\text{Maintenance dose} = \frac{C_p \times CL \times \tau}{F}$$

$C_{ss}$  = target plasma concentration at steady state

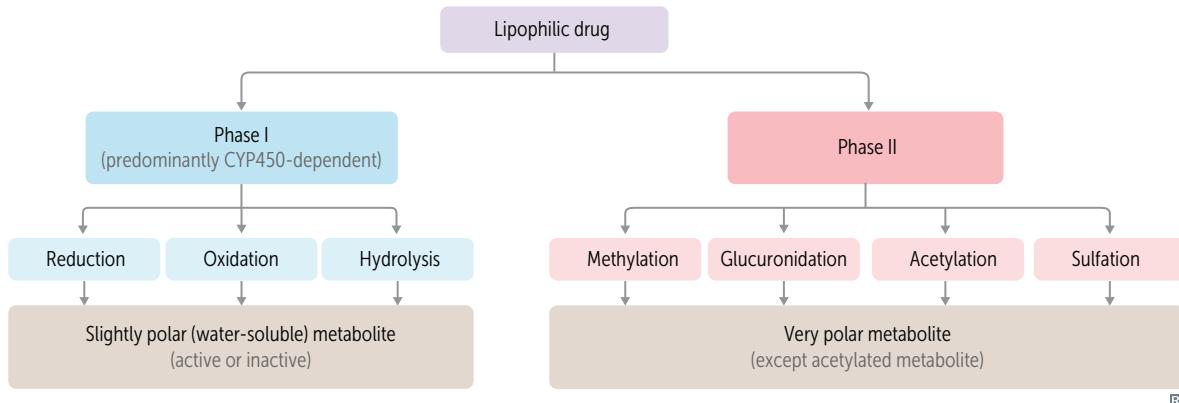
$\tau$  = dosage interval (time between doses), if not administered continuously

In renal or liver disease, maintenance dose  $\downarrow$  and loading dose is usually unchanged.

Time to steady state depends primarily on  $t_{1/2}$  and is independent of dose and dosing frequency.

**Drug metabolism**

Geriatric patients lose phase I first. Patients who are slow acetylators have ↑ side effects from certain drugs because of ↓ rate of metabolism (eg, isoniazid).

**Elimination of drugs****Zero-order elimination**

Rate of elimination is constant regardless of  $C_p$  (ie, constant amount of drug eliminated per unit time).  $C_p \downarrow$  linearly with time. Examples of drugs—**P**henytoin, **E**thanol, and **A**spirin (at high or toxic concentrations).

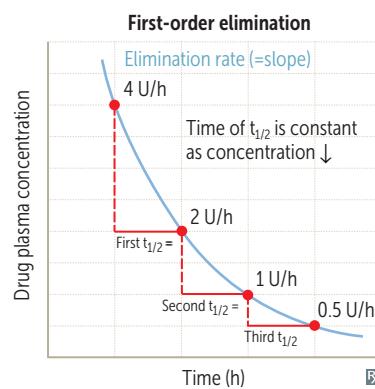
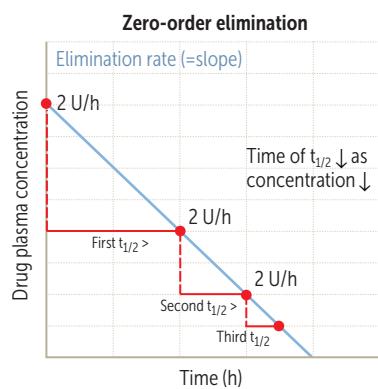
Capacity-limited elimination.

**PEA** (a pea is round, shaped like the “0” in zero-order).

**First-order elimination**

Rate of first-order elimination is directly proportional to the drug concentration (ie, constant fraction of drug eliminated per unit time).  $C_p \downarrow$  exponentially with time. Applies to most drugs.

Flow-dependent elimination.

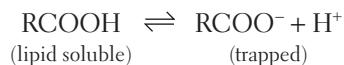


## Urine pH and drug elimination

Ionized species are trapped in urine and cleared quickly. Neutral forms can be reabsorbed.

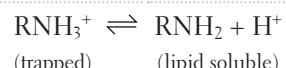
## Weak acids

Examples: phenobarbital, methotrexate, aspirin (salicylates). Trapped in basic environments. Treat overdose with sodium bicarbonate to alkalinize urine.



## Weak bases

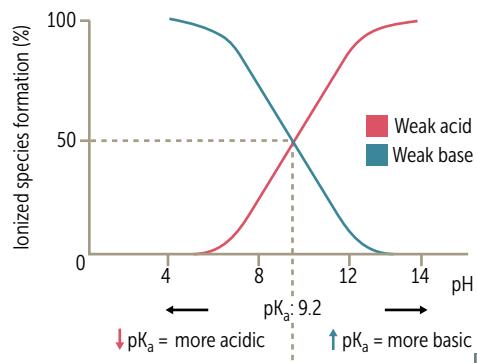
Examples: TCAs, amphetamines. Trapped in acidic environments. Treat overdose with ammonium chloride to acidify urine.



TCA toxicity is generally treated with sodium bicarbonate to overcome the sodium channel-blocking activity of TCAs, but not for accelerating drug elimination.

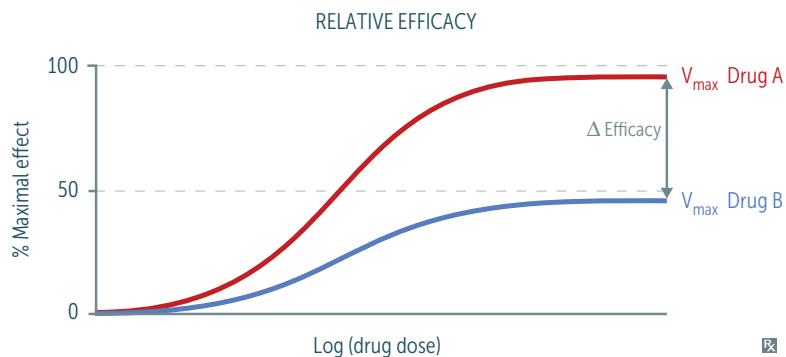
pKa

pH at which drugs (weak acid or base) are 50% ionized and 50% nonionized. The pKa represents the strength of the weak acid or base.

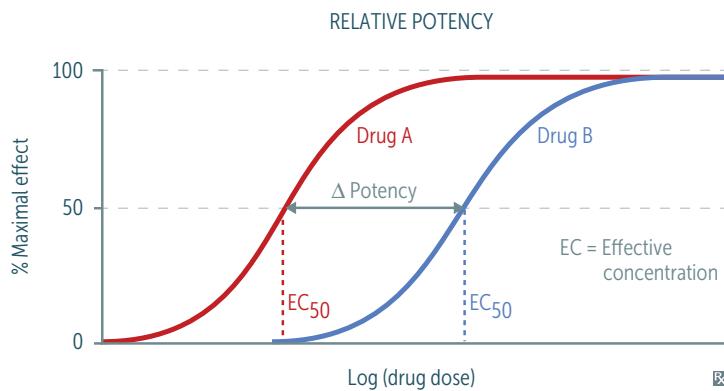


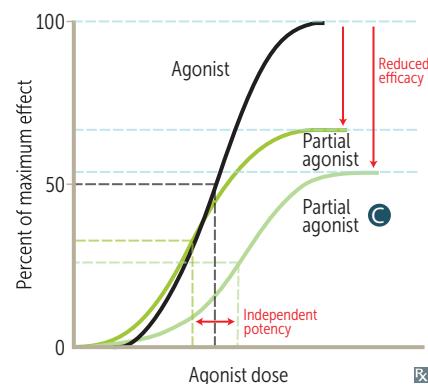
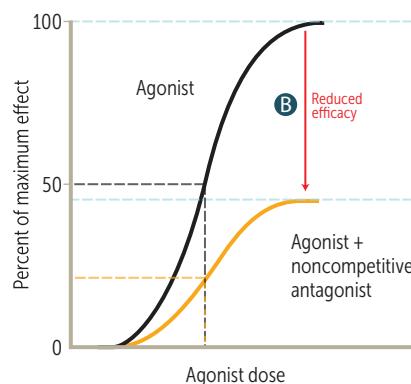
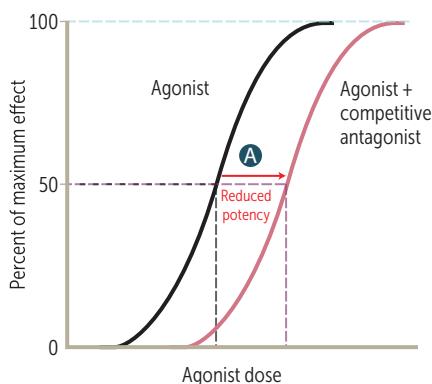
**Efficacy vs potency****Efficacy**

Maximal effect a drug can produce. Represented by the y-value ( $V_{max}$ ). ↑ y-value = ↑  $V_{max}$  = ↑ efficacy. Unrelated to potency (ie, efficacious drugs can have high or low potency). Partial agonists have less efficacy than full agonists.

**Potency**

Amount of drug needed for a given effect. Represented by the x-value ( $EC_{50}$ ). Left shifting = ↓  $EC_{50}$  = ↑ potency = ↓ drug needed. Unrelated to efficacy (ie, potent drugs can have high or low efficacy).



**Receptor binding**

AGONIST WITH	POTENCY	EFFICACY	REMARKS	EXAMPLE
<b>A Competitive antagonist</b>	↓	No change	Can be overcome by ↑ agonist concentration	Diazepam (agonist) + flumazenil (competitive antagonist) on GABA <sub>A</sub> receptor.
<b>B Noncompetitive antagonist</b>	No change	↓	Cannot be overcome by ↑ agonist concentration	Norepinephrine (agonist) + phenoxybenzamine (noncompetitive antagonist) on α-receptors.
<b>C Partial agonist (alone)</b>	Independent	↓	Acts at same site as full agonist	Morphine (full agonist) vs buprenorphine (partial agonist) at opioid μ-receptors.

**Therapeutic index**

Measurement of drug safety.

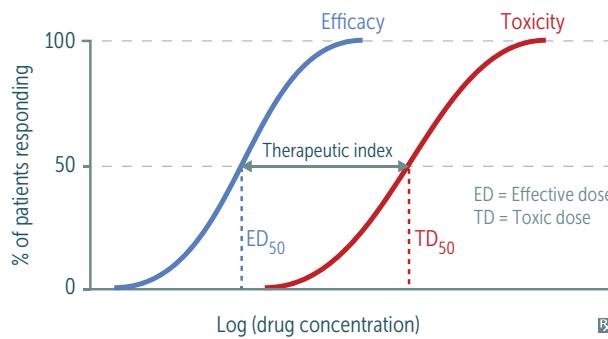
$$\text{TD}_{50} = \frac{\text{median toxic dose}}{\text{ED}_{50} \text{ median effective dose}}$$

Therapeutic window—range of drug concentrations that can safely and effectively treat disease.

**TITE:** Therapeutic Index =  $\text{TD}_{50} / \text{ED}_{50}$ .

Safer drugs have higher TI values. Drugs with lower TI values frequently require monitoring (eg, warfarin, theophylline, digoxin, antiepileptic drugs, lithium; **Warning!** These drugs are lethal!).

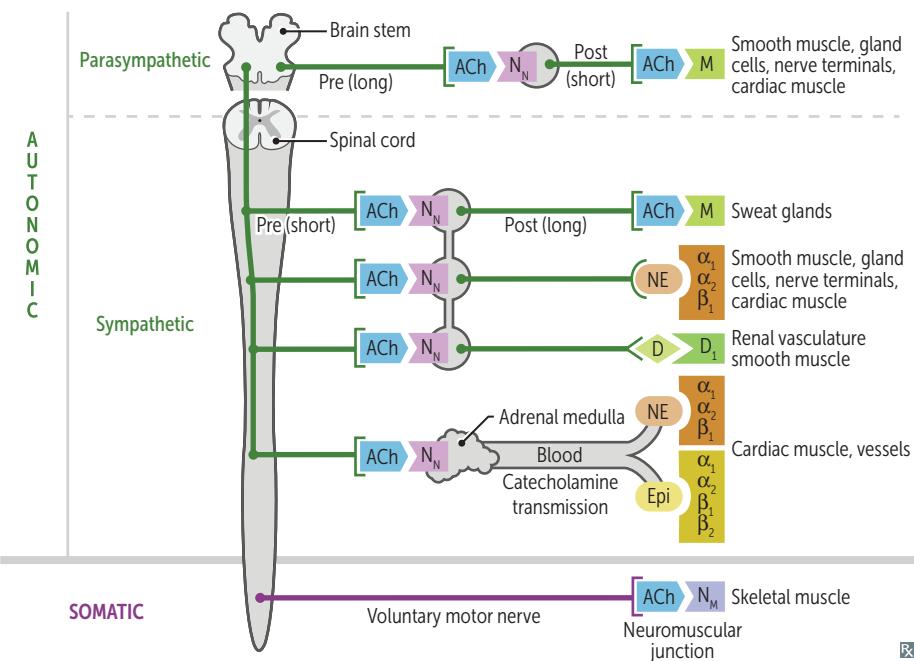
$\text{LD}_{50}$  (lethal median dose) often replaces  $\text{TD}_{50}$  in animal studies.



**Drug effect modifications**

TERM	DEFINITION	EXAMPLE
<b>Additive</b>	Effect of substances A and B together is equal to the sum of their individual effects	Aspirin and acetaminophen “2 + 2 = 4”
<b>Permissive</b>	Presence of substance A is required for the full effects of substance B	Cortisol on catecholamine responsiveness
<b>Synergistic</b>	Effect of substances A and B together is greater than the sum of their individual effects	Clopidogrel with aspirin “2 + 2 > 4”
<b>Potentiation</b>	Similar to synergism, but drug B with no therapeutic action enhances the therapeutic action of drug A	Carbidopa only blocks enzyme to prevent peripheral conversion of levodopa “2 + 0 > 2”
<b>Antagonistic</b>	Effect of substances A and B together is less than the sum of their individual effects	Ethanol antidote for methanol toxicity “2 + 2 < 4”
<b>Tachyphylactic</b>	Acute decrease in response to a drug after initial/repeated administration	Hydralazine, nitrates, niacin, phenylephrine, LSD, MDMA

## ► PHARMACOLOGY—AUTONOMIC DRUGS

**Autonomic receptors**

Pelvic splanchnic nerves and CNs III, VII, IX and X are part of the parasympathetic nervous system.  
Adrenal medulla is directly innervated by preganglionic sympathetic fibers.

**Sweat** glands are part of the **sympathetic** pathway but are innervated by **cholinergic** fibers  
(**sympathetic** nervous system results in a “**hold**” sweat).

**Acetylcholine receptors**

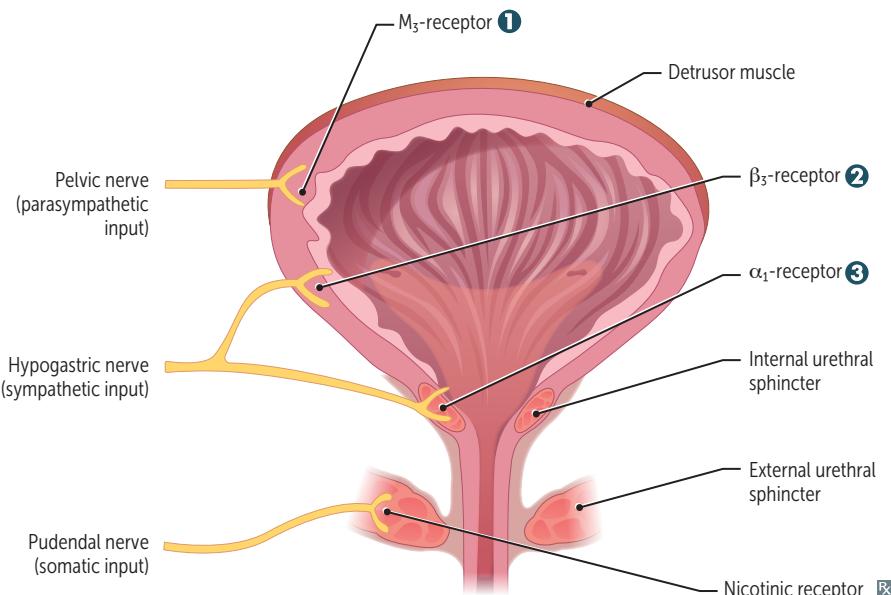
Nicotinic ACh receptors are ligand-gated channels allowing efflux of K<sup>+</sup> and influx of Na<sup>+</sup> and in some cases Ca<sup>2+</sup>. Two subtypes: N<sub>N</sub> (found in autonomic ganglia, adrenal medulla) and N<sub>M</sub> (found in neuromuscular junction of skeletal muscle).

Muscarinic ACh receptors are G-protein-coupled receptors that usually act through 2nd messengers. 5 subtypes: M<sub>1-5</sub> found in heart, smooth muscle, brain, exocrine glands, and on sweat glands (cholinergic sympathetic).

**Micturition control**

Micturition center in pons regulates involuntary bladder function via coordination of sympathetic and parasympathetic nervous systems.

- ⊕ sympathetic → ↑ urinary retention.
- ⊕ parasympathetic → ↑ urine voiding. Some autonomic drugs act on smooth muscle receptors to treat bladder dysfunction.



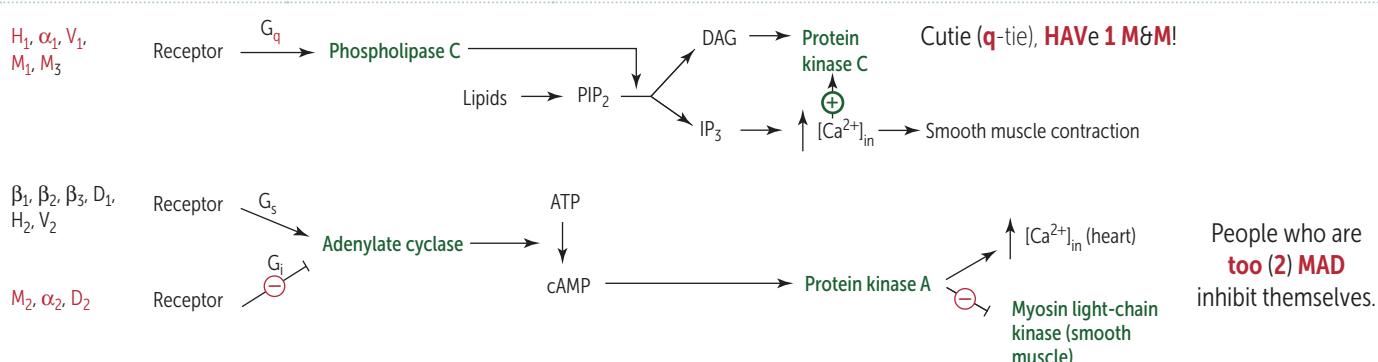
DRUGS	MECHANISM	APPLICATIONS
<b>① Muscarinic antagonists</b> (eg, oxybutynin)	⊖ M <sub>3</sub> receptor → relaxation of detrusor smooth muscle → ↓ detrusor overactivity	Urgency incontinence
<b>① Muscarinic agonists</b> (eg, bethanechol)	⊕ M <sub>3</sub> receptor → contraction of detrusor smooth muscle → ↑ bladder emptying	Urinary retention
<b>② Sympathomimetics</b> (eg, mirabegron)	⊕ β <sub>3</sub> receptor → relaxation of detrusor smooth muscle → ↑ bladder capacity	Urgency incontinence
<b>③ α<sub>1</sub>-blockers</b> (eg, tamsulosin)	⊖ α <sub>1</sub> -receptor → relaxation of smooth muscle (bladder neck, prostate) → ↓ urinary obstruction	BPH

**Tissue distribution of adrenergic receptors**

	α <sub>1</sub> receptors	α <sub>2</sub> receptors	β <sub>1</sub> receptors	β <sub>2</sub> receptors	β <sub>3</sub> receptors
Cardiac muscle	–	–	+++	+	+
Skeletal muscle	–	–	–	++	–
Vascular smooth muscle	+++	+	–	++	+
Bronchial smooth muscle	–	–	–	++	–
Liver	+	–	–	+++	–
Adipose tissue	+	+	+	–	++
CNS	++	++	++	++	–
Bladder neck/prostate	+++	+	–	–	+++

**G-protein-linked second messengers**

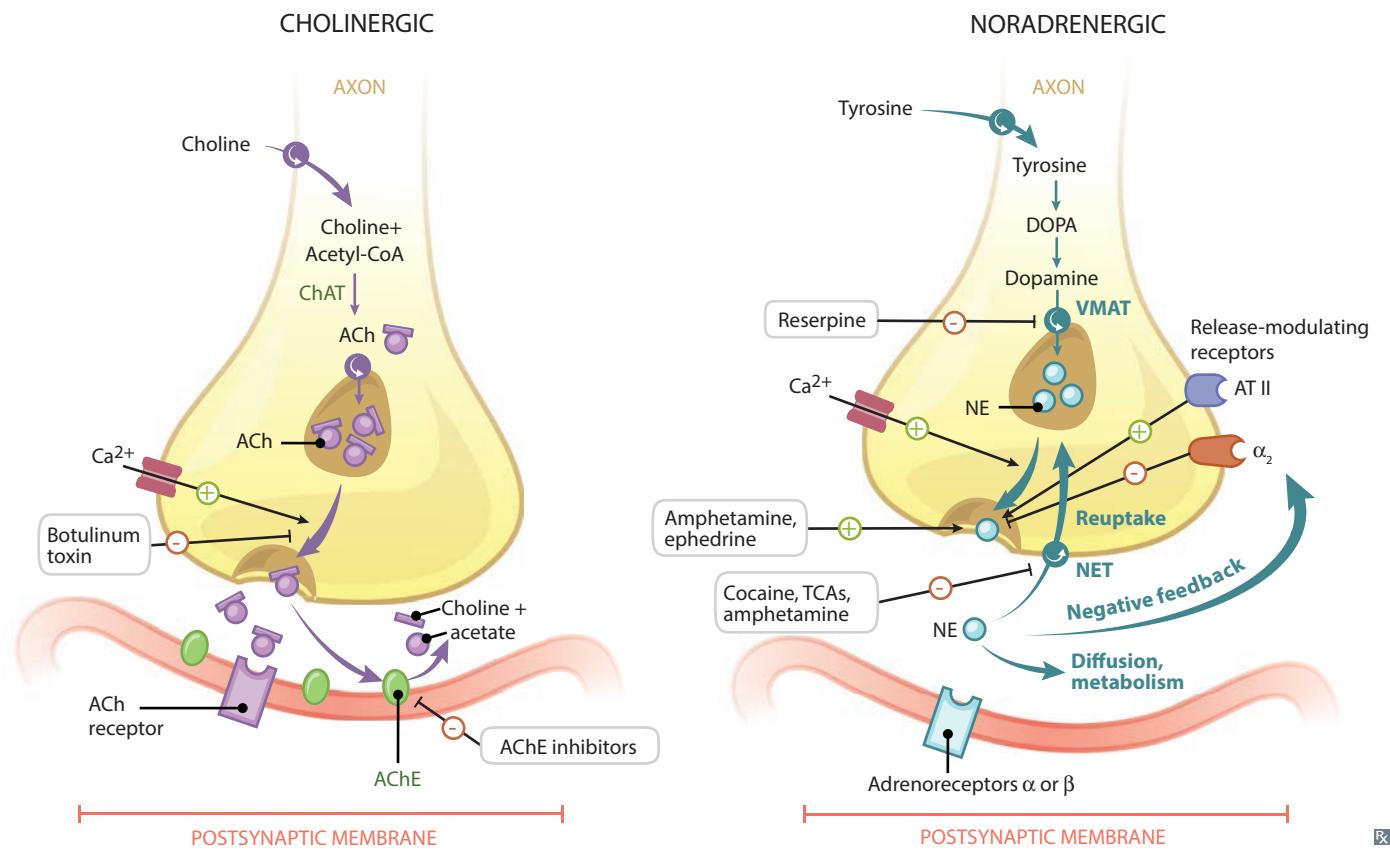
RECEPTOR	G-PROTEIN CLASS	MAJOR FUNCTIONS
<b>Adrenergic</b>		
$\alpha_1$	q	↑ vascular smooth muscle contraction, ↑ pupillary dilator muscle contraction (mydriasis), ↑ intestinal and bladder sphincter muscle contraction
$\alpha_2$	i	↓ sympathetic (adrenergic) outflow, ↓ insulin release, ↓ lipolysis, ↑ platelet aggregation, ↓ aqueous humor production
$\beta_1$	s	↑ heart rate, ↑ contractility (one heart), ↑ renin release, ↑ lipolysis
$\beta_2$	s	Vasodilation, bronchodilation (two lungs), ↑ lipolysis, ↑ insulin release, ↑ glycogenolysis, ↓ uterine tone (tocolysis), ↑ aqueous humor production, ↑ cellular K <sup>+</sup> uptake
$\beta_3$	s	↑ lipolysis, ↑ thermogenesis in skeletal muscle, ↑ bladder relaxation
<b>Cholinergic</b>		
$M_1$	q	Mediates higher cognitive functions, stimulates 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), ↑ insulin release, endothelium-mediated vasodilation
<b>Dopamine</b>		
$D_1$	s	Relaxes renal vascular smooth muscle, activates direct pathway of striatum
$D_2$	i	Modulates transmitter release, especially in brain, inhibits indirect pathway of striatum
<b>Histamine</b>		
$H_1$	q	↑ nasal and bronchial mucus production, ↑ vascular permeability, bronchoconstriction, pruritus, pain
$H_2$	s	↑ gastric acid secretion
<b>Vasopressin</b>		
$V_1$	q	↑ vascular smooth muscle contraction
$V_2$	s	↑ H <sub>2</sub> O permeability and reabsorption via upregulating aquaporin-2 in collecting tubules (tubules) of kidney, ↑ release of vWF



**Autonomic drugs**

Release of norepinephrine from a sympathetic nerve ending is modulated by NE itself, acting on presynaptic  $\alpha_2$ -autoreceptors  $\rightarrow$  negative feedback.

Amphetamines use the NE transporter (NET) to enter the presynaptic terminal, where they utilize the vesicular monoamine transporter (VMAT) to enter neurosecretory vesicles. This displaces NE from the vesicles. Once NE reaches a concentration threshold within the presynaptic terminal, the action of NET is reversed, and NE is expelled into the synaptic cleft, contributing to the characteristics and effects of  $\uparrow$  NE observed in patients taking amphetamines.



🕒 🚪 represents transporters.

### Cholinomimetic agents

Watch for exacerbation of COPD, asthma, and peptic ulcers in susceptible patients.

DRUG	ACTION	APPLICATIONS
<b>Direct agonists</b>		
<b>Bethanechol</b>	Activates <b>bladder smooth muscle</b> ; resistant to AChE. No nicotinic activity. “ <b>Bethany, call me to activate your bladder.</b> ”	Urinary retention.
<b>Carbachol</b>	<b>Carbon copy of acetylcholine</b> (but resistant to AChE).	Constricts pupil and relieves intraocular pressure in open-angle glaucoma.
<b>Methacholine</b>	Stimulates <b>muscarinic receptors</b> in airway when inhaled.	Challenge test for diagnosis of asthma.
<b>Pilocarpine</b>	Contracts ciliary muscle of eye (open-angle glaucoma), pupillary sphincter (closed-angle glaucoma); resistant to AChE, can cross blood-brain barrier (tertiary amine). “ <b>You cry, drool, and sweat on your ‘pillow.’</b> ”	Potent stimulator of sweat, tears, and saliva Open-angle and closed-angle glaucoma, xerostomia (Sjögren syndrome).
<b>Indirect agonists (anticholinesterases)</b>		
<b>Donepezil, rivastigmine, galantamine</b>	↑ ACh.	1st line for Alzheimer disease ( <b>Dona Riva</b> forgot to dance at the <b>gala</b> ).
<b>Edrophonium</b>	↑ ACh.	Historically used to diagnose myasthenia gravis; replaced by anti-AChR Ab (anti-acetylcholine receptor antibody) test.
<b>Neostigmine</b>	↑ ACh. <b>Neo CNS = no</b> CNS penetration due to positive charge (quaternary amine).	Postoperative and neurogenic ileus and urinary retention, myasthenia gravis, reversal of neuromuscular junction blockade (postoperative).
<b>Pyridostigmine</b>	↑ ACh; ↑ muscle strength. Used with glycopyrrolate, hyoscyamine, or propantheline to control pyridostigmine side effects. <b>Pyridostigmine gets rid of myasthenia gravis.</b>	Myasthenia gravis (long acting); does not penetrate CNS (quaternary amine).
<b>Physostigmine</b>	↑ ACh. <b>Phreely</b> (freely) crosses blood-brain barrier as not charged → CNS (tertiary amine).	Antidote for anticholinergic toxicity; <b>physostigmine “phyxes”</b> atropine overdose.
<b>Anticholinesterase poisoning</b>		
<b>Muscarinic effects</b>	Often due to organophosphates (eg, parathion) that irreversibly inhibit AChE. Organophosphates commonly used as insecticides; poisoning usually seen in farmers.	<b>DUMBBELSS.</b> Reversed by atropine, a competitive inhibitor. Atropine can cross BBB to relieve CNS symptoms.
<b>Nicotinic effects</b>	Neuromuscular blockade (mechanism similar to succinylcholine).	Reversed by pralidoxime, regenerates AChE via dephosphorylation if given early. Pralidoxime (quaternary amine) does not readily cross BBB.
<b>CNS effects</b>	Respiratory depression, lethargy, seizures, coma.	

**Muscarinic antagonists**

DRUGS	ORGAN SYSTEMS	APPLICATIONS
<b>Atropine, homatropine, tropicamide</b>	Eye	Produce mydriasis and cycloplegia
<b>Benztropine, trihexyphenidyl</b>	CNS	Parkinson disease (“park my Benz”) Acute dystonia
<b>Glycopyrrrolate</b>	GI, respiratory	Parenteral: preoperative use to reduce airway secretions Oral: reduces drooling, peptic ulcer Antispasmodics for irritable bowel syndrome
<b>Hyoscyamine, dicyclomine</b>	GI	
<b>Ipratropium, tiotropium</b>	Respiratory	COPD, asthma Duration: tiotropium > ipratropium
<b>Solifenacina, Oxybutynin, Flavoxate, Tolterodine</b>	Genitourinary	Reduce bladder spasms and urge urinary incontinence (overactive bladder) Make bladder SOFT
<b>Scopolamine</b>	CNS	Motion sickness

**Atropine**

Muscarinic antagonist. Used to treat bradycardia and for ophthalmic applications.

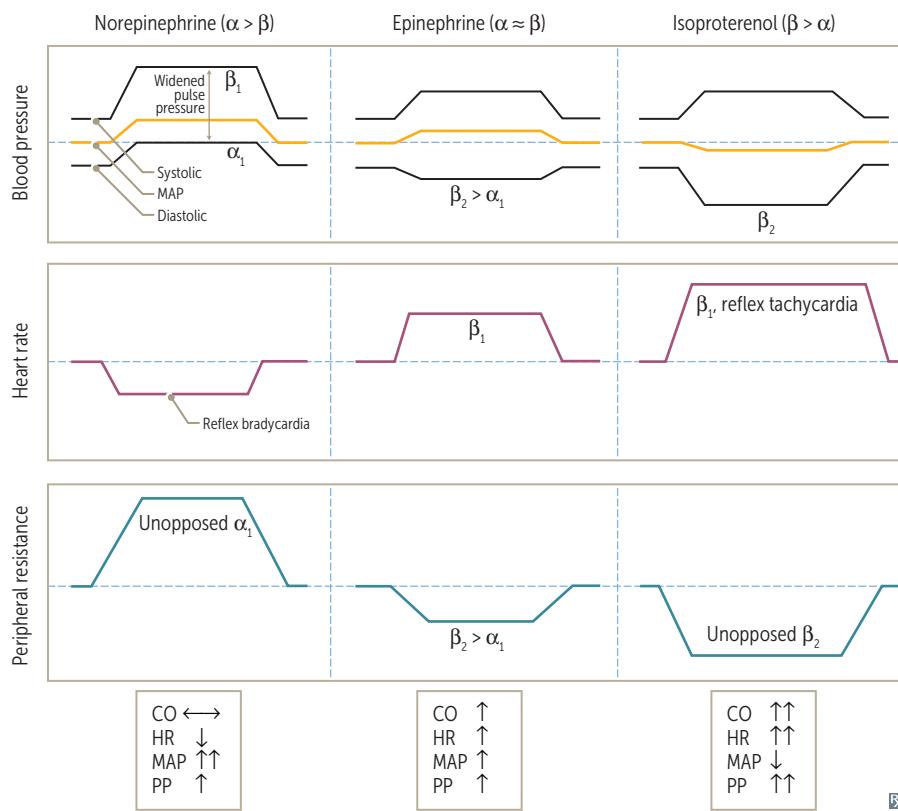
ORGAN SYSTEM	ACTION	NOTES
Eye	↑ pupil dilation, cycloplegia	Blocks muscarinic effects ( <b>DUMBELLS</b> ) of anticholinesterases, but not the nicotinic effects
Airway	Bronchodilation, ↓ secretions	
Stomach	↓ acid secretion	
Gut	↓ motility	
Bladder	↓ urgency in cystitis	
ADVERSE EFFECTS	<p>↑ body <b>temperature</b> (due to ↓ sweating); ↑ <b>HR</b>; dry mouth; <b>dry, flushed skin</b>; <b>cycloplegia</b>; constipation; <b>disorientation</b></p> <p>Can cause acute angle-closure glaucoma in elderly (due to mydriasis), <b>urinary retention</b> in men with prostatic hyperplasia, and hyperthermia in infants</p>	<p>Side effects:  <b>Hot</b> as a hare  <b>Fast</b> as a fiddle  <b>Dry</b> as a bone  <b>Red</b> as a beet  <b>Blind</b> as a bat  <b>Mad</b> as a hatter  <b>Full</b> as a flask</p> <p>Jimson weed (<i>Datura</i>) → gardener’s pupil (mydriasis due to plant alkaloids)</p>

**Sympathomimetics**

DRUG	ACTION	HEMODYNAMIC CHANGES	APPLICATIONS
<b>Direct sympathomimetics</b>			
<b>Albuterol, salmeterol, terbutaline</b>	$\beta_2 > \beta_1$	↑ HR (little effect)	Albuterol for acute asthma/COPD. Salmeterol for serial (long-term) asthma/COPD. Terbutaline for acute bronchospasm in asthma and tocolysis.
<b>Dobutamine</b>	$\beta_1 > \beta_2, \alpha$	—/↓ BP, ↑ HR, ↑ CO	Cardiac stress testing, acute decompensated heart failure (HF) with cardiogenic shock (inotrope)
<b>Dopamine</b>	$D_1 = D_2 > \beta > \alpha$	↑ BP (high dose), ↑ HR, ↑ CO	Unstable bradycardia, shock; inotropic and chronotropic effects at lower doses via $\beta$ effects; vasoconstriction at high doses via $\alpha$ effects.
<b>Epinephrine</b>	$\beta > \alpha$	↑ BP (high dose), ↑ HR, ↑ CO	Anaphylaxis, asthma, shock, open-angle glaucoma; $\alpha$ effects predominate at high doses. Stronger effect at $\beta_2$ -receptor than norepinephrine.
<b>Fenoldopam</b>	$D_1$	↓ BP (vasodilation), ↑ HR, ↑ CO	Postoperative hypertension, hypertensive crisis. Vasodilator (coronary, peripheral, renal, and splanchnic). Promotes natriuresis. Can cause hypotension, tachycardia, flushing, headache.
<b>Isoproterenol</b>	$\beta_1 = \beta_2$	↓ BP (vasodilation), ↑ HR, ↑ CO	Electrophysiologic evaluation of tachyarrhythmias. Can worsen ischemia. Has negligible $\alpha$ effect.
<b>Midodrine</b>	$\alpha_1$	↑ BP (vasoconstriction), ↓ HR, ↘/↓ CO	Autonomic insufficiency and postural hypotension. May exacerbate supine hypertension.
<b>Mirabegron</b>	$\beta_3$		Urinary urgency or incontinence or overactive bladder. Think “mirab3gron.”
<b>Norepinephrine</b>	$\alpha_1 > \alpha_2 > \beta_1$	↑ BP, ↓ HR (reflex bradycardia from ↑ BP due to $\alpha_1$ agonism outweighs direct $\beta_1$ chronotropic effect), —/↑ CO	Hypotension, septic shock.
<b>Phenylephrine</b>	$\alpha_1 > \alpha_2$	↑ BP (vasoconstriction), ↓ HR, —/↓ CO	Hypotension (vasoconstrictor), ocular procedures (mydriatic), rhinitis (decongestant), ischemic priapism.
<b>Indirect sympathomimetics</b>			
<b>Amphetamine</b>	Indirect general agonist, reuptake inhibitor, also releases stored catecholamines.		Narcolepsy, obesity, ADHD.
<b>Cocaine</b>	Indirect general agonist, reuptake inhibitor. Causes vasoconstriction and local anesthesia. Caution when giving $\beta$ -blockers if cocaine intoxication is suspected (unopposed $\alpha_1$ activation → ↑↑↑ BP, coronary vasospasm).		Causes mydriasis in eyes with intact sympathetic innervation → used to confirm Horner syndrome.
<b>Ephedrine</b>	Indirect general agonist, releases stored catecholamines.		Nasal decongestion (pseudoephedrine), urinary incontinence, hypotension.

### Physiologic effects of sympathomimetics

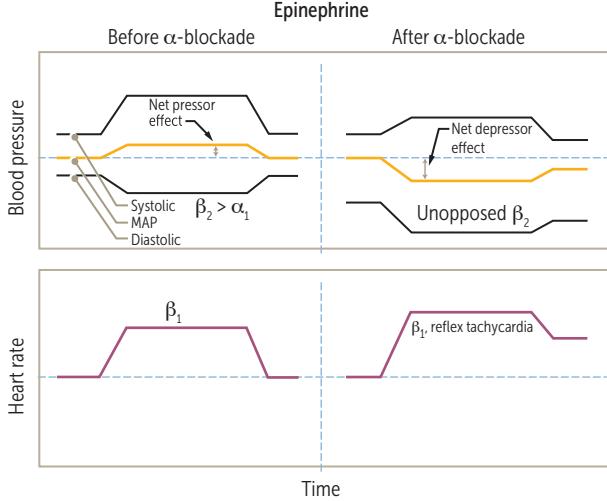
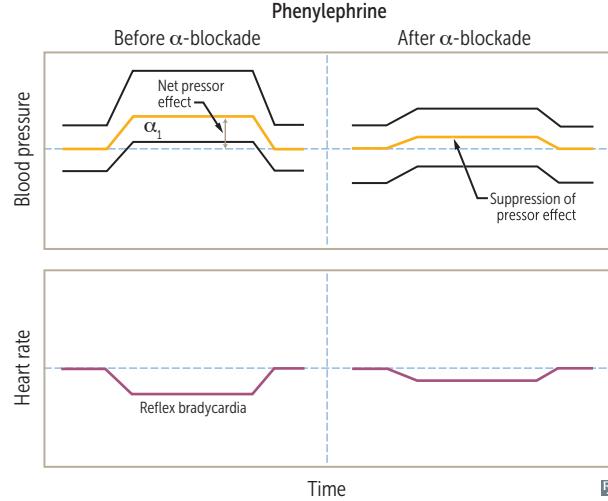
NE ↑ systolic and diastolic pressures as a result of  $\alpha_1$ -mediated vasoconstriction → ↑ mean arterial pressure → reflex bradycardia. However, isoproterenol (rarely used) has little  $\alpha$  effect but causes  $\beta_2$ -mediated vasodilation, resulting in ↓ mean arterial pressure and ↑ heart rate through  $\beta_1$  and reflex activity.



### Sympatholytics ( $\alpha_2$ -agonists)

DRUG	APPLICATIONS	ADVERSE EFFECTS
<b>Clonidine, guanfacine</b>	Hypertensive urgency (limited situations), ADHD, Tourette syndrome, symptom control in opioid withdrawal	CNS depression, bradycardia, hypotension, respiratory depression, miosis, rebound hypertension with abrupt cessation
<b><math>\alpha</math>-methyldopa</b>	Hypertension in pregnancy	Direct Coombs + hemolysis, drug-induced lupus, hyperprolactinemia
<b>Tizanidine</b>	Relief of spasticity	Hypotension, weakness, xerostomia

**$\alpha$ -blockers**

DRUG	APPLICATIONS	ADVERSE EFFECTS
<b>Nonselective</b>		
<b>Phenoxybenzamine</b>	Irreversible. Pheochromocytoma (used preoperatively) to prevent catecholamine (hypertensive) crisis.	
<b>Phentolamine</b>	Reversible. Given to patients on MAO inhibitors who eat tyramine-containing foods and for severe cocaine-induced hypertension (2nd line). Also used to treat norepinephrine extravasation.	Orthostatic hypotension, reflex tachycardia.
<b><math>\alpha_1</math> selective (-osin ending)</b>		
<b>Prazosin, terazosin, doxazosin, tamsulosin</b>	Urinary symptoms of BPH; PTSD (prazosin); hypertension (except tamsulosin).	1st-dose orthostatic hypotension, dizziness, headache.
<b><math>\alpha_2</math> selective</b>		
<b>Mirtazapine</b>	Depression.	Sedation, $\uparrow$ serum cholesterol, $\uparrow$ appetite.
 <p>The graph illustrates the cardiovascular effects of epinephrine. It shows two panels: 'Before <math>\alpha</math>-blockade' and 'After <math>\alpha</math>-blockade'. In the 'Before' panel, epinephrine causes a 'Net pressor effect' (increased blood pressure) due to <math>\alpha_1</math> receptor stimulation. This effect is partially offset by <math>\beta_2</math> receptor stimulation, resulting in a net increase above baseline. In the 'After' panel, the <math>\alpha_1</math> receptors are blocked, so the net effect is primarily the unopposed <math>\beta_2</math> response, which causes a decrease in blood pressure. Below the blood pressure graphs, heart rate is shown. Before blockade, epinephrine's <math>\beta_1</math> effect leads to tachycardia. After blockade, the lack of <math>\alpha_1</math> inhibition allows for a reflex bradycardia (indicated by a downward arrow) as the body attempts to restore blood pressure.</p>		
 <p>The graph illustrates the cardiovascular effects of phenylephrine. It shows two panels: 'Before <math>\alpha</math>-blockade' and 'After <math>\alpha</math>-blockade'. In the 'Before' panel, phenylephrine acts as a pure <math>\alpha_1</math> agonist, causing a strong net pressor effect (increased blood pressure). In the 'After' panel, the <math>\alpha_1</math> receptors are blocked, so the drug's effect is suppressed. The blood pressure remains relatively stable, although there is a slight decrease. Below the blood pressure graphs, heart rate is shown. The 'Reflex bradycardia' label points to a period where heart rate drops below baseline, likely due to the lack of <math>\alpha_1</math> stimulation and subsequent baroreceptor feedback.</p>		

Epinephrine response exhibits reversal of mean arterial pressure from a net increase (the  $\alpha$  response) to a net decrease (the  $\beta_2$  response).

Phenylephrine response is suppressed but not reversed because it is a “pure”  $\alpha$ -agonist (lacks  $\beta$ -agonist properties).

**β-blockers**

Acebutolol, atenolol, betaxolol, bisoprolol, carvedilol, esmolol, labetalol, metoprolol, nadolol, nebivolol, pindolol, propranolol, timolol.

APPLICATION	ACTIONS	NOTES/EXAMPLES
Angina pectoris	↓ heart rate and contractility → ↓ O <sub>2</sub> consumption	
Glaucoma	↓ production of aqueous humor	Timolol
Heart failure	Blockade of neurohormonal stress → prevention of deleterious cardiac remodeling → ↓ mortality	Bisoprolol, carvedilol, metoprolol (β-blockers curb mortality)
Hypertension	↓ cardiac output, ↓ renin secretion (due to β <sub>1</sub> -receptor blockade on JG cells)	
Hyperthyroidism/ thyroid storm	Symptom control (↓ heart rate, ↓ tremor)	Propranolol
Hypertrophic cardiomyopathy	↓ heart rate → ↑ filling time, relieving obstruction	
Myocardial infarction	↓ O <sub>2</sub> demand (short-term), ↓ mortality (long-term)	
Supraventricular tachycardia	↓ AV conduction velocity (class II antiarrhythmic)	Metoprolol, esmolol
Variceal bleeding	↓ hepatic venous pressure gradient and portal hypertension (prophylactic use)	Nadolol, propranolol, carvedilol
ADVERSE EFFECTS	Erectile dysfunction, cardiovascular (bradycardia, AV block, HF), CNS (seizures, sleep alterations), dyslipidemia (metoprolol), masked hypoglycemia, asthma/COPD exacerbations	Use of β-blockers for acute cocaine-associated chest pain remains controversial due to unsubstantiated concern for unopposed α-adrenergic stimulation
SELECTIVITY	<p>β<sub>1</sub>-selective antagonists (β<sub>1</sub> &gt; β<sub>2</sub>)—acebutolol (partial agonist), atenolol, betaxolol, bisoprolol, esmolol, metoprolol</p> <p>Nonselective antagonists (β<sub>1</sub> = β<sub>2</sub>)—nadolol, pindolol (partial agonist), propranolol, timolol</p> <p>Nonselective α- and β-antagonists—carvedilol, labetalol</p> <p>Nebivolol combines cardiac-selective β<sub>1</sub>-adrenergic blockade with stimulation of β<sub>3</sub>-receptors (activate NO synthase in the vasculature and ↓ SVR)</p>	<p>Selective antagonists mostly go from A to M (β<sub>1</sub> with 1st half of alphabet)</p> <p>NonZelective antagonists mostly go from N to Z (β<sub>2</sub> with 2nd half of alphabet)</p> <p>Nonselective α- and β-antagonists have modified suffixes (instead of “-olol”)</p> <p>NebivOlol increases NO</p>

### Phosphodiesterase inhibitors

Phosphodiesterase (PDE) inhibitors inhibit PDE, which catalyzes the hydrolysis of cAMP and/or cGMP, and thereby increase cAMP and/or cGMP. These inhibitors have varying specificity for PDE isoforms and thus have different clinical uses.

TYPE OF INHIBITOR	MECHANISM OF ACTION	CLINICAL USES	ADVERSE EFFECTS
<b>Nonspecific PDE inhibitor</b> Theophylline	↓ cAMP hydrolysis → ↑ cAMP → bronchial smooth muscle relaxation → bronchodilation	COPD/asthma (rarely used)	Cardiotoxicity (eg, tachycardia, arrhythmia), neurotoxicity (eg, seizures, headache), abdominal pain
<b>PDE-5 inhibitors</b> Sildenafil, vardenafil, tadalafil, avanafil	↓ hydrolysis of cGMP → ↑ cGMP → ↑ smooth muscle relaxation by enhancing NO activity → pulmonary vasodilation and ↑ blood flow in corpus cavernosum <b>fills</b> the penis	Erectile dysfunction Pulmonary hypertension Benign prostatic hyperplasia (tadalafil only)	Facial flushing, headache, dyspepsia, hypotension in patients taking nitrates; “hot and sweaty,” then headache, heartburn, hypotension <b>Sildenafil</b> only: cyanopia (blue-tinted vision) via inhibition of PDE-6 ( <b>six</b> ) in retina
<b>PDE-4 inhibitor</b> Roflumilast	↑ cAMP in neutrophils, granulocytes, and bronchial epithelium	Severe COPD	Abdominal pain, weight loss, depression, anxiety, insomnia
<b>PDE-3 inhibitor</b> Milrinone	In cardiomyocytes: ↑ cAMP → ↑ Ca <sup>2+</sup> influx → ↑ ionotropy and chronotropy In vascular smooth muscle: ↑ cAMP → MLCK inhibition → vasodilation → ↓ preload and afterload	Acute decompensated HF with cardiogenic shock (inotrope)	Tachycardia, ventricular arrhythmias, hypotension
<b>“Platelet inhibitors”</b> Cilostazol <sup>a</sup> Dipyridamole <sup>b</sup>	In platelets: ↑ cAMP → inhibition of platelet aggregation	Intermittent claudication Stroke or TIA prevention (with aspirin) Cardiac stress testing (dipyridamole only, due to coronary vasodilation) Prevention of coronary stent restenosis	Nausea, headache, facial flushing, hypotension, abdominal pain

<sup>a</sup>Cilostazol is a PDE-3 inhibitor, but due to its indications is categorized as a platelet inhibitor together with dipyridamole.

<sup>b</sup>Dipyridamole is a nonspecific PDE inhibitor, leading to inhibition of platelet aggregation. It also prevents adenosine reuptake by platelets → ↑ extracellular adenosine → ↑ vasodilation.

## ► PHARMACOLOGY—TOXICITIES AND SIDE EFFECTS

**Ingested seafood toxins** Toxin actions include histamine release, total block of  $\text{Na}^+$  channels, or opening of  $\text{Na}^+$  channels to cause depolarization.

TOXIN	SOURCE	ACTION	SYMPTOMS	TREATMENT
<b>Histamine (scombroid poisoning)</b>	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: oral burning sensation, facial flushing, erythema, urticaria, itching; may progress to bronchospasm, angioedema, hypotension	Antihistamines Albuterol +/- epinephrine
<b>Tetrodotoxin</b>	Pufferfish	Binds fast voltage-gated $\text{Na}^+$ channels in nerve tissue, preventing depolarization	Nausea, diarrhea, paresthesias, weakness, dizziness, loss of reflexes	Supportive
<b>Ciguatoxin</b>	Reef fish such as barracuda, snapper, and moray eel	Opens $\text{Na}^+$ channels, causing depolarization	Nausea, vomiting, diarrhea; perioral numbness; reversal of hot and cold sensations; bradycardia, heart block, hypotension	Supportive

**Age-related changes in pharmacokinetics** It's how aging bodies are MADE.

<b>Metabolism</b>	$\downarrow$ hepatic mass, $\downarrow$ hepatic blood flow and $\downarrow$ drug metabolism. Phase I metabolism lost first with aging. Drugs metabolized during phase II (eg, lorazepam, acetaminophen) are safer than drugs metabolized during phase I (eg, diazepam). Thus $\downarrow$ therapeutic doses may suffice in elderly.
<b>Absorption</b>	$\uparrow$ gastric pH, $\downarrow$ gastric emptying. Drug absorption influenced via drug-drug/food interactions.
<b>Distribution</b>	$\uparrow$ body fat content ( $\uparrow V_d$ for lipophilic drugs, eg, propofol). $\downarrow$ albumin ( $\downarrow$ binding of acidic drugs). $\downarrow$ total body water ( $\downarrow V_d$ for hydrophilic drugs, eg, digoxin).
<b>Elimination</b>	$\downarrow$ GFR and $\downarrow$ tubular secretion. $\uparrow$ plasma concentration of renally excreted drugs; thus $\downarrow$ therapeutic doses may suffice in elderly.

<b>Beers criteria</b>	Widely used criteria developed to reduce potentially inappropriate prescribing and harmful polypharmacy in the geriatric population. Includes $> 50$ medications that should be avoided in elderly patients due to $\downarrow$ efficacy and/or $\uparrow$ risk of adverse events. Examples: <ul style="list-style-type: none"> <li>■ <math>\alpha</math>-blockers (<math>\uparrow</math> risk of hypotension)</li> <li>■ Anticholinergics, antidepressants, antihistamines, opioids (<math>\uparrow</math> risk of delirium, sedation, falls, constipation, urinary retention)</li> <li>■ Benzodiazepines (<math>\uparrow</math> risk of delirium, sedation, falls)</li> <li>■ NSAIDs (<math>\uparrow</math> risk of GI bleeding, especially with concomitant anticoagulation)</li> <li>■ PPIs (<math>\uparrow</math> risk of <i>C. difficile</i> infection)</li> </ul>
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## Specific toxicity treatments

TOXIN	TREATMENT
Acetaminophen	N-acetylcysteine (replenishes glutathione)
AChE inhibitors, organophosphates	Atropine > pralidoxime
Antimuscarinic, anticholinergic agents	Physostigmine (crosses BBB), control hyperthermia
Arsenic	Dimercaprol, succimer
Benzodiazepines	Flumazenil
β-blockers	Atropine, glucagon, saline
Carbon monoxide	100% O <sub>2</sub> , hyperbaric O <sub>2</sub>
Copper	“Penny”cillamine (penicillamine), <b>trientine (3 copper pennies)</b>
Cyanide	Hydroxocobalamin, nitrites + sodium thiosulfate
Dabigatran	Idarucizumab
Digoxin	Digoxin-specific antibody fragments
Direct factor Xa inhibitors (eg, apixaban)	Andexanet alfa
Heparin	Protamine sulfate
Iron ( <b>Fe</b> )	Deferoxamine, deferasirox, deferiprone
Lead	Calcium disodium EDTA, dimercaprol, succimer, penicillamine
Mercury	Dimercaprol, succimer
Methanol, ethylene glycol (antifreeze)	Fomepizole > ethanol, dialysis
Methemoglobin	<b>M</b> ethylene blue, vitamin C (reducing agent)
Methotrexate	Leucovorin
Opioids	Naloxone
Salicylates	NaHCO <sub>3</sub> (alkalinize urine), dialysis
TCAs	NaHCO <sub>3</sub> (stabilizes cardiac cell membrane)
Warfarin	Vitamin K (delayed effect), PCC (prothrombin complex concentrate)/FFP (immediate effect)

## Drug reactions—cardiovascular

DRUG REACTION	CAUSAL AGENTS
Coronary vasospasm	Cocaine, Amphetamines, Sumatriptan, Ergot alkaloids ( <b>CASE</b> )
Cutaneous flushing	Vancomycin, Adenosine, Niacin, Ca <sup>2+</sup> channel blockers, Echinocandins, Nitrates ( <b>flushed from VANCEN</b> [dancing]) <b>Red man syndrome</b> —rate-dependent infusion reaction to vancomycin causing widespread pruritic erythema due to histamine release. Manage with diphenhydramine, slower infusion rate.
Dilated cardiomyopathy	Alcohol, anthracycline (eg, doxorubicin, daunorubicin; prevent with dexrazoxane), trastuzumab
Torsades de pointes	Agents that prolong QT interval: antiArrhythmics (class IA, III), antiBiotics (eg, macrolides, fluoroquinolones), anti“C”ychotics (eg, ziprasidone), antiDepressants (eg, TCAs), antiEmetics (eg, ondansetron), antiFungals (eg, fluconazole) ( <b>ABCDEF</b> )

**Drug reactions—endocrine/reproductive**

DRUG REACTION	CAUSAL AGENTS	NOTES
Adrenocortical insufficiency	HPA suppression 2° to glucocorticoid withdrawal	
Diabetes insipidus	Lithium, demeclocycline	
Gynecomastia	Ketoconazole, cimetidine, spironolactone, GnRH analogs/antagonists, androgen receptor inhibitors, 5α-reductase inhibitors	
Hot flashes	SERMs (eg, tamoxifen, clomiphene, raloxifene)	
Hyperglycemia	Tacrolimus, protease inhibitors, niacin, HCTZ, corticosteroids	The people need hard candies
Hyperprolactinemia	Typical antipsychotics (eg, haloperidol), atypical antipsychotics (eg, risperidone), metoclopramide, methyldopa, reserpine	Presents with hypogonadism (eg, infertility, amenorrhea, erectile dysfunction) and galactorrhea
Hyperthyroidism	Amiodarone, iodine, lithium	
Hypothyroidism	Amiodarone, lithium	I am lethargic
SIADH	Carbamazepine, Cyclophosphamide, SSRIs	Can't Concentrate Serum Sodium

**Drug reactions—gastrointestinal**

DRUG REACTION	CAUSAL AGENTS	NOTES
Acute cholestatic hepatitis, jaundice	Macrolides (eg, erythromycin)	
Diarrhea	Acamprosate, antidiabetic agents (acarbose, metformin, pramlintide), colchicine, cholinesterase inhibitors, lipid-lowering agents (eg, ezetimibe, orlistat), macrolides (eg, erythromycin), SSRIs, chemotherapy (eg, irinotecan)	
Focal to massive hepatic necrosis	Halothane, <i>Amanita phalloides</i> (death cap mushroom), valproic acid, acetaminophen	Liver “hAvac”
Hepatitis	Rifampin, isoniazid, pyrazinamide, statins, fibrates	
Pancreatitis	Didanosine, corticosteroids, alcohol, valproic acid, azathioprine, diuretics (eg, furosemide, HCTZ)	Drugs causing a violent abdominal distress
Pill-induced esophagitis	Bisphosphonates, ferrous sulfate, NSAIDs, potassium chloride, tetracyclines	Usually occurs at anatomic sites of esophageal narrowing (eg, near level of aortic arch); caustic effect minimized with upright posture and adequate water ingestion
Pseudomembranous colitis	Ampicillin, cephalosporins, clindamycin, fluoroquinolones, PPIs	Antibiotics predispose to superinfection by resistant <i>C difficile</i>

**Drug reactions—hematologic**

DRUG REACTION	CAUSAL AGENTS	NOTES
Agranulocytosis	Dapsone, clozapine, carbamazepine, propylthiouracil, methimazole, colchicine, ticlopidine, ganciclovir	Drugs can cause pretty major collapse to granulocytes
Aplastic anemia	Carbamazepine, methimazole, NSAIDs, benzene, chloramphenicol, propylthiouracil	Can't make New blood cells properly
Direct Coombs + hemolytic anemia	Penicillin, methylDopa, Cephalosporins	P Diddy Coombs
Drug reaction with eosinophilia and systemic symptoms <sup>a</sup>	Allopurinol, antiBiotics, antiConvulsants, sulfa drugs	ABCs
Gray baby syndrome	Chloramphenicol	
Hemolysis in G6PD deficiency	Isoniazid, sulfonamides, dapsone, primaquine, aspirin, ibuprofen, nitrofurantoin	Hemolysis is d pain
Megaloblastic anemia	Hydroxyurea, Phenytoin, Methotrexate, Sulfa drugs	You're having a mega blast with PMS
Thrombocytopenia	Indinavir, heparin, quinidine, ganciclovir, vancomycin, linezolid, abciximab	I have quickly gotten very low amounts
Thrombotic complications	Combined oral contraceptives, hormone replacement therapy, SERMs, epoetin alfa	Estrogen-mediated adverse effect

<sup>a</sup>DRESS is a delayed hypersensitivity reaction associated with latent herpesvirus reactivation. Latency period (2–8 weeks), then fever, morbilliform skin rash, multiorgan involvement. Treatment: withdrawal of offending drug, corticosteroids

**Drug reactions—musculoskeletal/skin/connective tissue**

DRUG REACTION	CAUSAL AGENTS	NOTES
Drug-induced lupus	Methyldopa, minocycline, hydralazine, isoniazid, phenytoin, sulfa drugs, etanercept, procainamide	Lupus makes my hips extremely painful
Fat redistribution	Protease inhibitors, glucocorticoids	Fat protects glutes
Gingival hyperplasia	Cyclosporine, Ca <sup>2+</sup> channel blockers, phenytoin	Can Cause puffy gums
Hyperuricemia (gout)	Pyrazinamide, thiazides, furosemide, niacin, cyclosporine	Painful tophi and feet need care
Myopathy	Statins, fibrates, niacin, colchicine, daptomycin, hydroxychloroquine, interferon-α, penicillamine, glucocorticoids	
Osteoporosis	Corticosteroids, depot medroxyprogesterone acetate, GnRH agonists, aromatase inhibitors, anticonvulsants, heparin, PPIs	
Photosensitivity	Sulfonamides, amiodarone, tetracyclines, 5-FU	Sat For photo
Rash (Stevens-Johnson syndrome)	Anti-epileptic drugs (especially lamotrigine), allopurinol, sulfa drugs, penicillin	Steven Johnson has epileptic allergy to sulfa drugs and penicillin
Teeth discoloration	Tetracyclines	Teethracyclines
Tendon/cartilage damage	Fluoroquinolones	

**Drug reactions—neurologic**

DRUG REACTION	CAUSAL AGENTS	NOTES
Cinchonism	Quinidine, quinine	Can present with tinnitus, hearing/vision loss, psychosis, and cognitive impairment
Parkinson-like syndrome	Antipsychotics, reserpine, metoclopramide	Cogwheel rigidity of arm
Peripheral neuropathy	Isoniazid, phenytoin, platinum agents (eg, cisplatin), paclitaxel, vincristine	
Idiopathic intracranial hypertension	Vitamin A, growth hormones, tetracyclines	Always grow head tension
Seizures	Isoniazid, bupropion, imipenem/cilastatin, tramadol, enflurane	With seizures, I bite my tongue
Tardive dyskinesia	Antipsychotics, metoclopramide	
Visual disturbance	Topiramate (blurred vision/diplopia, haloes), hydroxychloroquine (↓ visual acuity, visual field defects), digoxin (yellow-tinged vision), isoniazid (optic neuritis), vigabatrin (visual field defects), PDE-5 inhibitors (blue-tinged vision), ethambutol (color vision changes)	These horrible drugs irritate very Precious eyes

**Drug reactions—renal/genitourinary**

DRUG REACTION	CAUSAL AGENTS	NOTES
Fanconi syndrome	Cisplatin, ifosfamide, expired tetracyclines, tenofovir	
Hemorrhagic cystitis	Cyclophosphamide, ifosfamide	Prevent by coadministering with mesna
Interstitial nephritis	Diuretics (Pee), NSAIDs (Pain-free), Penicillins and cephalosporins, PPIs, rifampin, sulfa drugs	Remember the 5 P's

**Drug reactions—respiratory**

DRUG REACTION	CAUSAL AGENTS	NOTES
Dry cough	ACE inhibitors	
Pulmonary fibrosis	Methotrexate, nitrofurantoin, carmustine, bleomycin, busulfan, amiodarone	My nose cannot breathe bad air

**Drug reactions—multiorgan**

DRUG REACTION	CAUSAL AGENTS	NOTES
Antimuscarinic	Atropine, TCAs, H <sub>1</sub> -blockers, antipsychotics	
Disulfiram-like reaction	1st-generation sulfonylureas, procarbazine, certain cephalosporins, griseofulvin, metronidazole	Sorry pals, can't go mingle
Nephrotoxicity/ototoxicity	Loop diuretics, cisplatin, aminoglycosides, amphotericin, vancomycin	Listen Cis! Always adjust vancomycin in CKD. Cisplatin toxicity may respond to amifostine

<b>Drugs affecting pupil size</b>	<b>↑ pupil size (mydriasis)</b>	<b>↓ pupil size (miosis)</b>
	Anticholinergics (eg, atropine, TCAs, tropicamide, scopolamine, antihistamines)	Sympatholytics (eg, $\alpha_2$ -agonists)
	Indirect sympathomimetics (eg, amphetamines, cocaine, LSD), meperidine	Opioids (except meperidine)
	Direct sympathomimetics	Parasympathomimetics (eg, pilocarpine), organophosphates

<b>Cytochrome P-450 interactions (selected)</b>	<b>Inducers (+)</b>	<b>Substrates</b>	<b>Inhibitors (-)</b>
	<b>St. John's wort</b>	<b>Theophylline</b>	<b>Sodium valproate</b>
	<b>Griseofulvin</b>	<b>OCPs</b>	<b>Isoniazid</b>
	<b>Carbamazepine</b>	<b>Anti-epileptics</b>	<b>Cimetidine</b>
	<b>Chronic alcohol overuse</b>	<b>Warfarin</b>	<b>Ketoconazole</b>
	<b>Rifampin</b>		<b>Fluconazole</b>
	<b>Modafinil</b>		<b>Acute alcohol overuse</b>
	<b>Nevirapine</b>		<b>Chloramphenicol</b>
	<b>Phenytoin</b>		<b>Erythromycin/clarithromycin</b>
	<b>Phenobarbital</b>		<b>Sulfonamides</b>
			<b>Ciprofloxacin</b>
			<b>Omeprazole</b>
			<b>Metronidazole</b>
			<b>Amiodarone</b>
			<b>Ritonavir</b>
			<b>Grapefruit juice</b>
	<b>St. John grimaced at the carbs in chronic alcohol overuse, refused more, and never again forgot his phen-phen</b>	<b>The OCPs are anti-war</b>	<b>SICKFACES.COM (when I am really drinking grapefruit juice)</b>

<b>Sulfa drugs</b>	<b>Sulfonamide antibiotics, Sulfasalazine, Probenecid, Furosemide, Acetazolamide, Celecoxib, Thiazides, Sulfonylureas.</b> Patients with sulfa allergies may develop fever, urinary tract infection, Stevens-Johnson syndrome, hemolytic anemia, thrombocytopenia, agranulocytosis, acute interstitial nephritis, and urticaria (hives).	<b>Scary Sulfa Pharm FACTS</b>
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## ► PHARMACOLOGY—MISCELLANEOUS

**Drug names**

ENDING	CATEGORY	EXAMPLE
<b>Antimicrobial</b>		
<b>-asvir</b>	NS5A inhibitor	Ledipasvir
<b>-bendazole</b>	Antiparasitic/antihelminthic	Mebendazole
<b>-buvir</b>	NS5B inhibitor	Sofosbuvir
<b>-cillin</b>	Transpeptidase inhibitor	Ampicillin
<b>-conazole</b>	Ergosterol synthesis inhibitor	Ketoconazole
<b>-cycline</b>	Protein synthesis inhibitor	Tetracycline
<b>-floxacin</b>	Fluoroquinolone	Ciprofloxacin
<b>-mivir</b>	Neuraminidase inhibitor	Oseltamivir
<b>-navir</b>	Protease inhibitor	Ritonavir
<b>-ovir</b>	Viral DNA polymerase inhibitor	Acyclovir
<b>-previr</b>	NS3/4A inhibitor	Simeprevir
<b>-tegravir</b>	Integrase inhibitor	Elvitegravir
<b>-thromycin</b>	Macrolide	Azithromycin
<b>Antineoplastic</b>		
<b>-case</b>	Recombinant uricase	Rasburicase
<b>-mustine</b>	Nitrosourea	Carmustine
<b>-platin</b>	Platinum compound	Cisplatin
<b>-poside</b>	Topoisomerase II inhibitor	Etoposide
<b>-rubicin</b>	Anthracycline	Doxorubicin
<b>-taxel</b>	Taxane	Paclitaxel
<b>-tecan</b>	Topoisomerase I inhibitor	Irinotecan
<b>CNS</b>		
<b>-ane</b>	Inhaled anesthetic	Halothane
<b>-apine, -idone</b>	Atypical antipsychotic	Quetiapine, risperidone
<b>-azine</b>	Typical antipsychotic	Thioridazine
<b>-barbital</b>	Barbiturate	Phenobarbital
<b>-benazine</b>	VMAT inhibitor	Tetrabenazine
<b>-caine</b>	Local anesthetic	Lidocaine
<b>-capone</b>	COMT inhibitor	Entacapone
<b>-curium, -curonium</b>	Nondepolarizing neuromuscular blocker	Atracurium, pancuronium
<b>-giline</b>	MAO-B inhibitor	Selegiline
<b>-ipramine, -tryptiline</b>	TCA	Imipramine, amitriptyline
<b>-triptan</b>	5-HT <sub>1B/1D</sub> agonist	Sumatriptan
<b>-zepam, -zolam</b>	Benzodiazepine	Diazepam, alprazolam

**Drug names (*continued*)**

ENDING	CATEGORY	EXAMPLE
<b>Autonomic</b>		
<b>-chol</b>	Cholinergic agonist	Bethanechol
<b>-olol</b>	$\beta$ -blocker	Propranolol
<b>-stigmine</b>	AChE inhibitor	Neostigmine
<b>-terol</b>	$\beta_2$ -agonist	Albuterol
<b>-zosin</b>	$\alpha_1$ -blocker	Prazosin
<b>Cardiovascular</b>		
<b>-afil</b>	PDE-5 inhibitor	Sildenafil
<b>-dipine</b>	Dihydropyridine $\text{Ca}^{2+}$ channel blocker	Amlodipine
<b>-parin</b>	Low-molecular-weight heparin	Enoxaparin
<b>-plase</b>	Thrombolytic	Alteplase
<b>-pril</b>	ACE inhibitor	Captopril
<b>-sartan</b>	Angiotensin-II receptor blocker	Losartan
<b>-xaban</b>	Direct factor Xa inhibitor	Apixaban
<b>Metabolic</b>		
<b>-gliflozin</b>	SGLT-2 inhibitor	Dapagliflozin
<b>-glinide</b>	Meglitinide	Repaglinide
<b>-gliptin</b>	DPP-4 inhibitor	Sitagliptin
<b>-glitazone</b>	PPAR- $\gamma$ activator	Rosiglitazone
<b>-glutide</b>	GLP-1 analog	Liraglutide
<b>-statin</b>	HMG-CoA reductase inhibitor	Lovastatin
<b>Other</b>		
<b>-caftor</b>	CFTR modulator	Lumacaftor
<b>-donate</b>	Bisphosphonate	Alendronate
<b>-lukast</b>	CysLT1 receptor blocker	Montelukast
<b>-lutamide</b>	Androgen receptor inhibitor	Flutamide
<b>-pitant</b>	NK <sub>1</sub> blocker	Aprepitant
<b>-prazole</b>	Proton pump inhibitor	Omeprazole
<b>-prost</b>	Prostaglandin analog	Latanoprost
<b>-sentan</b>	Endothelin receptor antagonist	Bosentan
<b>-setron</b>	5-HT <sub>3</sub> blocker	Ondansetron
<b>-steride</b>	5 $\alpha$ -reductase inhibitor	Finasteride
<b>-tadine</b>	H <sub>1</sub> -antagonist	Loratadine
<b>-tidine</b>	H <sub>2</sub> -antagonist	Cimetidine
<b>-trozole</b>	Aromatase inhibitor	Anastrozole
<b>-vaptan</b>	ADH antagonist	Tolvaptan

**Biologic agents**

ENDING	CATEGORY	EXAMPLE
<b>Monoclonal antibodies (-mab)—target overexpressed cell surface receptors</b>		
-xi <sup>mab</sup>	Chimeric human-mouse monoclonal antibody	Rituximab
-zumab	Humanized monoclonal antibody	Bevacizumab
-umab	Human monoclonal antibody	Denosumab
<b>Small molecule inhibitors (-ib)—target intracellular molecules</b>		
-ciclib	Cyclin-dependent kinase inhibitor	Palbociclib
-coxib	COX-2 inhibitor	Celecoxib
-parib	Poly(ADP-ribose) polymerase inhibitor	Olaparib
-rafenib	BRAF inhibitor	Vemurafenib
-tinib	Tyrosine kinase inhibitor	Imatinib
-zomib	Proteasome inhibitor	Bortezomib
<b>Receptor fusion proteins (-cept)</b>		
-cept	TNF- $\alpha$ antagonist	Etanercept
<b>Interleukin receptor modulators (-kin)—agonists and antagonists of interleukin receptors</b>		
-leukin	Interleukin-2 agonist/analog	Aldesleukin
-kinra	Interleukin receptor antagonist	Anakinra

# Public Health Sciences

*“Medicine is a science of uncertainty and an art of probability.”*

—Sir William Osler

*“Whenever a doctor cannot do good, he must be kept from doing harm.”*

—Hippocrates

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

—Chuck Palahniuk, *Fight Club*

*“Of all forms of discrimination and inequalities, injustice in health is the most shocking and inhuman.”*

—Martin Luther King, Jr.

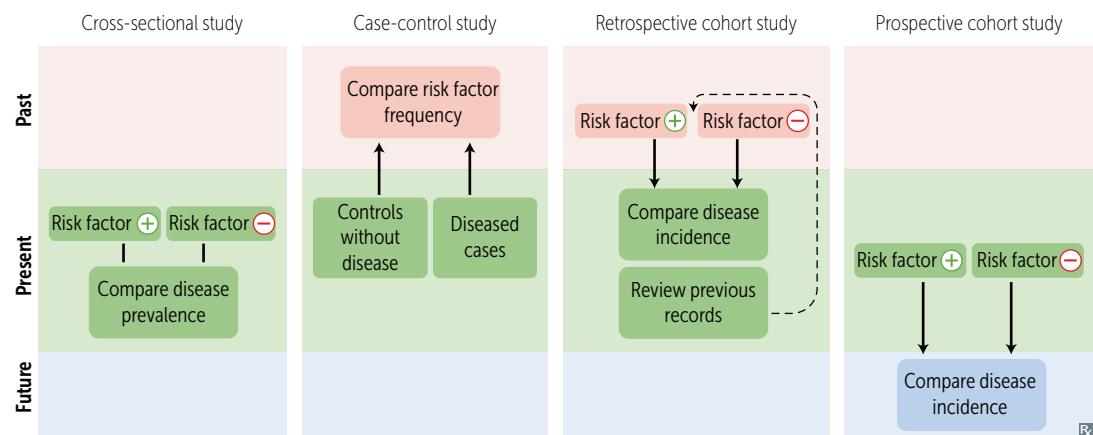
A heterogenous mix of epidemiology, biostatistics, ethics, law, healthcare delivery, patient safety, quality improvement, and more falls under the heading of public health sciences. Biostatistics and epidemiology are the foundations of evidence-based medicine and are very high yield. Make sure you can quickly apply biostatistical equations such as sensitivity, specificity, and predictive values in a problem-solving format. Also, know how to set up your own  $2 \times 2$  tables, and beware questions that switch the columns. Quality improvement and patient safety topics were introduced a few years ago on the exam and represent trends in health system science. Medical ethics questions often require application of principles. Typically, you are presented with a patient scenario and then asked how you would respond. For this edition, we have added a section on communication skills given their growing emphasis on the exam. Effective communication is essential to the physician-patient partnership. Physicians must seek opportunities to connect with patients, understand their perspectives, express empathy, and form shared decisions and realistic goals.

► Epidemiology and Biostatistics	260
► Ethics	270
► Communication Skills	273
► Healthcare Delivery	278
► Quality and Safety	280

## ► PUBLIC HEALTH SCIENCES—EPIDEMIOLOGY AND BIOSTATISTICS

**Observational studies**

STUDY TYPE	DESIGN	MEASURES/EXAMPLE
<b>Case series</b>	Describes several individual patients with the same diagnosis, treatment, or outcome.	Description of clinical findings and symptoms. Has no comparison group, thus cannot show risk factor association with disease.
<b>Cross-sectional study</b>	Frequency of disease and frequency of risk-related factors are assessed in the present. Asks, “What is happening?”	Disease prevalence. Can show risk factor association with disease, but does not establish causality.
<b>Case-control study</b>	Retrospectively compares a group of people with disease to a group without disease. Looks to see if odds of prior exposure or risk factor differ by disease state. Asks, “What happened?”	Odds ratio ( <b>OR</b> ). <b>Control</b> the case in the <b>OR</b> . Patients with COPD had higher odds of a smoking history than those without COPD.
<b>Cohort study</b>	Compares a group with a given exposure or risk factor to a group without such exposure. Looks to see if exposure or risk factor is associated with later development of disease. Can be prospective or retrospective.	Disease incidence. Relative risk (RR). People who smoke had a higher risk of developing COPD than people who do not. Cohort = relative risk.
<b>Twin concordance study</b>	Compares the frequency with which both monozygotic twins vs both dizygotic twins develop the same disease.	Measures heritability and influence of environmental factors (“nature vs nurture”).
<b>Adoption study</b>	Compares siblings raised by biological vs adoptive parents.	Measures heritability and influence of environmental factors.
<b>Ecological study</b>	Compares frequency of disease and frequency of risk-related factors across populations. Measures population data not necessarily applicable to individuals (ecological fallacy).	Used to monitor population health. COPD prevalence was higher in more polluted cities.



**Clinical trial**

Experimental study involving humans. Compares therapeutic benefits of ≥2 treatments, or of treatment and placebo. Study quality improves when study is randomized, controlled, and double-blinded (ie, neither patient nor researcher knows whether the patient is in the treatment or control group). Triple-blind refers to the additional blinding of the researchers analyzing the data. Five phases (“Can I SWIM?”).

**Crossover study**

Compares the effect of a series of ≥2 treatments on a participant. Order in which participants receive treatments is randomized. Washout period occurs between treatments. Allows participants to serve as own controls.

**Intention-to-treat analysis:** All patients are analyzed according to their original, randomly assigned treatment. No patients are excluded. Attempts to avoid misleading bias from patients dropping out.

**Per protocol analysis:** Only patients who complete the study “per protocol” are included in analysis. Patients who fail to complete treatment as originally, randomly assigned are excluded. Risk of bias from non-random noncompliance.

DRUG TRIALS	TYPICAL STUDY SAMPLE	PURPOSE
<b>Phase 0</b>	Very small number of either healthy volunteers or patients with disease of interest.	Initial pharmacokinetic and pharmacodynamic assessment. Uses <1% of therapeutic dose. No safety or toxicity assessment.
<b>Phase I</b>	Small number of either healthy volunteers or patients with disease of interest; more than Phase 0.	“Is it Safe?” Assesses safety, toxicity, dosage, pharmacokinetics, and pharmacodynamics.
<b>Phase II</b>	Moderate number of patients with disease of interest.	“Does it Work?” Assesses treatment efficacy, and adverse effects.
<b>Phase III</b>	Large number of patients with disease of interest randomly assigned either to the treatment under investigation or to the standard of care (or placebo).	“Is it as good or better?” Compares the new treatment to the current standard of care (any Improvement?).
<b>Phase IV</b>	Postmarketing surveillance of patients after treatment is approved.	“Can it stay on the Market?” Detects rare or long-term adverse effects and evaluates cost-effectiveness.
<b>Bradford Hill criteria</b>	A group of principles that provide limited support for establishing evidence of a causal relationship between presumed cause and effect.	
<b>Strength</b>	Association does not imply causation, but the stronger the association, the more evidence for causation.	
<b>Consistency</b>	Repeated observations of the findings in multiple distinct samples.	
<b>Specificity</b>	The more specific the presumed cause is to the effect, the stronger the evidence for causation.	
<b>Temporality</b>	The presumed cause precedes the effect by an expected amount of time.	
<b>Biological gradient</b>	Greater effect observed with greater exposure to the presumed cause (dose-response relationship).	
<b>Plausibility</b>	A conceivable mechanism exists by which the cause may lead to the effect.	
<b>Coherence</b>	The presumed cause and effect do not conflict with existing scientific consensus.	
<b>Experiment</b>	Empirical evidence supporting the presumed cause and effect (eg, animal studies, in vitro studies).	
<b>Analogy</b>	The presumed cause and effect are comparable to a similar, established cause and effect.	

**Quantifying risk**

Definitions and formulas are based on the classic  $2 \times 2$  or contingency table.

		Disease or outcome	
		⊕	⊖
Exposure or intervention	⊕	a	b
	⊖	c	d

TERM	DEFINITION	EXAMPLE	FORMULA								
<b>Odds ratio</b>	<p>Typically used in case-control studies. Represents the odds of exposure among cases (<math>a/c</math>) vs odds of exposure among controls (<math>b/d</math>).  <math>OR = 1 \rightarrow</math> odds of exposure are equal in cases and controls.  <math>OR &gt; 1 \rightarrow</math> odds of exposure are greater in cases.  <math>OR &lt; 1 \rightarrow</math> odds of exposure are greater in controls.</p>	<p>If in a case-control study, 20/30 patients with lung cancer and 5/25 healthy individuals report smoking, the OR is 8; so the patients with lung cancer are 8 times more likely to have a history of smoking.</p>	$OR = \frac{a/c}{b/d} = \frac{ad}{bc}$ <table border="1"> <tr> <td>a</td> <td>b</td> </tr> <tr> <td>20</td> <td>5</td> </tr> <tr> <td>c</td> <td>d</td> </tr> <tr> <td>10</td> <td>20</td> </tr> </table>	a	b	20	5	c	d	10	20
a	b										
20	5										
c	d										
10	20										
<b>Relative risk</b>	<p>Typically used in cohort studies. Risk of developing disease in the exposed group divided by risk in the unexposed group.  <math>RR = 1 \rightarrow</math> no association between exposure and disease.  <math>RR &gt; 1 \rightarrow</math> exposure associated with ↑ disease occurrence.  <math>RR &lt; 1 \rightarrow</math> exposure associated with ↓ disease occurrence.</p>	<p>If 5/10 people exposed to radiation are diagnosed with cancer, and 1/10 people not exposed to radiation are diagnosed with cancer, the RR is 5; so people exposed to radiation have a 5 times greater risk of developing cancer.</p> <p>For rare diseases (low prevalence), OR approximates RR.</p>	$RR = \frac{a/(a + b)}{c/(c + d)}$ <table border="1"> <tr> <td>a</td> <td>b</td> </tr> <tr> <td>5</td> <td>5</td> </tr> <tr> <td>c</td> <td>d</td> </tr> <tr> <td>1</td> <td>9</td> </tr> </table>	a	b	5	5	c	d	1	9
a	b										
5	5										
c	d										
1	9										
<b>Relative risk reduction</b>	The proportion of risk reduction attributable to the intervention as compared to a control.	If 2% of patients who receive a flu shot develop the flu, while 8% of unvaccinated patients develop the flu, then $RR = 2/8 = 0.25$ , and $RRR = 0.75$ .	$RRR = 1 - RR$								
<b>Attributable risk</b>	The difference in risk between exposed and unexposed groups.	If risk of lung cancer in people who smoke is 21% and risk in people who don't smoke is 1%, then the attributable risk is 20%.	$AR = \frac{a}{a + b} - \frac{c}{c + d}$ $AR\% = \frac{RR - 1}{RR} \times 100$								
<b>Absolute risk reduction</b>	The difference in risk (not the proportion) attributable to the intervention as compared to a control.	If 8% of people who receive a placebo vaccine develop the flu vs 2% of people who receive a flu vaccine, then $ARR = 8\% - 2\% = 6\% = 0.06$ .	$ARR = \frac{c}{c + d} - \frac{a}{a + b}$								
<b>Number needed to treat</b>	Number of patients who need to be treated for 1 patient to benefit. Lower number = better treatment.		$NNT = 1/ARR$								
<b>Number needed to harm</b>	Number of patients who need to be exposed to a risk factor for 1 patient to be harmed. Higher number = safer exposure.		$NNH = 1/AR$								
<b>Case fatality rate</b>	Percentage of deaths occurring among those with disease.	If 4 patients die among 10 cases of meningitis, case fatality rate is 40%.	$CFR\% = \frac{\text{deaths}}{\text{cases}} \times 100$								

**Quantifying risk (continued)**

TERM	DEFINITION	EXAMPLE	FORMULA
<b>Mortality rate</b>	Number of deaths (in general or due to specific cause) within a population over a period, typically scaled to deaths per 1000 people per year.	If 80 people in a town of 10,000 die over 2 years, mortality rate is 4 per 1000 per year.	
<b>Attack rate</b>	Proportion of exposed people who become ill.	If 80 people in a town are exposed and 60 people become ill, attack rate is 75%.	$\frac{\text{People who become ill}}{\text{Total people exposed}}$

**Likelihood ratio**

$$LR^+ = \frac{\text{probability of positive result in patient with disorder}}{\text{probability of positive result in patient without disorder}} = \frac{\text{sensitivity}}{1 - \text{specificity}} = \frac{\text{TP rate}}{\text{FP rate}}$$

$$LR^- = \frac{\text{probability of negative result in patient with disorder}}{\text{probability of negative result in patient without disorder}} = \frac{1 - \text{sensitivity}}{\text{specificity}} = \frac{\text{FN rate}}{\text{TN rate}}$$

$LR^+ > 10$  indicates a highly specific test, while  $LR^- < 0.1$  indicates a highly sensitive test.

## Evaluation of diagnostic tests

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

		Disease	
		+	-
Test	+	TP	FP
	-	FN	TN
	<b>Sensitivity</b> $= \frac{TP}{TP + FN}$	<b>Specificity</b> $= \frac{TN}{TN + FP}$	<b>Prevalence</b> $\frac{TP + FN}{(TP + FN + FP + TN)}$

### Sensitivity (true-positive rate)

Proportion of all people with disease who test positive, or the ability of a test to correctly identify those with the disease.

Value approaching 100% is desirable for **ruling out** disease and indicates a **low false-negative rate**.

### Specificity (true-negative rate)

Proportion of all people without disease who test negative, or the ability of a test to correctly identify those without the disease.

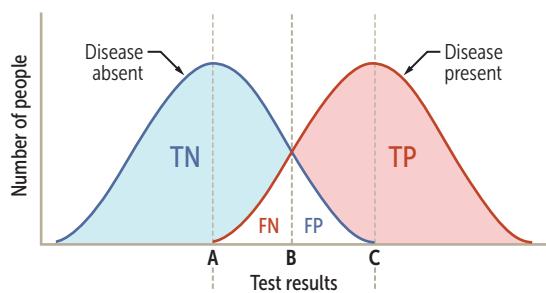
Value approaching 100% is desirable for **ruling in** disease and indicates a **low false-positive rate**.

### Positive predictive value

Probability that a person who has a positive test result actually has the disease.

### Negative predictive value

Probability that a person with a negative test result actually does not have the disease.



$$= \frac{TP}{TP + FN}$$

$$= 1 - FN \text{ rate}$$

**SN-N-OUT** = highly **SeNsitive** test, when **Negative**, rules **OUT** disease

High sensitivity test used for screening

$$= \frac{TN}{TN + FP}$$

$$= 1 - FP \text{ rate}$$

**SP-P-IN** = highly **SPecific** test, when **Positive**, rules **IN** disease

High specificity test used for confirmation after a positive screening test

$$\text{PPV} = \frac{TP}{TP + FP}$$

PPV varies directly with pretest probability

(baseline risk, such as prevalence of disease): high pretest probability → high PPV

$$\text{NPV} = \frac{TN}{TN + FN}$$

NPV varies inversely with prevalence or pretest probability

Possible cutoff values for  $\oplus$  vs  $\ominus$  test result

A = 100% sensitivity cutoff value

B = practical compromise between specificity and sensitivity

C = 100% specificity cutoff value

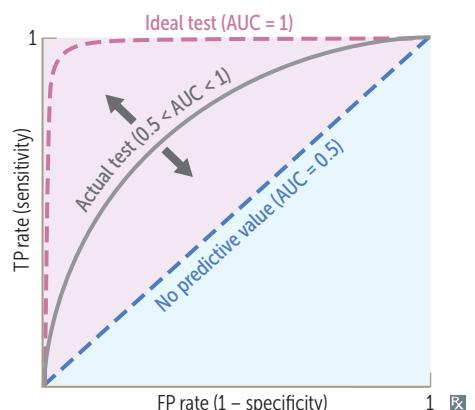
Lowering the cutoff value: ↑ Sensitivity ↑ NPV  
B → A ( $\uparrow FP \downarrow FN$ ) ↓ Specificity ↓ PPV

Raising the cutoff value: ↑ Specificity ↑ PPV  
B → C ( $\uparrow FN \downarrow FP$ ) ↓ Sensitivity ↓ NPV

## Receiver operating characteristic curve

ROC curve demonstrates how well a diagnostic test can distinguish between 2 groups (eg, disease vs healthy). Plots the true-positive rate (sensitivity) against the false-positive rate (1 – specificity).

The better performing test will have a higher area under the curve (AUC), with the curve closer to the upper left corner.



### Precision vs accuracy

#### Precision (reliability)

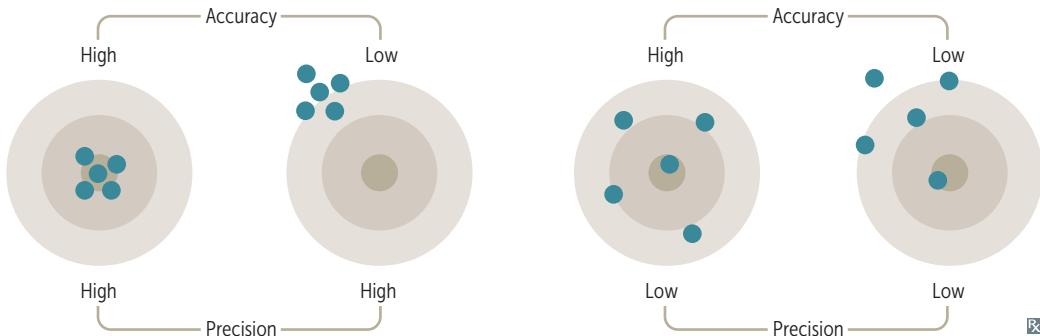
The consistency and **reproducibility** of a test.  
The absence of random variation in a test.

Random error  $\downarrow$  precision in a test.  
 $\uparrow$  precision  $\rightarrow \downarrow$  standard deviation.  
 $\uparrow$  precision  $\rightarrow \uparrow$  statistical power ( $1 - \beta$ ).

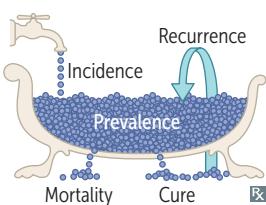
#### Accuracy (validity)

The closeness of test results to the true values.  
The absence of systematic error or bias in a test.

Systematic error  $\downarrow$  accuracy in a test.



### Incidence vs prevalence



$$\text{Incidence} = \frac{\# \text{ of new cases}}{\# \text{ of people at risk}} \quad (\text{per unit of time})$$

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

$$\frac{\text{Prevalence}}{1 - \text{prevalence}} = \text{Incidence rate} \times \frac{\text{average duration of disease}}{\text{of disease}}$$

Prevalence  $\approx$  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.

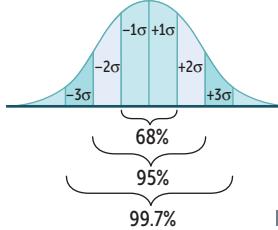
Prevalence  $\sim$  pretest probability.  
 $\uparrow$  prevalence  $\rightarrow \uparrow$  PPV and  $\downarrow$  NPV.

SITUATION	INCIDENCE	PREVALENCE
$\uparrow$ survival time	—	$\uparrow$
$\uparrow$ mortality	—	$\downarrow$
Faster recovery time	—	$\downarrow$
Extensive vaccine administration	$\downarrow$	$\downarrow$
$\downarrow$ risk factors	$\downarrow$	$\downarrow$
$\uparrow$ diagnostic sensitivity	$\uparrow$	$\uparrow$

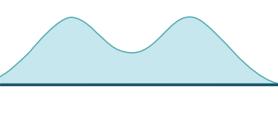
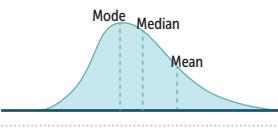
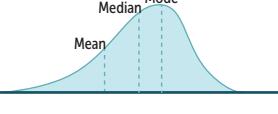
**Bias and study errors**

TYPE	DEFINITION	EXAMPLES	STRATEGIES TO REDUCE BIAS
<b>Recruiting participants</b>			
<b>Selection bias</b>	<p>Nonrandom sampling or treatment allocation of subjects such that study population is not representative of target population</p> <p>Most commonly a sampling bias</p>	<p><b>Berkson bias</b>—cases and/or controls selected from hospitals (<b>bedside bias</b>) are less healthy and have different exposures</p> <p><b>Attrition bias</b>—participants lost to follow up have a different prognosis than those who complete the study</p>	<p>Randomization (creates groups with similar distributions of known and unknown variables)</p> <p>Ensure the choice of the right comparison/reference group</p>
<b>Performing study</b>			
<b>Recall bias</b>	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
<b>Measurement bias</b>	Information is gathered in a systemically distorted manner	<p>Using a faulty automatic sphygmomanometer</p> <p><b>Hawthorne effect</b>—participants change behavior upon awareness of being observed</p>	<p>Use objective, standardized, and previously tested methods of data collection that are planned ahead of time</p> <p>Use placebo group</p>
<b>Procedure bias</b>	Subjects in different groups are not treated the same	Patients in treatment group spend more time in highly specialized hospital units	Blinding (masking) and use of placebo reduce influence of participants and researchers on procedures and interpretation of outcomes as neither are aware of group assignments
<b>Observer-expectancy bias</b>	Researcher's belief in the efficacy of a treatment changes the outcome of that treatment (aka, Pygmalion effect)	An observer expecting treatment group to show signs of recovery is more likely to document positive outcomes	
<b>Interpreting results</b>			
<b>Confounding bias</b>	Factor related to both exposure and outcome (but not on causal path) distorts effect of exposure on outcome (vs effect modification, in which the exposure leads to different outcomes in subgroups stratified by the factor)	An uncontrolled study shows an association between drinking coffee and lung cancer; however, people who drink coffee may smoke more, which could account for the association	<p>Multiple/repeated studies</p> <p>Crossover studies (subjects act as their own controls)</p> <p>Matching (patients with similar characteristics in both treatment and control groups)</p>
<b>Lead-time bias</b>	Early detection interpreted as ↑ survival, but the disease course has not changed	Breast cancer diagnosed early by mammography may appear to exaggerate survival time because patients are known to have the cancer for longer	Measure “back-end” survival (adjust survival according to the severity of disease at the time of diagnosis)
<b>Length-time bias</b>	Screening test detects diseases with long latency period, while those with shorter latency period become symptomatic earlier	A slowly progressive cancer is more likely detected by a screening test than a rapidly progressive cancer	A randomized controlled trial assigning subjects to the screening program or to no screening

## Statistical distribution

<b>Measures of central tendency</b>	Mean = (sum of values)/(total number of values). Median = middle value of a list of data sorted from least to greatest. Mode = most common value.	Most affected by outliers (extreme values). If there is an even number of values, the median will be the average of the middle two values. Least affected by outliers.
<b>Measures of dispersion</b>	Standard deviation = how much variability exists in a set of values, around the mean of these values. Standard error = an estimate of how much variability exists in a (theoretical) set of sample means around the true population mean.	$\sigma = SD$ ; $n = \text{sample size}$ . Variance = $(SD)^2$ . $SE = \sigma/\sqrt{n}$ . $SE \downarrow$ as $n \uparrow$ .
<b>Normal distribution</b>	Gaussian, also called bell-shaped. Mean = median = mode. For normal distribution, mean is the best measure of central tendency.	

## Nonnormal distributions

<b>Bimodal</b>	Suggests two different populations (eg, metabolic polymorphism such as fast vs slow acetylators; age at onset of Hodgkin lymphoma; suicide rate by age).	
<b>Positive skew</b>	Typically, mean > median > mode. Asymmetry with longer tail on right.	
<b>Negative skew</b>	Typically, mean < median < mode. Asymmetry with longer tail on left.	

### Statistical hypothesis testing

<b>Null hypothesis (<math>H_0</math>)</b>	Hypothesis of no difference or relationship (eg, there is no association between the disease and the risk factor in the population).
<b>Alternative hypothesis (<math>H_1</math>)</b>	Hypothesis of some difference or relationship (eg, there is some association between the disease and the risk factor in the population).
<b>p-value</b>	The probability of obtaining test results at least as extreme as those observed during the test, assuming that $H_0$ is correct.

### Outcomes of statistical hypothesis testing

<b>Correct result</b>	Reality	
	$H_1$	$H_0$
Stating that there is an effect or difference when one exists ( $H_0$ rejected in favor of $H_1$ ).	Power ( $1 - \beta$ )	$\alpha$ Type I error
Stating that there is no effect or difference when none exists ( $H_0$ not rejected).	$\beta$ Type II error	

Blue shading = correct result. 

### Testing errors

<b>Type I error (<math>\alpha</math>)</b>	<p>Stating that there is an effect or difference when none exists (<math>H_0</math> incorrectly rejected in favor of <math>H_1</math>).</p> <p><math>\alpha</math> is the probability of making a type I error (usually 0.05 is chosen). If <math>p &lt; \alpha</math>, then assuming <math>H_0</math> is true, the probability of obtaining the test results would be less than the probability of making a type I error. <math>H_0</math> is therefore rejected as false.</p> <p>Statistical significance ≠ clinical significance.</p>	<p>Also called false-positive error.</p> <p>1st time boy cries wolf, the town believes there is a wolf, but there is not (false positive).</p> <p>You can never “prove” <math>H_1</math>, but you can reject the <math>H_0</math> as being very unlikely.</p>
<b>Type II error (<math>\beta</math>)</b>	<p>Stating that there is not an effect or difference when one exists (<math>H_0</math> is not rejected when it is in fact false).</p> <p><math>\beta</math> is the probability of making a type II error. <math>\beta</math> is related to statistical power (<math>1 - \beta</math>), which is the probability of rejecting <math>H_0</math> when it is false.</p> <p>↑ power and ↓ <math>\beta</math> by:</p> <ul style="list-style-type: none"> <li>■ ↑ sample size</li> <li>■ ↑ expected effect size</li> <li>■ ↑ precision of measurement</li> </ul>	<p>Also called false-negative error.</p> <p>2nd time boy cries wolf, the town believes there is no wolf, but there is one.</p> <p>If you ↑ sample size, you ↑ power. There is <b>power in numbers</b>.</p>

**Confidence interval**

Range of values within which the true mean of the population is expected to fall, with a specified probability.

$CI = 1 - \alpha$ . The 95% CI (corresponding to  $\alpha = 0.05$ ) is often used. As sample size increases, CI narrows.

CI for sample mean =  $\bar{x} \pm Z(SE)$

For the 95% CI,  $Z = 1.96$ .

For the 99% CI,  $Z = 2.58$ .

$H_0$  is rejected (and results are significant) when:

- 95% CI for mean difference excludes 0
- 95% CI OR or RR excludes 1
- CIs between two groups do not overlap

$H_0$  is accepted (and results are significant) when:

- 95% CI for mean difference includes 0
- 95% CI OR or RR includes 1
- CIs between two groups do overlap

**Meta-analysis**

A method of statistical analysis that pools summary data (eg, means, RRs) from multiple studies for a more precise estimate of the size of an effect. Also estimates heterogeneity of effect sizes between studies.

Improves power, strength of evidence, and generalizability (external validity) of study findings.  
Limited by quality of individual studies and bias in study selection.

**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 **O**f **V**Ariance.

Example: comparing the mean blood pressure between members of 3 different ethnic groups.

**Fisher's exact test**

Checks differences between 2 percentages or proportions of categorical, nominal outcomes. Use instead of chi-square test with small populations.

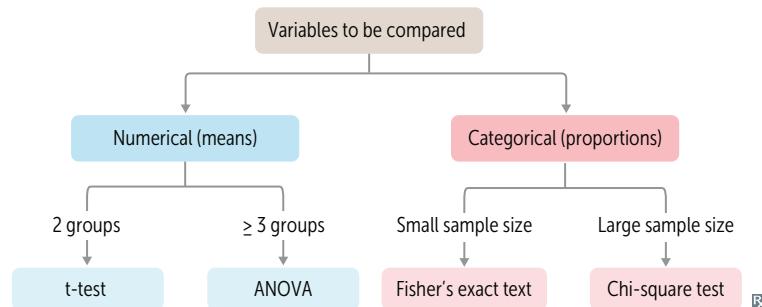
Example: comparing the percentage of 20 men and 20 women with hypertension.

**Chi-square ( $\chi^2$ )**

Checks differences between 2 or more percentages or proportions of **categorical** outcomes (not mean values).

Pronounce **chi-tegorical**.

Example: comparing the proportion of members of 3 age groups who have essential hypertension.



### Pearson correlation coefficient

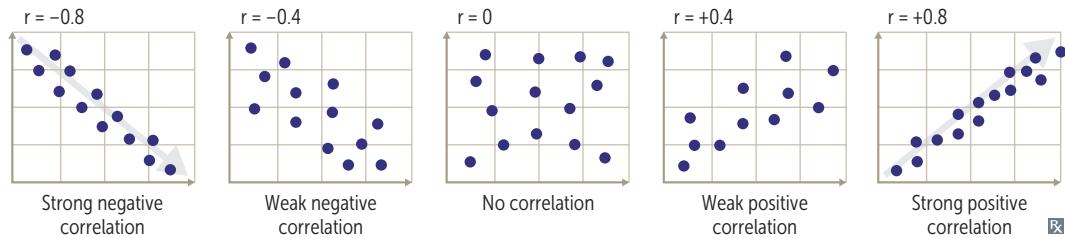
A measure of the linear correlation between two variables.  $r$  is always between  $-1$  and  $+1$ . The closer the absolute value of  $r$  is to  $1$ , the stronger the linear correlation between the 2 variables.

Variance is how much the measured values differ from the average value in a data set.

Positive  $r$  value → positive correlation (as one variable ↑, the other variable ↑).

Negative  $r$  value → negative correlation (as one variable ↑, the other variable ↓).

Coefficient of determination =  $r^2$  (amount of variance in one variable that can be explained by variance in another variable).



### ► PUBLIC HEALTH SCIENCES—ETHICS

#### Core ethical principles

##### Autonomy

Obligation to respect patients as individuals (truth-telling, confidentiality), to create conditions necessary for autonomous choice (informed consent), and to honor their preference in accepting or not accepting medical care.

##### Beneficence

Physicians have a special ethical (fiduciary) duty to act in the patient's best interest. May conflict with autonomy (an informed patient has the right to decide) or what is best for society (eg, mandatory TB treatment). Traditionally, patient interest supersedes.

##### Nonmaleficence

"Do no harm." Must be balanced against beneficence; if the benefits outweigh the risks, a patient may make an informed decision to proceed (most surgeries and medications fall into this category).

##### Justice

To treat persons fairly and equitably. This does not always imply equally (eg, triage).

**Decision-making capacity**

Physician must determine whether the patient is psychologically and legally capable of making a particular healthcare decision. Note that decisions made with capacity cannot be revoked simply if the patient later loses capacity. Intellectual disabilities and mental illnesses are not exclusion criteria for informed decision-making unless their condition presently impairs their ability to make healthcare decisions.

Capacity is determined by a physician for a specific healthcare-related decision (eg, to refuse medical care). Competency is determined by a judge and usually refers to more global categories of decision making (eg, legally unable to make any healthcare-related decision).

Components (assessing capacity) is of **MASSIVE** importance:

- Decision is not a result of **M**ental illness exacerbation
- Patient is  $\geq$  18 years of **A**ge or otherwise legally emancipated
- Decision is not a result of altered mental **S**tatus (eg, delirium, intoxication)
- Decision remains **S**table over time
- Patient is **I**nformed and understands
- Decision is consistent with patient's **V**alues and goals
- Patient **E**xpresses preferences

**Informed consent**

A process (not just a document/signature) that requires:

- Disclosure: discussion of pertinent information (using medical interpreter, if needed)
- 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 a comprehensive understanding of their diagnosis and the risks/benefits of proposed treatment and alternative options, including no treatment.

Patient must be informed of their right to revoke written consent at any time, even orally.

Exceptions to informed consent (**WIPE** it away):

- **Waiver**—patient explicitly relinquishes the right of informed consent
- Legally **I**ncompetent—patient lacks decision-making capacity (obtain consent from legal surrogate)
- Therapeutic **P**rivilege—withholding information when disclosure would severely harm the patient or undermine informed decision-making capacity
- **E**mergency situation—implied consent may apply

<b>Consent for minors</b>	A minor is generally any person < 18 years old. Parental consent laws in relation to healthcare vary by state. In general, parental consent should be obtained, but exceptions exist for emergency treatment (eg, blood transfusions) or if minor is legally emancipated (eg, married, self-supporting, or in the military).	Situations in which parental consent is usually not required: <ul style="list-style-type: none"><li>▪ <b>Sex</b> (contraception, STIs, prenatal care—usually not abortion)</li><li>▪ <b>Drugs</b> (substance use disorder treatment)</li><li>▪ <b>Rock and roll</b> (emergency/trauma)</li></ul> Physicians should always encourage healthy minor-guardian communication. Physician should seek a minor's assent (agreement of someone unable to legally consent) even if their consent is not required.
<b>Advance directives</b>	Instructions given by a patient in anticipation of the need for a medical decision. Details vary per state law.	
<b>Oral advance directive</b>	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.	
<b>Written advance directive</b>	Delineates specific healthcare interventions that patient anticipates accepting or rejecting during treatment for a critical or life-threatening illness. A living will is an example.	
<b>Medical power of attorney</b>	Patient designates an agent to make medical decisions in the event that the patient 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.	
<b>Do not resuscitate order</b>	DNR order prohibits cardiopulmonary resuscitation (CPR). Patient may still consider other life-sustaining measures (eg, intubation, feeding tube, chemotherapy).	
<b>Surrogate decision-maker</b>	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: <b>spouse</b> → adult <b>children</b> → <b>parents</b> → <b>siblings</b> → other relatives (the <b>spouse ChiPS</b> in).	

**Confidentiality**

Confidentiality respects patient privacy and autonomy. If the patient is incapacitated or the situation is emergent, disclosing information to family and friends should be guided by professional judgment of patient's best interest. The patient may voluntarily waive the right to confidentiality (eg, insurance company request).

General principles for exceptions to confidentiality:

- Potential physical harm to self or others is serious and imminent
- Alternative means to warn or protect those at risk is not possible
- Steps can be taken to prevent harm

Examples of exceptions to patient confidentiality (many are state specific) include the following (“The physician's good judgment **SAVED** the day”):

- Patients with **Suicidal/homicidal** ideation
- **Abuse** (children, elderly, and/or prisoners)
- Duty to protect—state-specific laws that sometimes allow physician to inform or somehow protect potential **Victim** from harm
- Patients with **Epilepsy** and other impaired automobile drivers
- Reportable **Diseases** (eg, STIs, hepatitis, food poisoning); physicians may have a duty to warn public officials, who will then notify people at risk. Dangerous communicable diseases, such as TB or Ebola, may require involuntary treatment.

**► PUBLIC HEALTH SCIENCES—COMMUNICATION SKILLS****Patient-centered interviewing techniques**

<b>Introduction</b>	Introduce yourself and address the patient by preferred name. Sit at eye-level near the patient.
<b>Agenda setting</b>	Identify concerns and set goals by developing joint agenda between the physician and the patient.
<b>Reflection</b>	Actively listen and synthesize information offered by the patient, particularly with respect to primary concern(s).
<b>Validation</b>	Legitimize or affirm the patient's perspectives.
<b>Recapitulation</b>	Summarize what the patient has said so far to ensure correct interpretation.
<b>Facilitation</b>	Encourage the patient to speak freely without guiding responses or leading questions. Allow the patient to ask questions throughout the encounter.

**Expressing empathy****PEARLS**

<b>Partnership</b>	Reassure the patient that you will work together through difficult times, and offer appropriate resources.
<b>Empathy</b>	Acknowledge the emotions displayed and demonstrate understanding of why the patient is feeling that way.
<b>Apology</b>	Take personal responsibility when appropriate, or offer condolences for the patient's situation.
<b>Respect</b>	Commend the patient for coming in to discuss a problem, pushing through challenging circumstances, keeping a positive attitude, or other constructive behaviors.
<b>Legitimization</b>	Assure the patient that emotional responses are understandable or common.
<b>Support</b>	Offer to help the patient through difficult times.

**Delivering bad news****SPIKES**

<b>Setting</b>	Offer in advance for the patient to bring support. Eliminate distractions, ensure privacy, and sit down with the patient to talk.
<b>Perception</b>	Determine the patient's understanding and expectations of the situation.
<b>Invitation</b>	Obtain the patient's permission to disclose the news and what level of detail is desired.
<b>Knowledge</b>	Share the information in small pieces without medical jargon, allowing time to process. Assess the patient's understanding.
<b>Emotions</b>	Acknowledge the patient's emotions, and provide opportunity to express them. Listen and offer empathetic responses.
<b>Strategy</b>	If the patient feels ready, discuss treatment options and goals of care. Offer an agenda for the next appointment.

**Gender- and sexuality-inclusive history taking**

Avoid making assumptions about sexual orientation, gender identity, gender expression, and behavior (eg, a patient who identifies as heterosexual may engage in same-sex sexual activity). Use gender-neutral terms (eg, refer to a patient's "partner" rather than assuming a spouse's gender). A patient's sex assigned at birth and gender identity may differ. Consider stating what pronouns you use when you introduce yourself (eg, "I'm Dr. Smith, and I use she/her pronouns") and asking patients how they would like to be addressed. Reassure them about the confidentiality of their appointments and be sensitive to the fact that patients may not be open about their sexual orientation or gender identity to others in their life. Do not bring up gender or sexuality if it is not relevant to the visit (eg, a gender-nonconforming patient seeking care for a hand laceration).

**Trauma-informed communication**

Patients with a history of a traumatic experience should receive thorough behavioral health screenings. Regularly assess mood, substance use, social supports, and suicide risk. Focus assessments on trauma-related symptoms that interfere with social and occupational function. Do not ask invasive questions requiring the patient to describe trauma in detail. Before the physical exam, reassure patients that they may signal to end it immediately if they experience too much physical or emotional discomfort. Offer the presence of additional staff for support.

**Motivational interviewing**

Counseling technique to facilitate behavior modification by helping patients resolve ambivalence about change. Useful for many conditions (eg, nicotine dependence, obesity). Helpful when patient has some desire to change, but it does not require that the patient be committed to making the change. May involve asking patients to examine how their behavior interferes with their life or why they might want to change it. Assess barriers (eg, food access, untreated trauma) that may make behavior change difficult.

Assessing a patient's readiness for change is also important for guiding physician-suggested goals. These goals should be **S**pecific, **M**easurable, **A**chievable, **R**elevant, and **T**ime bound (**SMART**).

**Communicating with patients with disabilities**

Use "person-first" language, which refers to "a person with a disability" rather than "a disabled person." Consider asking patients what terms they use to describe themselves. Under most circumstances, talk directly to the patient. Do not assume that nonverbal patients do not understand. Accompanying caregivers can add information to any discussion as needed. Ask if assistance is desired rather than assuming the patient cannot do something alone. Most people, including people with disabilities, value their independence. For patients with speech difficulties, provide extra time for the interview. If their speech is difficult to understand, consider asking them to write down a few words or ask them to rephrase their sentence. Repeat what they said to ensure you understood it correctly. For patients with a cognitive impairment, use concrete, specific language. Ask simple, direct questions. Eliminate background noise and distractions. Do not assume the patient can read. Adjust to how the patient understands best (eg, use hand gestures or ask them to demonstrate a task). Ask patients who are deaf or hard of hearing their preferred mode of communication. Use light touch or waving to get their attention. For patients who prefer to speak and lipread, eliminate background noise, face the patient, and do not change your mode of speaking. As with other parts of a medical history, do not bring up a disability if it is not relevant to a visit (eg, a patient in a wheelchair with an ear infection). Do not skip relevant parts of the physical exam even if the disability makes the exam challenging.

**Use of interpreters**

Visits with a patient who speaks little English should utilize a professionally trained medical interpreter unless the physician is also fluent in the patient's preferred language. Interpretation services may be provided in person, by telephone, or by video call. If the patient prefers to utilize a family member, this should be recorded in the chart. Do not assume that a patient is a poor English speaker because of name, skin tone, or accent. Ask the patient what language is preferred. The physician should make eye contact with the patient and speak to them normally, without use of third-person statements such as "tell him." Allow extra time for the interview, and ask one question at a time. For in-person spoken language interpretation, the interpreter should ideally be next to or slightly behind the patient. For sign language interpretation, the interpreter should be next to or slightly behind the physician.

### Challenging patient and ethical scenarios

The most appropriate response is usually one that is open ended, empathetic, and patient centered. It often honors one or more of the principles of autonomy, beneficence, nonmaleficence, and justice. Appropriate responses are respectful of patients and other members of the healthcare team.

SITUATION	APPROPRIATE RESPONSE
Patient is not adherent.	Determine whether there are financial, logistical, or other obstacles preventing the patient's adherence. Do not coerce the patient into adhering or refer the patient 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 to another physician. Avoid performing unnecessary procedures.
Patient has difficulty taking medications.	Determine what factors are involved in the patient's difficulties. If comprehension or memory are issues, use techniques such as providing written instructions, using the teach-back method, or simplifying treatment regimens.
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."	Explore why the family member believes this would be detrimental, including possible cultural factors. Explain that if the patient would like to know information concerning care, it will not be withheld. However, if you believe the patient might seriously harm self or others if informed, you may invoke therapeutic privilege and withhold the information.
A 17-year-old is pregnant and requests an abortion.	Many states require parental notification or consent for minors for an abortion. Unless there are specific medical risks associated with pregnancy, a physician should not sway the patient's decision for, or against, an elective abortion (regardless of patient's age or fetal condition). Discuss options for terminating the pregnancy and refer to abortion care, if needed.
A 15-year-old is pregnant and wants to raise 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 aspects of caring for a baby. Discuss options for terminating the pregnancy, if requested. Encourage discussion between the teenager and her parents to reach the best decision.
A terminally ill patient requests physician-assisted dying.	The overwhelming majority of states prohibit most forms of physician-assisted dying. Physicians may, however, prescribe medically appropriate analgesics even if they potentially shorten the patient's life.
Patient is suicidal.	Assess the seriousness of the threat. If patient is actively suicidal with a plan, suggest remaining in the hospital voluntarily; patient may be hospitalized involuntarily if needed.
Patient states that you are attractive and asks if you would go on a date.	Use a chaperone if necessary. Romantic relationships with patients are never appropriate. It may be necessary to transition care to another physician.
A woman who had a mastectomy says she now feels "ugly."	Find out why the patient feels this way. Do not offer falsely reassuring statements (eg, "You still look good").
Patient is angry about the long time spent in the waiting room.	Acknowledge the patient's anger, but do not take a patient's anger personally. Thank the patient for being patient and apologize for any inconvenience. Stay away from efforts to explain the delay.
Patient is upset with treatment received from another physician.	Suggest that the patient speak directly to that physician regarding the concern. 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.

**Challenging patient and ethical scenarios (*continued*)**

SITUATION	APPROPRIATE RESPONSE
A patient requires a treatment not covered by insurance.	Discuss all treatment options with patients, even if some are not covered by their insurance companies. Inform patient of financial assistance programs.
A 7-year-old boy loses a sister to cancer and now feels responsible.	At ages 5–7, children begin to understand that death is permanent, that all life functions end completely at death, and that everything that is alive eventually dies. Provide a direct, concrete description of his sister's death. Avoid clichés and euphemisms. Reassure the boy that he is not responsible. Identify and normalize fears and feelings. Encourage play and healthy coping behaviors (eg, remembering her in his own way).
Patient is victim of intimate partner violence.	Ask if patient is safe and help devise an emergency plan if there isn't one. Educate patient on intimate partner violence resources. Do not necessarily pressure patient to leave a partner or disclose the incident to the authorities (unless required by state law).
Patient wants to try alternative or holistic medicine.	Explore any underlying reasons with the patient in a supportive, nonjudgmental manner. Advise the patient of known benefits and risks of treatment, including adverse effects, contraindications, and medication interactions.
Physician colleague presents to work impaired.	This presents a potential risk to patient safety. You have an ethical and usually a legal obligation to report impaired colleagues so they can cease patient care and receive appropriate assistance in a timely manner. Seek guidance in reporting as procedures and applicable law vary by institution and state.
Patient is officially determined to suffer brain death. Patient's family insists on maintaining life support indefinitely because patient is still moving when touched.	Gently explain to family that there is no chance of recovery, and that brain death is equivalent to death. Movement is due to spinal arc reflex and is not voluntary. Bring case to appropriate ethics board regarding futility of care and withdrawal of life support.
A pharmaceutical company offers you a sponsorship in exchange for advertising its new drug.	Reject this offer. Generally, decline gifts and sponsorships to avoid any conflict of interest. The AMA Code of Ethics does make exceptions for gifts directly benefitting patients; special funding for medical education of students, residents, fellows; grants whose recipients are chosen by independent institutional criteria; and funds that are distributed without attribution to sponsors.
Patient requests a nonemergent procedure that is against your personal or religious beliefs.	Provide accurate and unbiased information so patients can make an informed decision. In a neutral, nonjudgmental manner, explain to the patient that you do not perform the procedure but offer to refer to another physician.
Mother and 15-year-old daughter are unresponsive following a car accident and are bleeding internally. Father says do not transfuse because they are Jehovah's Witnesses.	Transfuse daughter, but do not transfuse mother. Emergent care can be refused by the healthcare proxy for an adult, particularly when patient preferences are known or reasonably inferred, but not for a minor based solely on faith.
A dependent patient presents with injuries inconsistent with caretaker's story.	Document detailed history and physical. If possible and appropriate, interview the patient alone. Provide any necessary medical care. If suspicion remains, contact the appropriate agencies or authorities (eg, child or adult protective services) for an evaluation. Inform the caretaker of your obligation to report. Physicians are required by law to report any reasonable suspicion of abuse, neglect, or endangerment.
A pediatrician recommends standard vaccinations for a patient, but the child's parent refuses.	Address any concerns the parent has. Explain the risks and benefits of vaccinations and why they are recommended. Do not administer routine vaccinations without the parent's consent.

## ► PUBLIC HEALTH SCIENCES—HEALTHCARE DELIVERY

**Disease prevention**

<b>Primary disease prevention</b>	Prevent disease before it occurs (eg, HPV vaccination)
<b>Secondary disease prevention</b>	Screen early for and manage existing but asymptomatic disease (eg, Pap smear for cervical cancer)
<b>Tertiary disease prevention</b>	Treatment to reduce complications from disease that is ongoing or has long-term effects (eg, chemotherapy)
<b>Quaternary disease prevention</b>	Quit (avoid) unnecessary medical interventions to minimize incidental harm (eg, imaging studies, optimizing medications to reduce polypharmacy)

**Major medical insurance plans**

PLAN	PROVIDERS	PAYMENTS	SPECIALIST CARE
<b>Exclusive provider organization</b>	Restricted to limited panel (except emergencies)		No referral required
<b>Health maintenance organization</b>	Restricted to limited panel (except emergencies)	Most affordable	Requires referral from primary care provider
<b>Point of service</b>	Patient can see providers outside network	Higher copays and deductibles for out-of-network services	Requires referral from primary care provider
<b>Preferred provider organization</b>	Patient can see providers outside network	Higher copays and deductibles for all services	No referral required
<b>Accountable care organization</b>	Providers voluntarily enroll	Medicare	Specialists voluntarily enroll

**Healthcare payment models**

<b>Bundled payment</b>	Healthcare organization receives a set amount per service, regardless of ultimate cost, to be divided among all providers and facilities involved.
<b>Capitation</b>	Physicians receive a set amount per patient assigned to them per period of time, regardless of how much the patient uses the healthcare system. Used by some HMOs.
<b>Discounted fee-for-service</b>	Insurer and/or patient pays for each individual service at a discounted rate predetermined by providers and payers (eg, PPOs).
<b>Fee-for-service</b>	Insurer and/or patient pays for each individual service.
<b>Global payment</b>	Insurer and/or patient pays for all expenses associated with a single incident of care with a single payment. Most commonly used during elective surgeries, as it covers the cost of surgery as well as the necessary pre- and postoperative visits.

**Medicare and Medicaid**

Medicare and Medicaid—federal social healthcare programs that originated from amendments to the Social Security Act.

Medicare is available to patients ≥ 65 years old, < 65 with certain disabilities, and those with end-stage renal disease.

Medicaid is joint federal and state health assistance for people with limited income and/or resources.

Medicare is for Elderly.  
Medicaid is for Disadvantaged.

The 4 parts of Medicare:

- Part A: hospital Admissions, including hospice, skilled nursing
- Part B: Basic medical bills (eg, physician fees, diagnostic testing)
- Part C: (parts A + B = Combo) delivered by approved private companies
- Part D: prescription Drugs

**Hospice care**

Medical care focused on providing comfort and palliation instead of definitive cure. Available to patients on Medicare or Medicaid and in most private insurance plans whose life expectancy is < 6 months.

During end-of-life care, priority is given to improving the patient's comfort and relieving pain (often includes opioid, sedative, or anxiolytic medications). Facilitating comfort is prioritized over potential side effects (eg, respiratory depression). This prioritization of positive effects over negative effects is called the **principle of double effect**.

**Common causes of death (US) by age**

	<1 YR	1–14 YR	15–34 YR	35–44 YR	45–64 YR	65+ YR
#1	Congenital malformations	Unintentional injury	Unintentional injury	Unintentional injury	Cancer	Heart disease
#2	Preterm birth	Cancer	Suicide	Cancer	Heart disease	Cancer
#3	Pregnancy complications	Congenital malformations	Homicide	Heart disease	Unintentional injury	Chronic respiratory disease

## ► PUBLIC HEALTH SCIENCES—QUALITY AND SAFETY

**Safety culture**

Organizational environment in which everyone can freely bring up safety concerns without fear of penalty. Facilitates error identification.

Event reporting systems collect data on errors for internal and external monitoring.

**Human factors design**

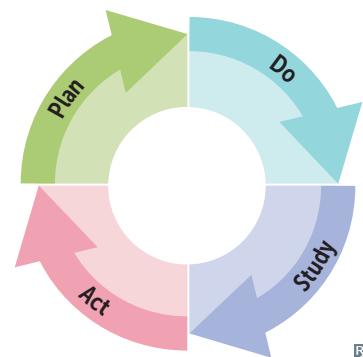
Forcing functions (those that prevent undesirable actions [eg, connecting feeding syringe to IV tubing]) are the most effective. Standardization improves process reliability (eg, clinical pathways, guidelines, checklists). Simplification reduces wasteful activities (eg, consolidating electronic medical records).

Deficient designs hinder workflow and lead to staff workarounds that bypass safety features (eg, patient ID barcodes affixed to computers due to unreadable wristbands).

**PDSA cycle**

Process improvement model to test changes in real clinical setting. Impact on patients:

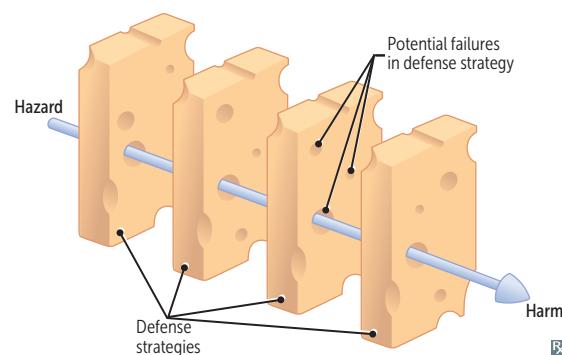
- **Plan**—define problem and solution
- **Do**—test new process
- **Study**—measure and analyze data
- **Act**—integrate new process into workflow

**Quality measurements**

	MEASURE	EXAMPLE
Structural	Physical equipment, resources, facilities	Number of diabetes educators
Process	Performance of system as planned	Percentage of patients with diabetes whose HbA <sub>1c</sub> was measured in the past 6 months
Outcome	Impact on patients	Average HbA <sub>1c</sub> of patients with diabetes
Balancing	Impact on other systems/outcomes	Incidence of hypoglycemia among patients who tried an intervention to lower HbA <sub>1c</sub>

**Swiss cheese model**

Focuses on systems and conditions rather than an individual's error. The risk of a threat becoming a reality is mitigated by differing layers and types of defenses. Patient harm can occur despite multiple safeguards when "the holes in the cheese line up."



<b>Types of medical errors</b>	May involve patient identification, diagnosis, monitoring, nosocomial infection, medications, procedures, devices, documentation, handoffs. Medical errors should be disclosed to patients, independent of immediate outcome (harmful or not).	
<b>Active error</b>	Occurs at level of frontline operator (eg, wrong IV pump dose programmed).	Immediate impact.
<b>Latent error</b>	Occurs in processes indirect from operator but impacts patient care (eg, different types of IV pumps used within same hospital).	Accident waiting to happen.
<b>Never event</b>	Adverse event that is identifiable, serious, and usually preventable (eg, scalpel retained in a surgical patient's abdomen).	Major error that should never occur.
<b>Near miss</b>	Unplanned event that does not result in harm but has the potential to do so (eg, pharmacist recognizes a medication interaction and cancels the order).	Narrow prevention of harm that exposes dangers.

**Burnout vs fatigue**

<b>Burnout</b>	Prolonged, excessive stress → cynicism, detachment, ↓ motivation and interest, sense of failure and helplessness, ↓ immunity. Medical errors due to reduced professional efficacy.
<b>Fatigue</b>	Sleep deprivation → ↓ energy and motivation, cognitive impairment. Medical errors due to compromised intellectual function.

**Medical error analysis**

	DESIGN	METHODS
<b>Root cause analysis</b>	Retrospective approach. Applied after failure event to prevent recurrence.	Uses records and participant interviews to identify all the underlying problems (eg, process, people, environment, equipment, materials, management) that led to an error.
<b>Failure mode and effects analysis</b>	Forward-looking approach. Applied before process implementation to prevent failure occurrence.	Uses inductive reasoning to identify all the ways a process might fail and prioritizes them by their probability of occurrence and impact on patients.

▶ NOTES

## SECTION III

# High-Yield Organ Systems

*“Symptoms, then, are in reality nothing but the cry from suffering organs.”*  
—Jean-Martin Charcot

*“Man is an intelligence in servitude to his organs.”*  
—Aldous Huxley

*“When every part of the machine is correctly adjusted and in perfect harmony, health will hold dominion over the human organism by laws as natural and immutable as the laws of gravity.”*

—Andrew T. Still

► Approaching the Organ Systems	284
► Cardiovascular	287
► Endocrine	333
► Gastrointestinal	367
► Hematology and Oncology	413
► Musculoskeletal, Skin, and Connective Tissue	455
► Neurology and Special Senses	503
► Psychiatry	575
► Renal	601
► Reproductive	635
► Respiratory	683

## ► 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.

While studying, emphasize 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; learn where and how they are synthesized, their regulatory mechanisms and sites of action.

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 recognize the clinical descriptions of these high-yield physical exam 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, alcohol use disorder, diabetes, hypertension, heart failure, ischemic heart disease, infectious disease). Be prepared to think one step beyond the simple diagnosis to treatment or complications.

The examination includes a number of color photomicrographs and photographs of gross specimens that are presented in the setting of a brief clinical history. However, read the question and the choices carefully before looking at the illustration, because the history will help you identify the pathologic process. Flip through an illustrated pathology textbook, color atlases, and appropriate Web sites in order to look at the pictures in the days before the exam. Pay attention to potential clues such as age, sex, ethnicity, occupation, recent activities and exposures, and specialized lab tests.

### Pharmacology

Preparation for questions on pharmacology is straightforward. Learning all the key drugs and their characteristics (eg, mechanisms, clinical use, and important side effects) is high yield. Focus on understanding the prototype drugs in each class. Avoid memorizing obscure derivatives. Learn the “classic” and distinguishing toxicities of the major drugs. Do not bother with drug dosages or brand 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.

▶ NOTES

# 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

*“The art of medicine has its roots in the heart.”*

—Paracelsus

*“It is not the size of the man but the size of his heart that matters.”*

—Evander Holyfield

► Embryology	288
► Anatomy	292
► Physiology	293
► Pathology	306
► Pharmacology	324

The cardiovascular system is one of the highest yield areas for the boards and, for some students, may be the most challenging. Focusing on understanding the mechanisms instead of memorizing the details can make a big difference, especially for this topic. Pathophysiology of atherosclerosis and heart failure, MOA of drugs (particular physiology interactions) and their adverse effects, ECGs of heart blocks, the cardiac cycle, and the Starling curve are some of the more high-yield topics. Differentiating between systolic and diastolic dysfunction is also very important. Heart murmurs and maneuvers that affect these murmurs have also been high yield and may be asked in a multimedia format.

## ► CARDIOVASCULAR—EMBRYOLOGY

**Heart morphogenesis** First functional organ in vertebrate embryos; beats spontaneously by week 4 of development.

**Cardiac looping**

Primary heart tube loops to establish left-right polarity; begins in week 4 of development.

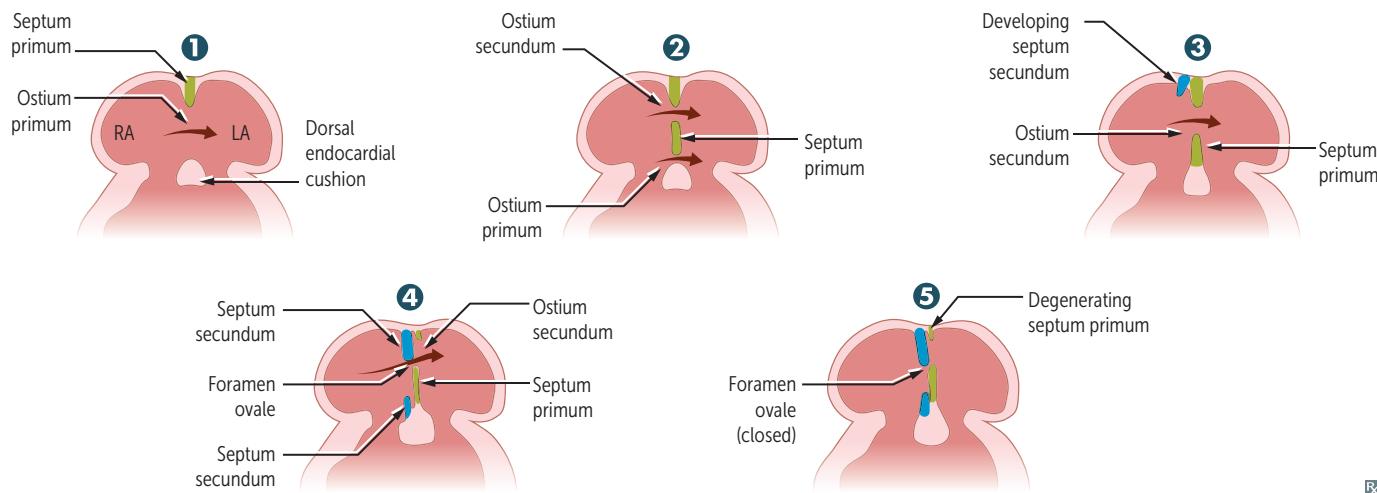
Defect in left-right dynein (involved in left-right asymmetry) can lead to dextrocardia, as seen in Kartagener syndrome.

**Septation of the chambers****Atria**

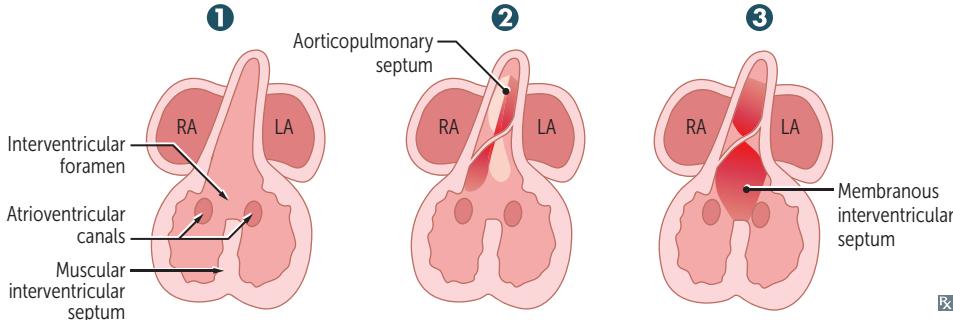
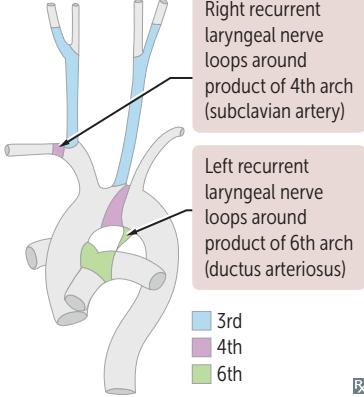
- ① Septum primum grows toward endocardial cushions, narrowing ostium primum.
- ② Ostium secundum forms in septum primum due to cell death (ostium primum regresses).
- ③ Septum secundum develops on the right side of septum primum, as ostium secundum maintains right-to-left shunt.
- ④ Septum secundum expands and covers most of ostium secundum. The residual foramen is the foramen ovale.
- ⑤ Remaining portion of septum primum forms the one-way valve of the foramen ovale.

6. Septum primum closes against septum secundum, sealing the foramen ovale soon after birth because of ↑ LA pressure and ↓ RA pressure.
7. Septum secundum and septum primum fuse during infancy/early childhood, forming the atrial septum.

**Patent foramen ovale**—caused by failure of septum primum and septum secundum to fuse after birth; most are left untreated. Can lead to paradoxical emboli (venous thromboemboli entering the systemic arterial circulation through right-to-left shunt) as can occur in atrial septal defect (ASD).

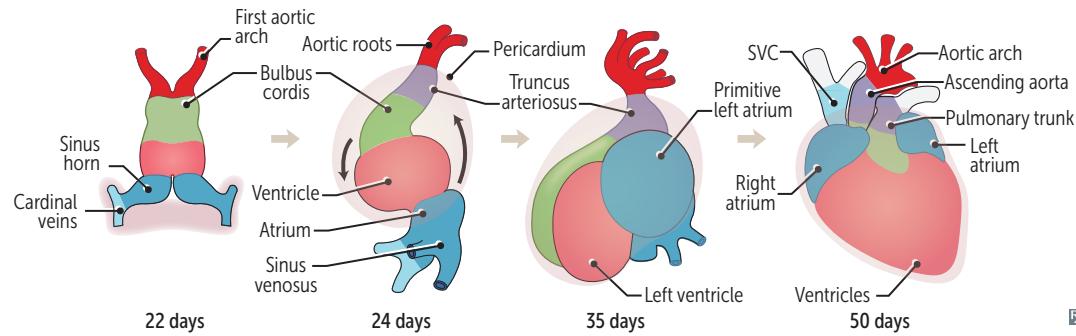


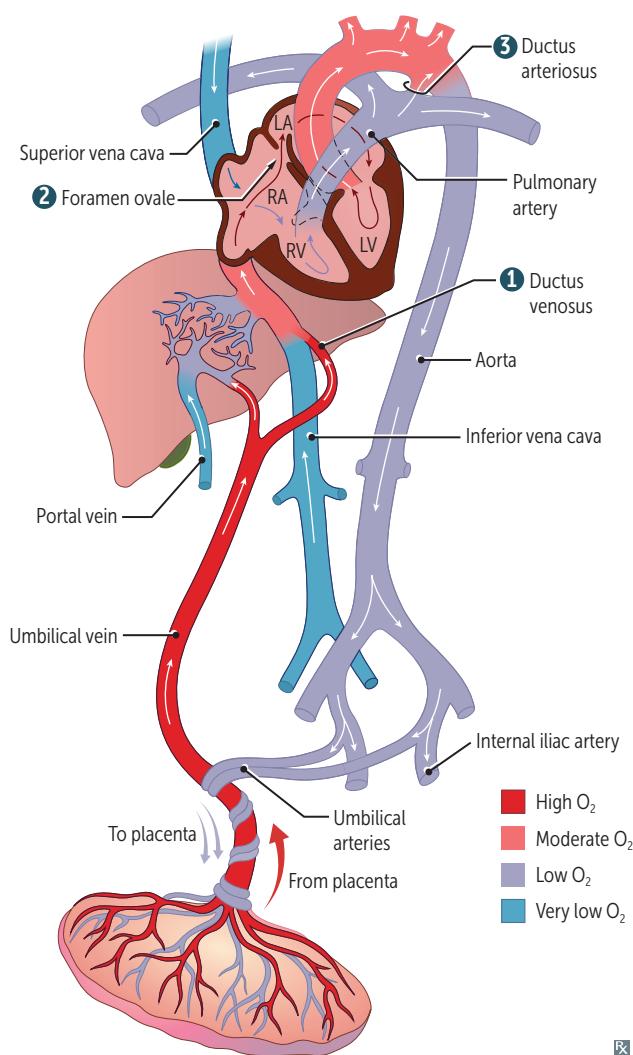
**Heart morphogenesis (continued)**

<b>Ventricles</b>	<p><b>1</b> Muscular interventricular septum forms. Opening is called interventricular foramen.</p> <p><b>2</b> Aorticopulmonary septum rotates and fuses with muscular ventricular septum to form membranous interventricular septum, closing interventricular foramen.</p> <p><b>3</b> Growth of endocardial cushions separates atria from ventricles and contributes to both atrial septation and membranous portion of the interventricular septum.</p>	<b>Ventricular septal defect</b> —most common congenital cardiac anomaly, usually occurs in membranous septum.
		
<b>Outflow tract formation</b>	Neural crest 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: <ul style="list-style-type: none"> <li>Transposition of great vessels.</li> <li>Tetralogy of Fallot.</li> <li>Persistent truncus arteriosus.</li> </ul>
<b>Valve development</b>	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).
<b>Aortic arch derivatives</b>	Develop into arterial system.	
<b>1st</b>	Part of <b>maxillary artery</b> (branch of external carotid). <b>1st</b> arch is <b>maximal</b> .	
<b>2nd</b>	<b>Stapedial artery</b> and hyoid artery. <b>Second</b> = <b>stapedial</b> .	
<b>3rd</b>	<b>Common carotid artery</b> and proximal part of <b>internal carotid artery</b> . <b>C</b> is <b>3rd</b> letter of alphabet.	
<b>4th</b>	On left, aortic arch; on right, proximal part of right subclavian artery. <b>4th</b> arch ( <b>4</b> limbs) = systemic.	
<b>6th</b>	Proximal part of pulmonary arteries and (on left only) <b>ductus arteriosus</b> . <b>6th</b> arch = pulmonary and the pulmonary-to-systemic shunt (ductus arteriosus).	

**Heart embryology**

EMBRYONIC STRUCTURE	GIVES RISE TO
Truncus arteriosus	Ascending aorta and pulmonary trunk
Bulbus cordis	Smooth parts (outflow tract) of left and right ventricles
Primitive ventricle	Trabeculated part of left and right ventricles
Primitive atrium	Trabeculated part of left and right atria
Left horn of sinus venosus	Coronary sinus
Right horn of sinus venosus	Smooth part of right atrium (sinus venarum)
Endocardial cushion	Atrial septum, membranous interventricular septum; AV and semilunar valves
Right common cardinal vein and right anterior cardinal vein	Superior vena cava (SVC)
Posterior, subcardinal, and supracardinal veins	Inferior vena cava (IVC)
Primitive pulmonary vein	Smooth part of left atrium



**Fetal circulation**

Blood in umbilical vein has a Po<sub>2</sub> of ≈ 30 mm Hg and is ≈ 80% saturated with O<sub>2</sub>. Umbilical arteries have low O<sub>2</sub> 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** into the left atrium.
- ③ Deoxygenated blood from the SVC passes through the RA → RV → main pulmonary artery → **ductus arteriosus** → descending aorta; shunt is due to high fetal pulmonary artery resistance.

At birth, infant takes a breath → ↓ resistance in pulmonary vasculature → ↑ left atrial pressure vs right atrial pressure → foramen ovale closes (now called fossa ovalis); ↑ in O<sub>2</sub> (from respiration) and ↓ in prostaglandins (from placental separation) → closure of ductus arteriosus.

Indomethacin helps close the patent ductus arteriosus → ligamentum arteriosum (remnant of ductus arteriosus). “Endomethacin” ends the PDA.

Prostaglandins E<sub>1</sub> and E<sub>2</sub> keep PDA open.

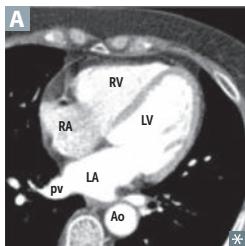
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**Fetal-postnatal derivatives**

FETAL STRUCTURE	POSTNATAL DERIVATIVE	NOTES
<b>Ductus arteriosus</b>	Ligamentum arteriosum	Near the left recurrent laryngeal nerve
<b>Ductus venosus</b>	Ligamentum venosum	
<b>Foramen ovale</b>	Fossa ovalis	
<b>Allantois → urachus</b>	Median umbilical ligament	Urachus is part of allantois between bladder and umbilicus
<b>Umbilical arteries</b>	Medial umbilical ligaments	
<b>Umbilical vein</b>	Ligamentum teres hepatitis (round ligament)	Contained in falciform ligament

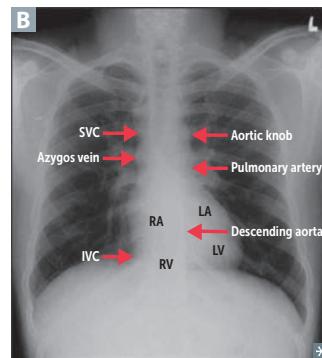
## ► CARDIOVASCULAR—ANATOMY

## Anatomy of the heart



LA is the most posterior part of the heart **A B**; enlargement of the LA (eg, in mitral stenosis) can lead to compression of the esophagus (dysphagia) and/or the left recurrent laryngeal nerve, a branch of the vagus nerve, causing hoarseness (**Ortner syndrome**).

RV is the most anterior part of the heart and most commonly injured in trauma.



## Pericardium

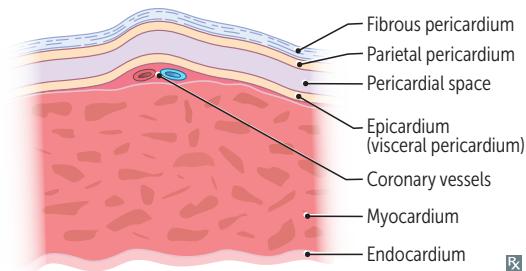
Consists of 3 layers (from outer to inner):

- Fibrous pericardium
- Parietal pericardium
- Epicardium (visceral pericardium)

Pericardial space lies between parietal pericardium and epicardium.

Pericardium innervated by phrenic nerve.

Pericarditis can cause referred pain to the neck, arms, or one or both shoulders (often left).



## Coronary blood supply

LAD and its branches supply anterior 2/3 of interventricular septum, anterolateral papillary muscle, and anterior surface of LV. Most commonly occluded.

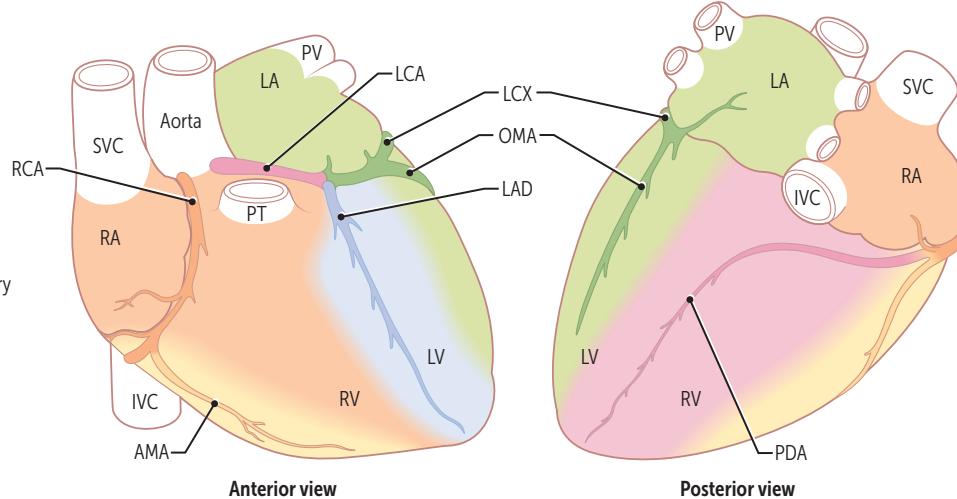
PDA supplies posterior 1/3 of interventricular septum, posterior 2/3 walls of ventricles, and posteromedial papillary muscle.

RCA supplies AV node and SA node. Infarct may cause nodal dysfunction (bradycardia or heart block). Right (acute) marginal artery supplies RV.

## Dominance:

- Right-dominant circulation (most common) = PDA arises from RCA
- Left-dominant circulation = PDA arises from LCX
- Codominant circulation = PDA arises from both LCX and RCA

Coronary blood flow to LV and interventricular septum peaks in early diastole.



## Key:

- AMA = Acute marginal artery
- LAD = Left anterior descending artery
- LCA = Left coronary artery
- LCX = Left circumflex artery
- OMA = Obtuse marginal artery
- PDA = Posterior descending artery
- PT = Pulmonary trunk
- PV = Pulmonary vein
- RCA = Right coronary artery

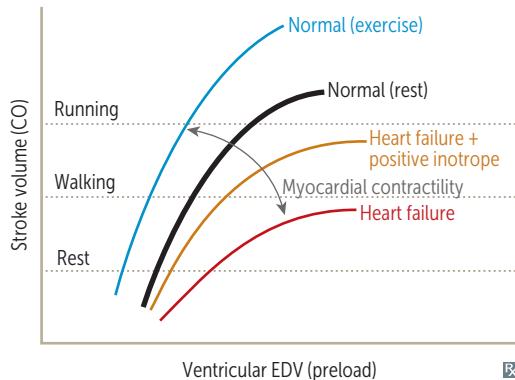
## ► CARDIOVASCULAR—PHYSIOLOGY

**Cardiac output variables**

<b>Stroke volume</b>	Stroke Volume affected by <b>Contractility</b> , <b>Afterload</b> , and <b>Preload</b> . ↑ SV with: <ul style="list-style-type: none"><li>▪ ↑ Contractility (eg, anxiety, exercise)</li><li>▪ ↑ Preload (eg, early pregnancy)</li><li>▪ ↓ Afterload</li></ul>	<b>SV CAP.</b> A failing heart has ↓ SV (systolic and/or diastolic dysfunction).
<b>Contractility</b>	Contractility (and SV) ↑ with: <ul style="list-style-type: none"><li>▪ Catecholamine stimulation via <math>\beta_1</math> receptor:<ul style="list-style-type: none"><li>▪ Activated protein kinase A<ul style="list-style-type: none"><li>→ phospholamban phosphorylation</li><li>→ active <math>\text{Ca}^{2+}</math> ATPase → ↑ <math>\text{Ca}^{2+}</math> storage in sarcoplasmic reticulum</li></ul></li><li>▪ Activated protein kinase A → <math>\text{Ca}^{2+}</math> channel phosphorylation → ↑ <math>\text{Ca}^{2+}</math> entry → ↑ <math>\text{Ca}^{2+}</math>-induced <math>\text{Ca}^{2+}</math> release</li><li>▪ ↑ intracellular <math>\text{Ca}^{2+}</math></li><li>▪ ↓ extracellular <math>\text{Na}^+</math> (↓ activity of <math>\text{Na}^+/\text{Ca}^{2+}</math> exchanger)</li><li>▪ Digoxin (blocks <math>\text{Na}^+/\text{K}^+</math> pump<ul style="list-style-type: none"><li>→ ↑ intracellular <math>\text{Na}^+</math> → ↓ <math>\text{Na}^+/\text{Ca}^{2+}</math> exchanger activity → ↑ intracellular <math>\text{Ca}^{2+}</math>)</li></ul></li></ul></li></ul>	Contractility (and SV) ↓ with: <ul style="list-style-type: none"><li>▪ <math>\beta_1</math>-blockade (↓ cAMP)</li><li>▪ HF with systolic dysfunction</li><li>▪ Acidosis</li><li>▪ Hypoxia/hypercapnia (↓ <math>\text{Po}_2</math>/↑ <math>\text{Pco}_2</math>)</li><li>▪ Nondihydropyridine <math>\text{Ca}^{2+}</math> channel blockers</li></ul>
<b>Preload</b>	Preload approximated by ventricular end-diastolic volume (EDV); depends on venous tone and circulating blood volume.	Vasodilators (eg, nitroglycerin) ↓ preload.
<b>Afterload</b>	Afterload approximated by MAP. ↑ wall tension per Laplace's law → ↑ pressure → ↑ afterload.  LV compensates for ↑ afterload by thickening (hypertrophy) in order to ↓ wall stress.	Arterial vasodilators (eg, hydralazine) ↓ afterload. ACE inhibitors and ARBs ↓ both preload and afterload. Chronic hypertension (↑ MAP) → LV hypertrophy.  Wall tension follows Laplace's law: Wall tension = pressure × radius Wall stress $\propto \frac{\text{pressure} \times \text{radius}}{2 \times \text{wall thickness}}$
<b>Myocardial oxygen demand</b>	Myocardial $\text{O}_2$ demand is ↑ by: <ul style="list-style-type: none"><li>▪ ↑ contractility</li><li>▪ ↑ afterload (proportional to arterial pressure)</li><li>▪ ↑ heart rate</li><li>▪ ↑ diameter of ventricle (↑ wall tension)</li></ul>	

**Cardiac output equations**

	EQUATION	NOTES
<b>Stroke volume</b>	$SV = EDV - ESV$	$ESV =$ end-systolic volume.
<b>Ejection fraction</b>	$EF = \frac{SV}{EDV} = \frac{EDV - ESV}{EDV}$	$EF$ is an index of ventricular contractility ( $\downarrow$ in systolic HF; usually normal in diastolic HF).
<b>Cardiac output</b>	$CO = SV \times HR$	In early stages of exercise, CO maintained by $\uparrow$ HR and $\uparrow$ SV. In later stages, CO maintained by $\uparrow$ HR only (SV plateaus). Diastole is shortened with $\uparrow\uparrow$ HR (eg, ventricular tachycardia) $\rightarrow \downarrow$ diastolic filling time $\rightarrow \downarrow$ SV $\rightarrow \downarrow$ CO.
<b>Pulse pressure</b>	$PP = \text{systolic blood pressure (SBP)} - \text{diastolic blood pressure (DBP)}$	PP directly proportional to SV and inversely proportional to arterial compliance. $\uparrow$ PP in hyperthyroidism, aortic regurgitation, aortic stiffening (isolated systolic hypertension in elderly), obstructive sleep apnea ( $\uparrow$ sympathetic tone), anemia, exercise (transient). $\downarrow$ PP in aortic stenosis, cardiogenic shock, cardiac tamponade, advanced HF.
<b>Mean arterial pressure</b>	$MAP = CO \times \text{total peripheral resistance (TPR)}$	$MAP$ (at resting HR) = $2/3 DBP + 1/3 SBP = DBP + 1/3 PP$ .

**Starling curves**

Force of contraction is proportional to end-diastolic length of cardiac muscle fiber (preload).

$\uparrow$  contractility with catecholamines, positive inotropes (eg, dobutamine, milrinone, digoxin).  
 $\downarrow$  contractility with loss of functional myocardium (eg, MI),  $\beta$ -blockers (acutely), nondihydropyridine  $\text{Ca}^{2+}$  channel blockers, HF.

### Resistance, pressure, flow

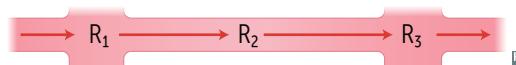
Volumetric flow rate ( $Q$ ) = flow velocity ( $v$ )  $\times$  cross-sectional area ( $A$ )

Resistance

$$= \frac{\text{driving pressure } (\Delta P)}{Q} = \frac{8\eta \text{ (viscosity)} \times \text{length}}{\pi r^4}$$

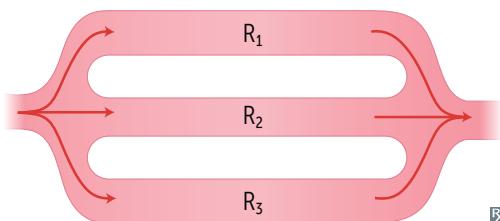
Total resistance of vessels in series:

$$R_T = R_1 + R_2 + R_3 \dots$$



Total resistance of vessels in parallel:

$$\frac{1}{R_T} = \frac{1}{R_1} + \frac{1}{R_2} + \frac{1}{R_3} \dots$$



$$Q \propto r^4$$

$$R \propto 1/r^4$$

Capillaries have highest total cross-sectional area and lowest flow velocity.

Pressure gradient drives flow from high pressure to low pressure.

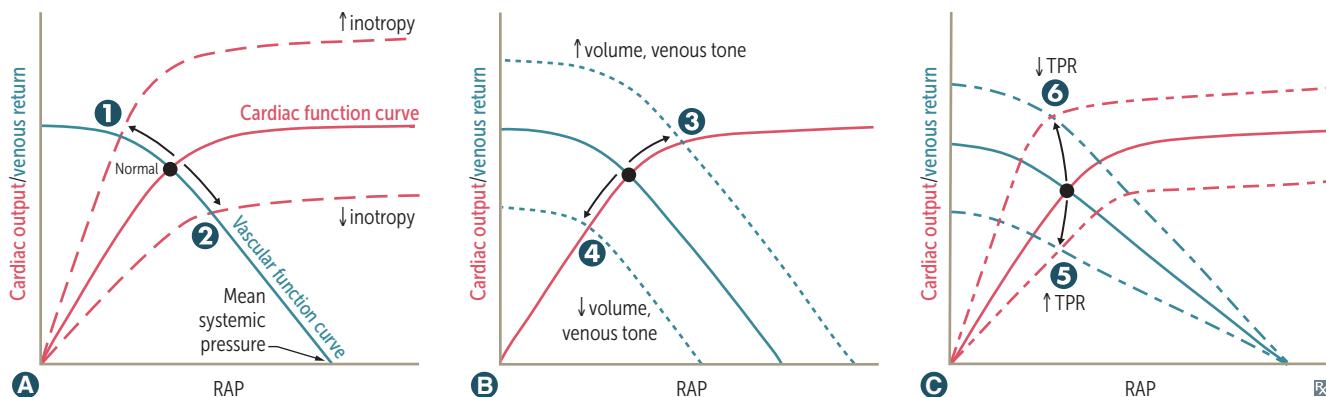
Arterioles account for most of TPR. Veins provide most of blood storage capacity.

Viscosity depends mostly on hematocrit.

Viscosity  $\uparrow$  in hyperproteinemic states (eg, multiple myeloma), polycythemia.

Viscosity  $\downarrow$  in anemia.

### Cardiac and vascular function curves

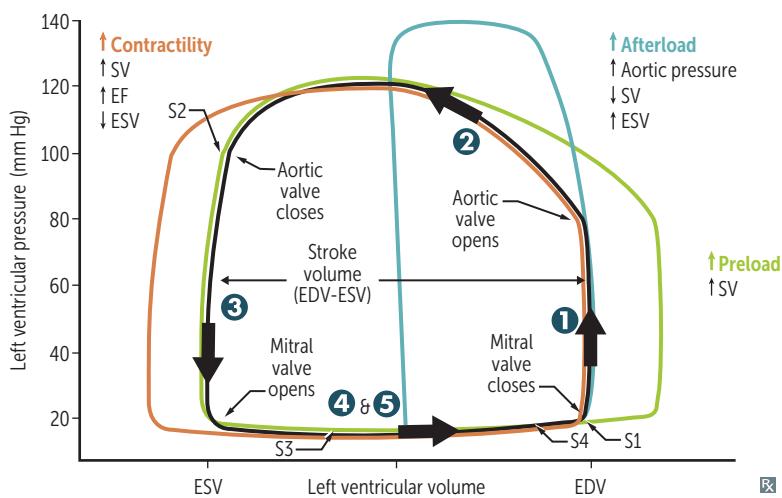


Intersection of curves = operating point of heart (ie, venous return and CO are equal, as circulatory system is a closed system).

GRAPH	EFFECT	EXAMPLES
<b>A Inotropy</b>	Changes in contractility $\rightarrow$ altered SV $\rightarrow$ altered CO/VR and RA pressure (RAP)	<ul style="list-style-type: none"> <li>① Catecholamines, dobutamine, milrinone, digoxin, exercise <math>\oplus</math></li> <li>② HF with reduced EF, narcotic overdose, sympathetic inhibition <math>\ominus</math></li> </ul>
<b>B Venous return</b>	Changes in circulating volume $\rightarrow$ altered RAP $\rightarrow$ altered SV $\rightarrow$ change in CO	<ul style="list-style-type: none"> <li>③ Fluid infusion, sympathetic activity <math>\oplus</math></li> <li>④ Acute hemorrhage, spinal anesthesia <math>\ominus</math></li> </ul>
<b>C Total peripheral resistance</b>	Changes in TPR $\rightarrow$ altered CO Change in RAP unpredictable	<ul style="list-style-type: none"> <li>⑤ Vasopressors <math>\oplus</math></li> <li>⑥ Exercise, arteriovenous shunt <math>\ominus</math></li> </ul>

Changes often occur in tandem, and may be reinforcing (eg, exercise  $\uparrow$  inotropy and  $\downarrow$  TPR to maximize CO) or compensatory (eg, HF  $\downarrow$  inotropy  $\rightarrow$  fluid retention to  $\uparrow$  preload to maintain CO).

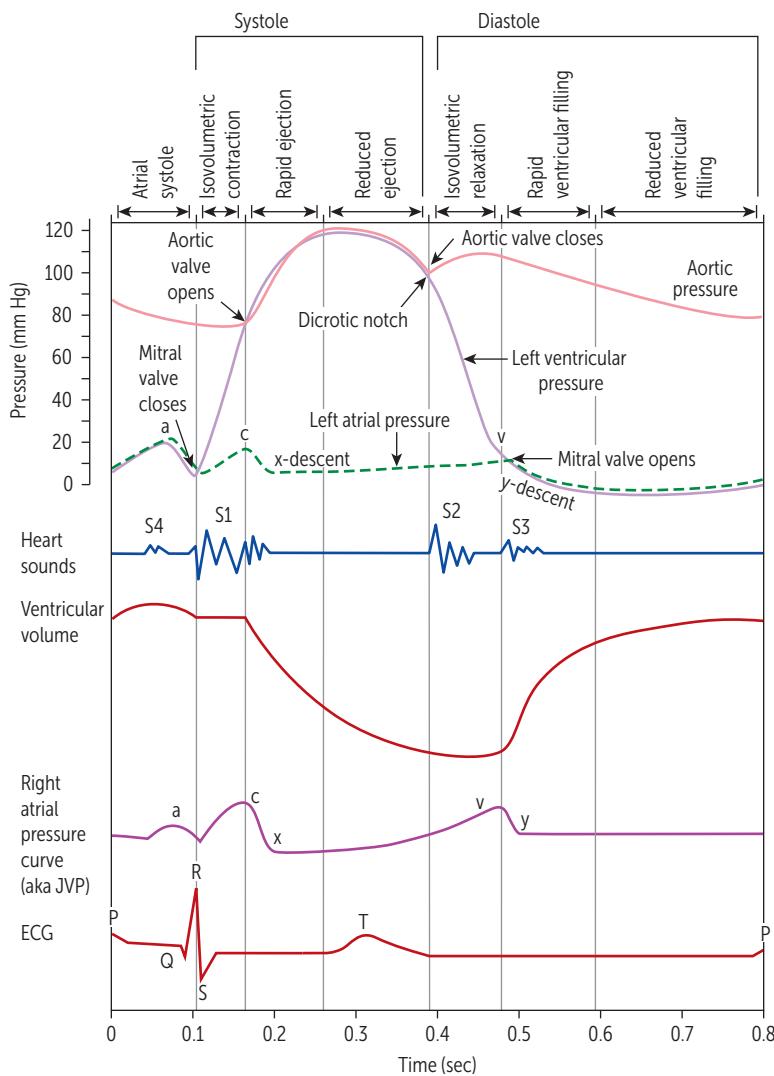
### Pressure-volume loops and cardiac cycle



The black loop represents normal cardiac physiology.

Phases—left ventricle:

- ❶ Isovolumetric contraction—period between mitral valve closing and aortic valve opening; period of highest O<sub>2</sub> consumption
- ❷ Systolic ejection—period between aortic valve opening and closing
- ❸ Isovolumetric relaxation—period between aortic valve closing and mitral valve opening
- ❹ Rapid filling—period just after mitral valve opening
- ❺ Reduced filling—period just before mitral valve closing



Heart sounds:

S1—mitral and tricuspid valve closure. Loudest at mitral area.

S2—aortic and pulmonary valve closure. Loudest at left upper sternal border.

S3—in early diastole during rapid ventricular filling phase. Best heard at apex with patient in left lateral decubitus position. Associated with ↑ filling pressures (eg, MR, AR, HF, thyrotoxicosis) and more common in dilated ventricles (but can be normal in children, young adults, athletes, and pregnancy). Turbulence caused by blood from LA mixing with ↑ ESV.

S4—in late diastole (“atrial kick”). Turbulence caused by blood entering stiffened LV. Best heard at apex with patient in left lateral decubitus position. High atrial pressure. Associated with ventricular noncompliance (eg, hypertrophy). Can be normal in older adults. Considered abnormal if palpable.

Jugular venous pulse (JVP):

**a** wave—atrial contraction. Absent in atrial fibrillation.

**c** wave—RV contraction (**c**losed tricuspid valve bulging into atrium).

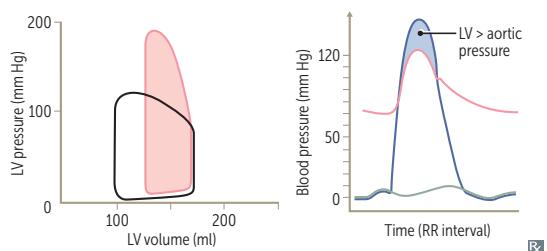
**x** descent—atrial relaxation and downward displacement of closed tricuspid valve during rapid ventricular ejection phase. Reduced or absent in tricuspid regurgitation and right HF because pressure gradients are reduced.

**v** wave—↑ RA pressure due to ↑ volume against closed tricuspid valve.

**y** descent—RA emptying into RV. Prominent in constrictive pericarditis, absent in cardiac tamponade.

### Pressure-volume loops and valvular disease

#### Aortic stenosis



↑ LV pressure

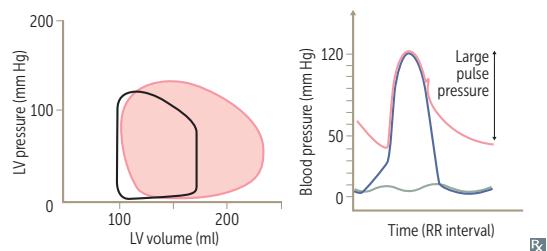
↑ ESV

No change in EDV (if mild)

↓ SV

Ventricular hypertrophy → ↓ ventricular compliance → ↑ EDP for given EDV

#### Aortic regurgitation



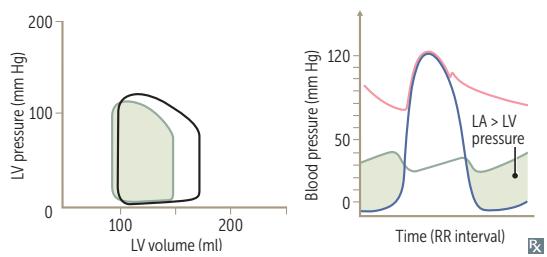
No true isovolumetric phase

↑ EDV

↑ SV

Loss of dicrotic notch

#### Mitral stenosis



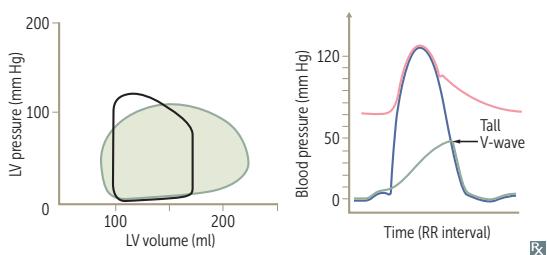
↑ LA pressure

↓ EDV because of impaired ventricular filling

↓ ESV

↓ SV

#### Mitral regurgitation



No true isovolumetric phase

↓ ESV due to ↓ resistance and

↑ regurgitation into LA during systole

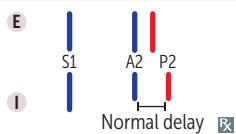
↑ EDV due to ↑ LA volume/pressure from regurgitation → ↑ ventricular filling

↑ SV (forward flow into systemic circulation plus backflow into LA)

### Splitting of S2

#### Physiologic splitting

Inspiration → drop in intrathoracic pressure  
 → ↑ venous return → ↑ RV filling → ↑ RV stroke volume → ↑ RV ejection time  
 → delayed closure of pulmonic valve.  
 ↓ pulmonary impedance (↑ capacity of the pulmonary circulation) also occurs during inspiration, which contributes to delayed closure of pulmonic valve.

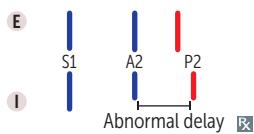


E = Expiration

I = Inspiration

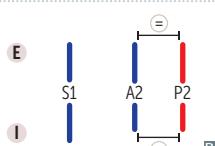
#### Wide splitting

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.



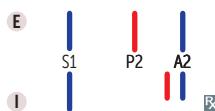
#### Fixed splitting

Heard in ASD. ASD → left-to-right shunt  
 → ↑ RA and RV volumes → ↑ flow through pulmonic valve → delayed pulmonic valve closure (independent of respiration).

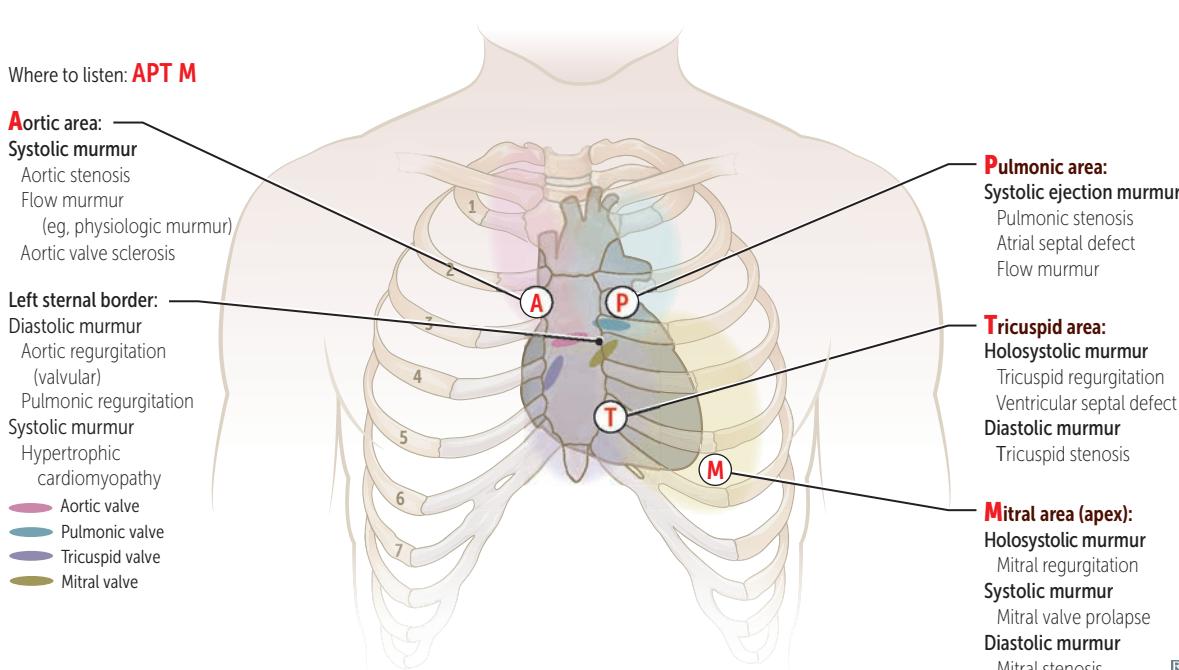


#### Paradoxical splitting

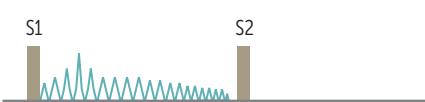
Heard in conditions that delay aortic valve closure (eg, aortic stenosis, left bundle branch block). Normal order of semilunar valve closure is reversed: in paradoxical splitting P2 occurs before A2. On inspiration, P2 closes later and moves closer to A2, “paradoxically” eliminating the split. On expiration, the split can be heard (opposite to physiologic splitting).



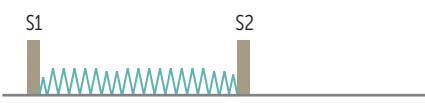
## Auscultation of the heart



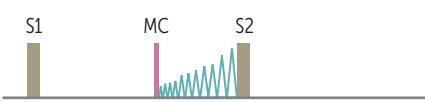
MANEUVER	CARDIOVASCULAR CHANGES	MURMURS THAT INCREASE WITH MANEUVER	MURMURS THAT DECREASE WITH MANEUVER
Standing Valsalva (strain phase)	↓ preload (↓ LV volume)	MVP (↓ LV volume) with earlier midsystolic click HCM (↓ LV volume)	Most murmurs (↓ flow through stenotic or regurgitant valve)
Passive leg raise	↑ preload (↑ LV volume)		MVP (↑ LV volume) with later midsystolic click
Squatting	↑ preload, ↑ afterload (↑ LV volume)	Most murmurs (↑ flow through stenotic or regurgitant valve)	HCM (↑ LV volume)
Hand grip	↑↑ afterload → ↑ reverse flow across aortic valve (↑ LV volume)	Most other left-sided murmurs (AR, MR, VSD)	AS (↓ transaortic valve pressure gradient) HCM (↑ LV volume)
Inspiration	↑ venous return to right heart, ↓ venous return to left heart	Most right-sided murmurs	Most left-sided murmurs

**Heart murmurs****Systolic****Aortic stenosis**

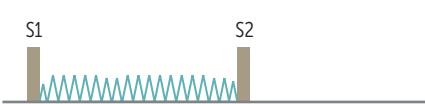
Crescendo-decrescendo systolic ejection murmur and soft S2 (ejection click may be present). LV >> aortic pressure during systole. Loudest at heart base; radiates to carotids. “Pulsus parvus et tardus”—pulses are weak with a delayed peak. Can lead to **Syncope**, **Angina**, and **Dyspnea** on exertion (**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**

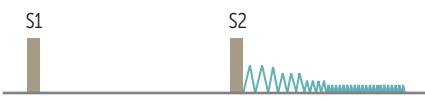
Holosystolic, high-pitched “blowing murmur.”  
Mitral—loudest at apex and radiates toward axilla. MR is often due to ischemic heart disease (post-MI), MVP, LV dilatation.  
Tricuspid—loudest at tricuspid area. TR commonly caused by RV dilatation.  
Rheumatic fever and infective endocarditis can cause either MR or TR.

**Mitral valve prolapse**

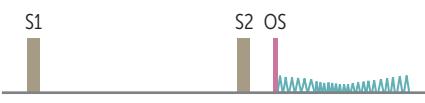
Late systolic crescendo murmur with midsystolic click (MC) due to sudden tensing of chordae tendineae as mitral leaflets prolapse into the LA (click cause crescendo with click). Best heard over apex. Loudest just before S2. Usually benign. Can predispose to infective endocarditis. Can be caused by myxomatous degeneration (1° or 2° to connective tissue disease such as Marfan or Ehlers-Danlos syndrome), rheumatic fever (particularly in developing countries), chordae rupture.

**Ventricular septal defect**

Holosystolic, harsh-sounding murmur. Loudest at tricuspid area. Larger VSDs have a lower intensity murmur than smaller VSDs.

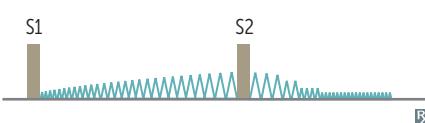
**Diastolic****Aortic regurgitation**

High-pitched “blowing” early diastolic decrescendo murmur. Best heard at base (aortic root dilation) or left sternal border (valvular disease). Long diastolic murmur, hyperdynamic pulse, and head bobbing when severe and chronic. Wide pulse pressure. Causes include **Bicuspid** aortic valve, **Endocarditis**, **Aortic** root dilation, **Rheumatic** fever (**BEAR**). 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 mid-to-late diastolic murmur (↓ interval between S2 and OS correlates with ↑ severity). LA >> LV pressure during diastole.

Often a late (and highly specific) sequela of rheumatic fever. Chronic MS can result in pulmonary congestion/hypertension and LA dilation → atrial fibrillation and Ortner syndrome.

**Continuous****Patent ductus arteriosus**

Continuous **machine**-like murmur. Best heard at left infraclavicular area. Loudest at S2. Often due to congenital rubella or prematurity.

You need a **patent** for that **machine**.

Rx

## Myocardial action potential

**Phase 0** = rapid upstroke and depolarization—voltage-gated  $\text{Na}^+$  channels open.

**Phase 1** = initial repolarization—inactivation of voltage-gated  $\text{Na}^+$  channels. Voltage-gated  $\text{K}^+$  channels begin to open.

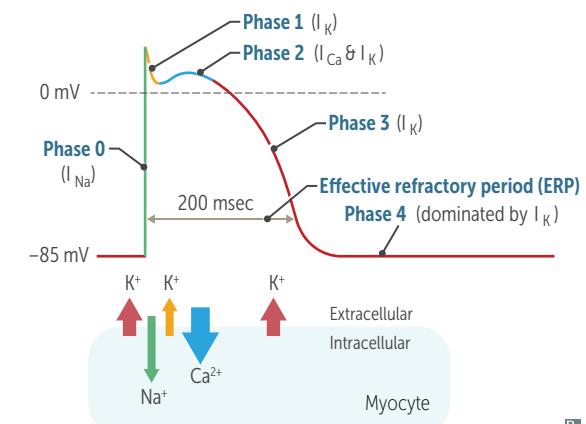
**Phase 2** = plateau— $\text{Ca}^{2+}$  influx through voltage-gated  $\text{Ca}^{2+}$  channels balances  $\text{K}^+$  efflux.  $\text{Ca}^{2+}$  influx triggers  $\text{Ca}^{2+}$  release from sarcoplasmic reticulum and myocyte contraction (excitation-contraction coupling).

**Phase 3** = rapid repolarization—massive  $\text{K}^+$  efflux due to opening of voltage-gated slow delayed-rectifier  $\text{K}^+$  channels and closure of voltage-gated  $\text{Ca}^{2+}$  channels.

**Phase 4** = resting potential—high  $\text{K}^+$  permeability through  $\text{K}^+$  channels.

In contrast to skeletal muscle:

- Cardiac muscle action potential has a plateau due to  $\text{Ca}^{2+}$  influx and  $\text{K}^+$  efflux.
- Cardiac muscle contraction requires  $\text{Ca}^{2+}$  influx from ECF to induce  $\text{Ca}^{2+}$  release from sarcoplasmic reticulum ( $\text{Ca}^{2+}$ -induced  $\text{Ca}^{2+}$  release).
- Cardiac myocytes are electrically coupled to each other by gap junctions.



Occurs in all cardiac myocytes except for those in the SA and AV nodes.

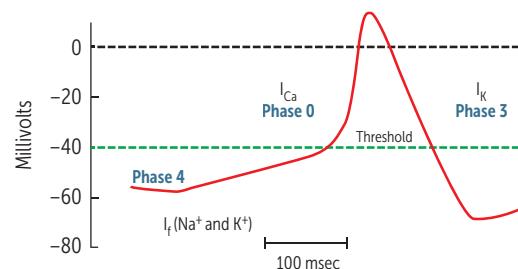
## Pacemaker action potential

Occurs in the SA and AV nodes. Key differences from the ventricular action potential include:

**Phase 0** = upstroke—opening of voltage-gated  $\text{Ca}^{2+}$  channels. Fast voltage-gated  $\text{Na}^+$  channels are permanently inactivated because of the less negative resting potential of these cells. Results in a slow conduction velocity that is used by the AV node to prolong transmission from the atria to ventricles. Phases 1 and 2 are absent.

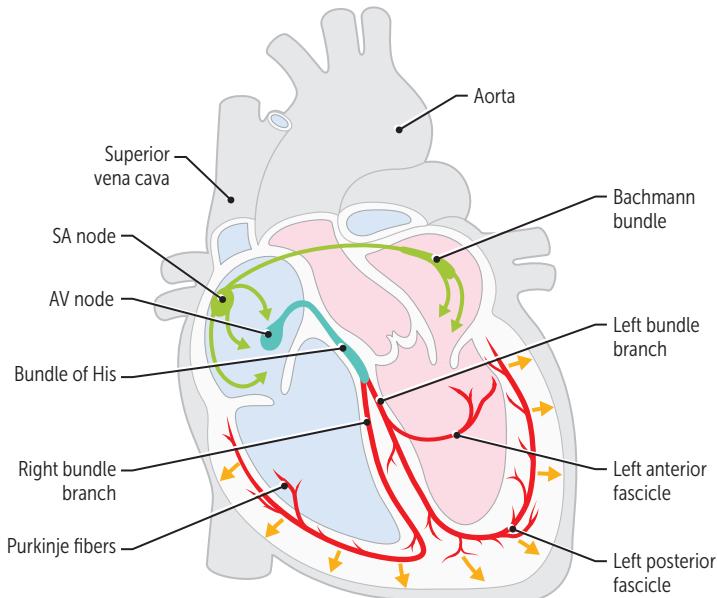
**Phase 3** = repolarization—inactivation of the  $\text{Ca}^{2+}$  channels and ↑ activation of  $\text{K}^+$  channels → ↑  $\text{K}^+$  efflux.

**Phase 4** = slow spontaneous diastolic depolarization due to  $I_f$  (“funny current”).  $I_f$  channels responsible for a slow, mixed  $\text{Na}^+/\text{K}^+$  inward current; different from  $I_{\text{Na}}$  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 ↓ the rate of diastolic depolarization and ↓ HR, while catecholamines ↑ depolarization and ↑ HR. Sympathetic stimulation ↑ the chance that  $I_f$  channels are open and thus ↑ HR.

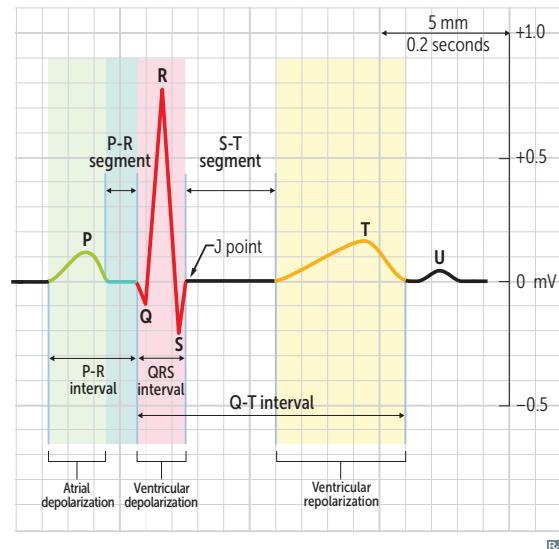


**Electrocardiogram**

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—located at junction of RA and SVC;  
 “pacemaker” inherent dominance with slow phase of upstroke.  
 AV node—located in posteroinferior part of interatrial septum. Blood supply usually from RCA. 100-msec delay allows time for ventricular filling.  
 Pacemaker rates: SA > AV > bundle of His/Purkinje/ventricles.  
 Speed of conduction: **His-Purkinje > Atria > Ventricles > AV node.** **He Parks At Ventura AVenue.**



P wave—atrial depolarization.  
 PR interval—time from start of atrial depolarization to start of ventricular depolarization (normally 120-200 msec).  
 QRS complex—ventricular depolarization (normally < 100 msec).  
 QT interval—ventricular depolarization, mechanical contraction of the ventricles, ventricular repolarization.  
 T wave—ventricular repolarization. T-wave inversion may indicate ischemia or recent MI.  
 J point—junction between end of QRS complex and start of ST segment.  
 ST segment—iselectric, ventricles depolarized.  
 U wave—prominent in hypokalemia (think hyp“U”kalemia), bradycardia.

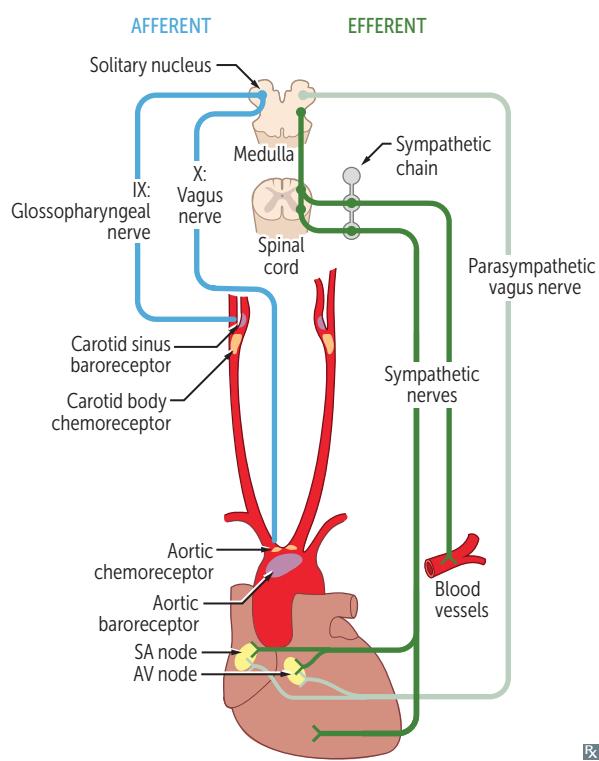


**Atrial natriuretic peptide**

Released from **atrial myocytes** in response to ↑ blood volume and atrial pressure. Acts via cGMP. Causes vasodilation and ↓  $\text{Na}^+$  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 ↑ tension. Similar physiologic action to ANP, with longer half-life. BNP blood test used for diagnosing HF (very good negative predictive value). Available in recombinant form (nesiritide) for treatment of HF.

**Baroreceptors and chemoreceptors****Receptors:**

- Aortic arch transmits via vagus nerve to solitary nucleus of medulla (responds to changes in BP).
- Carotid sinus (dilated region superior to bifurcation of carotid arteries) transmits via glossopharyngeal nerve to solitary nucleus of medulla (responds to changes in BP).

**Chemoreceptors:**

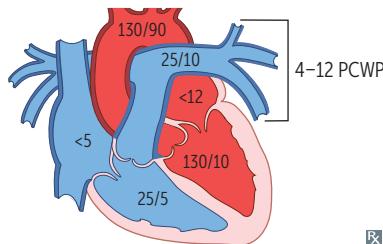
- Peripheral—carotid and aortic bodies are stimulated by ↑  $\text{PCO}_2$ , ↓ pH of blood, and ↓  $\text{PO}_2$  (< 60 mm Hg).
- Central—are stimulated by changes in pH and  $\text{PCO}_2$  of brain interstitial fluid, which in turn are influenced by arterial  $\text{CO}_2$  as  $\text{H}^+$  cannot cross the blood-brain barrier. Do not directly respond to  $\text{PO}_2$ . Central chemoreceptors become less responsive with chronically ↑  $\text{PCO}_2$  (eg, COPD) → ↑ dependence on peripheral chemoreceptors to detect ↓  $\text{O}_2$  to drive respiration.

**Baroreceptors:**

- Hypotension—↓ arterial pressure → ↓ stretch → ↓ afferent baroreceptor firing → ↑ efferent sympathetic firing and ↓ efferent parasympathetic stimulation → vasoconstriction, ↑ HR, ↑ contractility, ↑ BP. Important in the response to severe hemorrhage.
- Carotid massage—↑ pressure on carotid sinus → ↑ stretch → ↑ afferent baroreceptor firing → ↑ AV node refractory period → ↓ HR.
- Component of Cushing reflex (triad of hypertension, bradycardia, and respiratory depression)—↑ intracranial pressure constricts arterioles → cerebral ischemia → ↑  $\text{pCO}_2$  and ↓ pH → central reflex sympathetic ↑ in perfusion pressure (hypertension) → ↑ stretch → peripheral reflex baroreceptor-induced bradycardia.

**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).



Rx

**Autoregulation**

How blood flow to an organ remains constant over a wide range of perfusion pressures.

ORGAN	FACTORS DETERMINING AUTOREGULATION	
Lungs	Hypoxia causes vasoconstriction	The pulmonary vasculature is unique in that alveolar hypoxia causes vasoconstriction so that only well-ventilated areas are perfused. In other organs, hypoxia causes vasodilation
Heart	Local metabolites (vasodilatory): NO, CO <sub>2</sub> , ↓ O <sub>2</sub>	
Brain	Local metabolites (vasodilatory): CO <sub>2</sub> (pH)	
Kidneys	Myogenic and tubuloglomerular feedback	
Skeletal muscle	Local metabolites during exercise (vasodilatory): CO <sub>2</sub> , H <sup>+</sup> , Adenosine, Lactate, K <sup>+</sup> At rest: sympathetic tone in arteries	<b>CHALK</b>
Skin	Sympathetic vasoconstriction most important mechanism for temperature control	

### Capillary fluid exchange

Starling forces determine fluid movement through capillary membranes:

- $P_c$  = capillary hydrostatic pressure—pushes fluid out of capillary
- $P_i$  = interstitial hydrostatic pressure—pushes fluid into capillary
- $\pi_c$  = plasma oncotic pressure—pulls fluid into capillary
- $\pi_i$  = interstitial fluid oncotic pressure—pulls fluid out of capillary

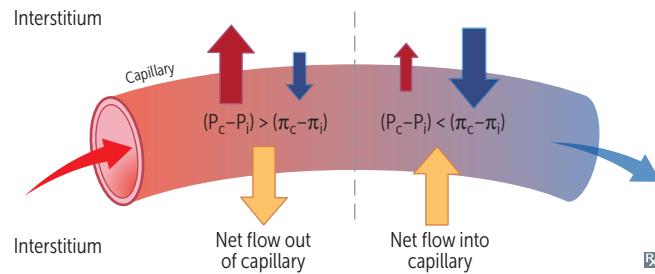
$$J_v = \text{net fluid flow} = K_f [(P_c - P_i) - \sigma(\pi_c - \pi_i)]$$

$K_f$  = capillary permeability to fluid

$\sigma$  = reflection coefficient (measure of capillary permeability to protein)

Edema—excess fluid outflow into interstitium commonly caused by:

- ↑ capillary pressure ( $\uparrow P_c$ ; eg, HF)
- ↑ capillary permeability ( $\uparrow K_f$ ; eg, toxins, infections, burns)
- ↑ interstitial fluid oncotic pressure ( $\uparrow \pi_i$ ; eg, lymphatic blockage)
- ↓ plasma proteins ( $\downarrow \pi_c$ ; eg, nephrotic syndrome, liver failure, protein malnutrition)



## ► CARDIOVASCULAR—PATHOLOGY

**Congenital heart diseases****RIGHT-TO-LEFT SHUNTS**

Early cyanosis—“blue babies.” Often diagnosed prenatally or become evident immediately after birth. Usually require urgent surgical treatment and/or maintenance of a PDA.

The **5 T's**:

1. Truncus arteriosus (1 vessel)
2. Transposition (2 switched vessels)
3. Tricuspid atresia (3 = Tri)
4. Tetralogy of Fallot (4 = Tetra)
5. TAPVR (5 letters in the name)

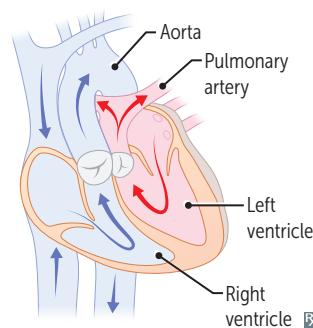
**Persistent truncus arteriosus**

Truncus arteriosus fails to divide into pulmonary trunk and aorta due to failure of aorticopulmonary septum formation; most patients have accompanying VSD.

**D-transposition of great vessels**

Aorta leaves RV (anterior) and pulmonary trunk leaves LV (posterior) → separation of systemic and pulmonary circulations. Not compatible with life unless a shunt is present to allow mixing of blood (eg, VSD, PDA, or patent foramen ovale).

Due to failure of the aorticopulmonary septum to spiral (“egg on a string” appearance on CXR) **A**. Without surgical intervention, most infants die within the first few months of life.

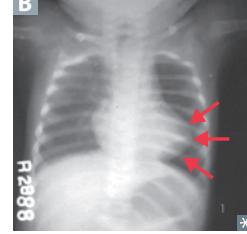
**Tricuspid atresia**

Absence of tricuspid valve and hypoplastic RV; requires both ASD and VSD for viability.

**PROVe.**

Squatting: ↑ SVR, ↓ right-to-left shunt, improves cyanosis.

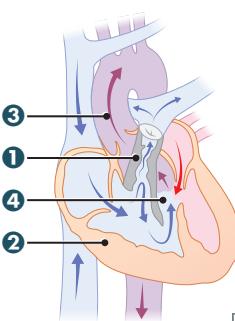
Associated with 22q11 syndromes.

**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 **B**
- 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).

**Total anomalous pulmonary venous return**

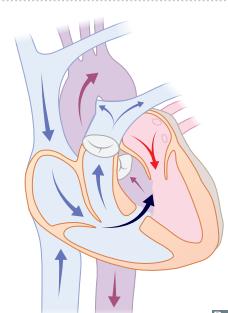
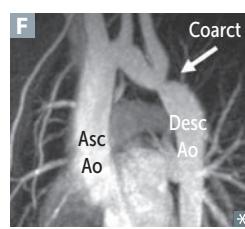
Pulmonary veins drain into right heart circulation (SVC, coronary sinus, etc); associated with ASD and sometimes PDA to allow for right-to-left shunting to maintain CO.

Can be caused by lithium exposure in utero.

**Ebstein anomaly**

Displacement of tricuspid valve leaflets downward into RV, artificially “atrializing” the ventricle. Associated with tricuspid regurgitation, accessory conduction pathways, right-sided HF.

**Congenital heart diseases (continued)**

<b>LEFT-TO-RIGHT SHUNTS</b>	Acyanotic at presentation; cyanosis may occur years later. Frequency: VSD > ASD > PDA.	Right-to-left shunts: early cyanosis. Left-to-right shunts: “later” cyanosis.
<b>Ventricular septal defect</b>	Asymptomatic at birth, may manifest weeks later or remain asymptomatic throughout life. Most self resolve; larger lesions <b>C</b> may lead to LV overload and HF.	O <sub>2</sub> saturation ↑ in RV and pulmonary artery.
<b>Atrial septal defect</b>	Defect in interatrial septum <b>D</b> ; wide, fixed split S2. Ostium secundum defects most common and usually an isolated finding; ostium primum defects rarer and usually occur with other cardiac anomalies. Symptoms range from none to HF. Distinct from patent foramen ovale in that septa are missing tissue rather than unfused.	O <sub>2</sub> saturation ↑ in RA, RV, and pulmonary artery. May lead to paradoxical emboli (systemic venous emboli use ASD to bypass lungs and become systemic arterial emboli). Associated with Down syndrome.
<b>Patent ductus arteriosus</b>	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 O <sub>2</sub> tension. Uncorrected PDA <b>E</b> can eventually result in late cyanosis in the lower extremities (differential cyanosis).	PDA is normal in utero and normally closes only after birth.
<b>Eisenmenger syndrome</b>	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, and polycythemia. Age of onset varies depending on size and severity of initial left-to-right shunt.	
<b>OTHER ANOMALIES</b>		
<b>Coarctation of the aorta</b>	Aortic narrowing <b>F</b> 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**

ASSOCIATION	DEFECT
Prenatal alcohol exposure (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 patient with diabetes during pregnancy	Transposition of great vessels, VSD
Marfan syndrome	MVP, thoracic aortic aneurysm and dissection, aortic regurgitation
Prenatal lithium exposure	Ebstein anomaly
Turner syndrome	Bicuspid aortic valve, coarctation of aorta
Williams syndrome	Supravalvular aortic stenosis
22q11 syndromes	Truncus arteriosus, tetralogy of Fallot

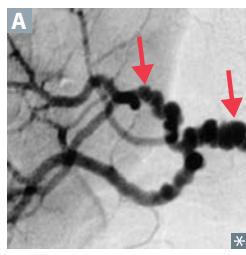
**Hypertension**

## RISK FACTORS

Persistent systolic BP  $\geq 130$  mm Hg and/or diastolic BP  $\geq 80$  mm Hg.

↑ age, obesity, diabetes, physical inactivity, high-sodium diet, excess alcohol intake, tobacco smoking, family history; incidence greatest in Black > White > Asian populations.

## FEATURES



90% of hypertension is 1° (essential) and related to ↑ CO or ↑ TPR. Remaining 10% mostly 2° to renal/renovascular diseases such as fibromuscular dysplasia (characteristic “string of beads” appearance of renal artery **A**, usually seen in adult females) and atherosclerotic renal artery stenosis or to 1° hyperaldosteronism.

**Hypertensive urgency**—severe ( $\geq 180/\geq 120$  mm Hg) hypertension without acute end-organ damage.

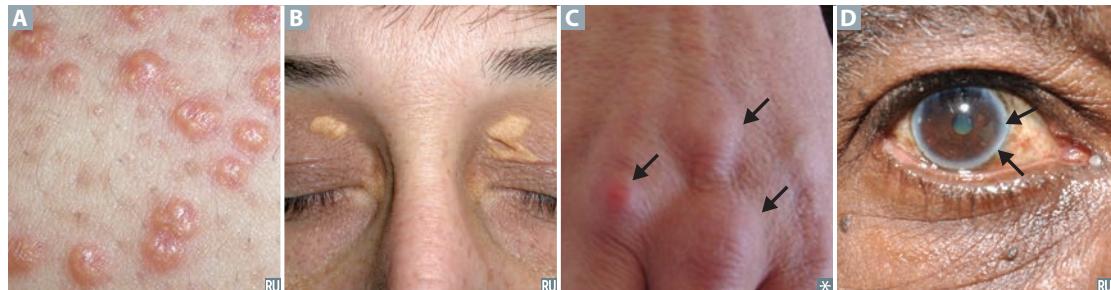
**Hypertensive emergency**—severe hypertension with evidence of acute end-organ damage (eg, encephalopathy, stroke, retinal hemorrhages and exudates, papilledema, MI, HF, aortic dissection, kidney injury, microangiopathic hemolytic anemia, eclampsia).

## PREDISPOSES TO

CAD, LVH, HF, atrial fibrillation; aortic dissection, aortic aneurysm; stroke; CKD (hypertensive nephropathy); retinopathy.

### Hyperlipidemia signs

<b>Xanthomas</b>	Plaques or nodules composed of lipid-laden histiocytes in skin <b>A</b> , especially the eyelids (xanthelasma <b>B</b> ).
<b>Tendinous xanthoma</b>	Lipid deposit in tendon <b>C</b> , especially Achilles tendon and finger extensors.
<b>Corneal arcus</b>	Lipid deposit in cornea. Common in elderly (arcus senilis <b>D</b> ), but appears earlier in life with hypercholesterolemia.



### Arteriosclerosis

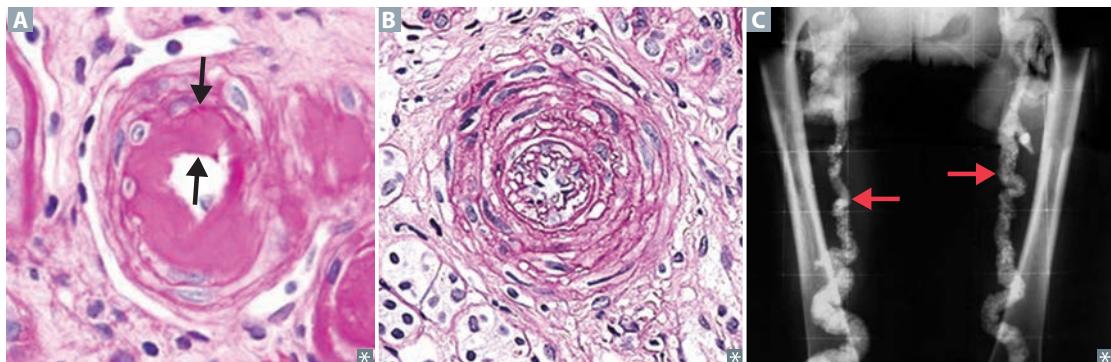
Hardening of arteries, with arterial wall thickening and loss of elasticity.

**Arteriolosclerosis** Common. Affects small arteries and arterioles. Two types:

- Hyaline—thickening of vessel walls 2° to plasma protein leak into endothelium in essential hypertension or diabetes mellitus **A**.
- Hyperplastic—“onion skinning” **B** in severe hypertension with proliferation of smooth muscle cells.

### Mönckeberg sclerosis

Also called 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 in intima.

**LOCATION**

Abdominal aorta > coronary artery > popliteal artery > carotid artery > circle of Willis.  
A copy cat named Willis.

**RISK FACTORS**

Modifiable: hypertension, tobacco smoking, dyslipidemia ( $\uparrow$  LDL,  $\downarrow$  HDL), diabetes.  
Non-modifiable: age, male sex, postmenopausal status, family history.

**SYMPTOMS**

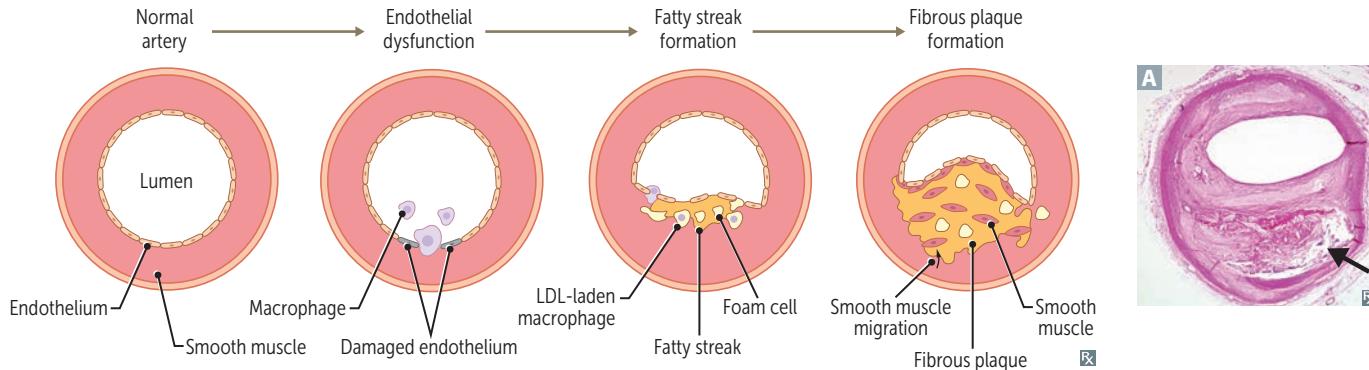
Angina, claudication, but can be asymptomatic.

**PROGRESSION**

Inflammation important in pathogenesis: endothelial cell dysfunction  $\rightarrow$  macrophage and LDL accumulation  $\rightarrow$  foam cell formation  $\rightarrow$  fatty streaks  $\rightarrow$  smooth muscle cell migration (involves PDGF and FGF), proliferation, and extracellular matrix deposition  $\rightarrow$  fibrous plaque  $\rightarrow$  complex atheromas **A**  $\rightarrow$  calcification (calcium content correlates with risk of complications).

**COMPLICATIONS**

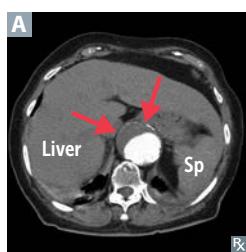
Aneurysms, ischemia, infarcts, peripheral vascular disease, thrombus, emboli.

**Aortic aneurysm**

Localized pathologic dilation of the aorta. May cause abdominal and/or back pain, which is a sign of leaking, dissection, or imminent rupture.

**Abdominal aortic aneurysm**

Usually associated with atherosclerosis. Risk factors include history of tobacco use,  $\uparrow$  age, male sex, family history. May present as palpable pulsatile abdominal mass (arrows in **A** point to outer dilated calcified aortic wall, with partial crescent-shaped nonopacification of aorta due to flap/clot). Most often infrarenal (distal to origin of renal arteries).

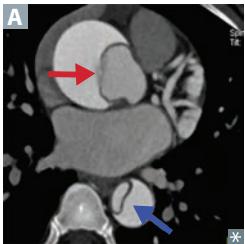
**Thoracic aortic aneurysm**

Associated with cystic medial degeneration. Risk factors include hypertension, bicuspid aortic valve, connective tissue disease (eg, Marfan syndrome). Also associated with 3° syphilis (obliterative endarteritis of the vasa vasorum). Aortic root dilatation may lead to aortic valve regurgitation.

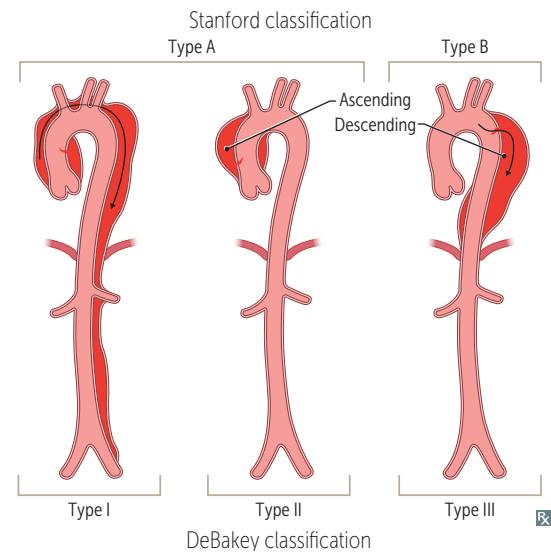
### Traumatic aortic rupture

Due to trauma and/or deceleration injury, most commonly at aortic isthmus (proximal descending aorta just distal to origin of left subclavian artery). X-ray may reveal widened mediastinum.

### Aortic dissection

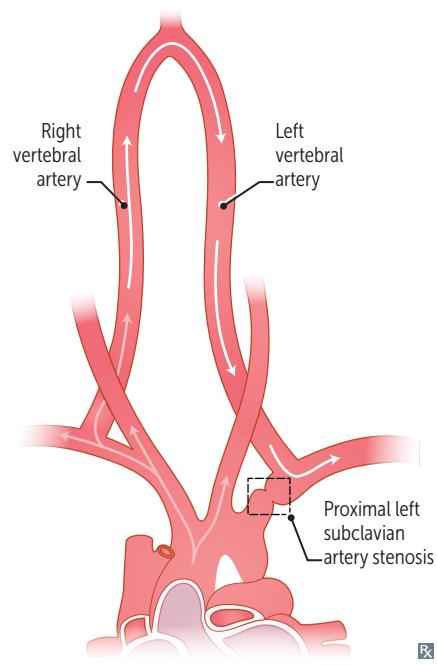


Longitudinal intimal tear forming a false lumen. Associated with hypertension, bicuspid aortic valve, inherited connective tissue disorders (eg, Marfan syndrome). Can present with tearing, sudden-onset chest pain radiating to the back +/- markedly unequal BP in arms. CXR can show mediastinal widening. Can result in organ ischemia, aortic rupture, death. Stanford type **A** (proximal): involves Ascending aorta (red arrow in **A**). May extend to aortic arch or descending aorta (blue arrow in **A**). May result in acute aortic regurgitation or cardiac tamponade. Treatment: surgery. Stanford type **B** (distal): involves only descending aorta (**B** Below left subclavian artery). Treatment:  $\beta$ -blockers, then vasodilators.



### Subclavian steal syndrome

Stenosis of subclavian artery proximal to origin of vertebral artery  $\rightarrow$  hypoperfusion distal to stenosis  $\rightarrow$  reversed blood flow in ipsilateral vertebral artery  $\rightarrow$  reduced cerebral perfusion on exertion of affected arm. Causes arm ischemia, pain, paresthesia, vertebrobasilar insufficiency (dizziness, vertigo).  $>15$  mm Hg difference in systolic BP between arms. Associated with arteriosclerosis, Takayasu arteritis, heart surgery.



### Ischemic heart disease manifestations

#### Angina

Chest pain due to ischemic myocardium 2° to coronary artery narrowing or spasm; no necrosis.

- **Stable**—usually 2° to atherosclerosis ( $\geq 70\%$  occlusion); exertional chest pain in classic distribution (usually with ST depression on ECG), resolving with rest or nitroglycerin.
- **Vasospastic** (also called **Prinzmetal** or **Variant**)—occurs at rest 2° to coronary artery spasm; transient ST elevation on ECG. Tobacco smoking is a risk factor; hypertension and hypercholesterolemia are not. Triggers include cocaine, alcohol, and triptans. Treat with  $\text{Ca}^{2+}$  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);  $\uparrow$  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 → blood is shunted toward well-perfused areas → ischemia in myocardium perfused by stenosed vessels. Principle behind pharmacologic stress tests with coronary vasodilators.

#### Sudden cardiac death

Death occurs within 1 hour of symptoms, most commonly due to lethal arrhythmia (eg, ventricular fibrillation). Associated with CAD (up to 70% of cases), cardiomyopathy (hypertrophic, dilated), and hereditary ion channelopathies (eg, long QT syndrome, Brugada syndrome). Prevent with ICD.

#### Chronic ischemic heart disease

Progressive onset of HF over many years due to chronic ischemic myocardial damage.  
**Myocardial hibernation**—potentially reversible LV systolic dysfunction in the setting of chronic ischemia. Contrast with **myocardial stunning**, a transient LV systolic dysfunction after a brief episode of acute ischemia.

#### Myocardial infarction

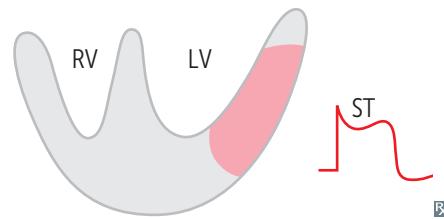
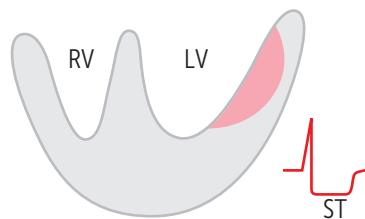
Most often due to rupture of coronary artery atherosclerotic plaque → acute thrombosis.  $\uparrow$  cardiac biomarkers (CK-MB, troponins) are diagnostic.

##### Non-ST-segment elevation MI (NSTEMI)

Subendocardial infarcts  
 Subendocardium (inner 1/3) especially vulnerable to ischemia  
 ST depression on ECG

##### ST-segment elevation MI (STEMI)

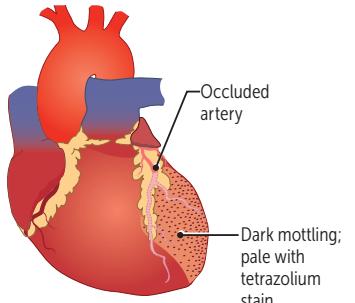
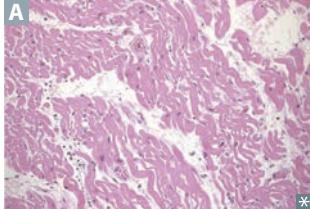
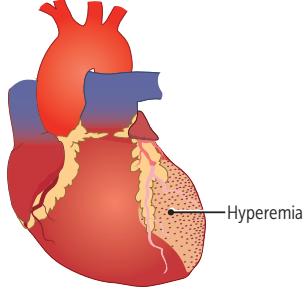
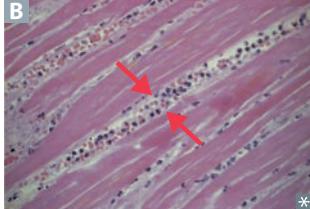
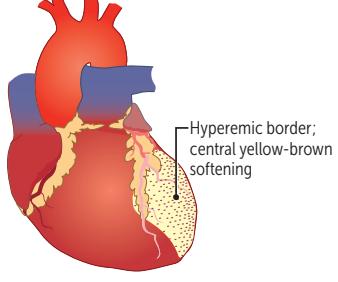
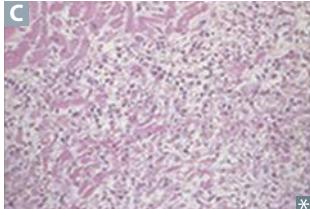
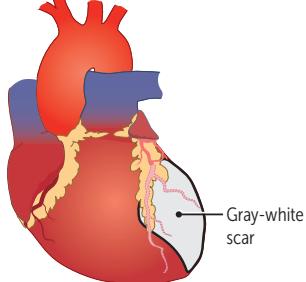
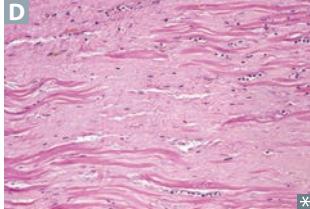
Transmural infarcts  
 Full thickness of myocardial wall involved  
 ST elevation, pathologic Q waves on ECG



### 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 hours	 <p>Occluded artery Dark mottling; pale with tetrazolium stain</p>	<p>Wavy fibers (0–4 hr), early coagulative necrosis (4–24 hr)</p> <p><b>A</b> → cell content released into blood; edema, hemorrhage</p> <p>Reperfusion injury → free radicals and ↑ Ca<sup>2+</sup> influx</p> <p>→ hypercontraction of myofibrils (dark eosinophilic stripes)</p>  <p>* A</p>	Ventricular arrhythmia, HF, cardiogenic shock
1–3 days	 <p>Hyperemia</p>	<p>Extensive coagulative necrosis</p> <p>Tissue surrounding infarct shows acute inflammation with neutrophils <b>B</b></p>  <p>* B</p>	Postinfarction fibrinous pericarditis
3–14 days	 <p>Hyperemic border; central yellow-brown softening</p>	<p>Macrophages, then granulation tissue at margins <b>C</b></p>  <p>* C</p>	<p>Free wall rupture → tamponade; papillary muscle rupture</p> <p>→ mitral regurgitation; interventricular septal rupture due to macrophage-mediated structural degradation → left-to-right shunt</p> <p>LV pseudoaneurysm (risk of rupture)</p>
2 weeks to several months	 <p>Gray-white scar</p>	<p>Contracted scar complete <b>D</b></p>  <p>* D</p>	Dressler syndrome, HF, arrhythmias, true ventricular aneurysm (risk of mural thrombus)

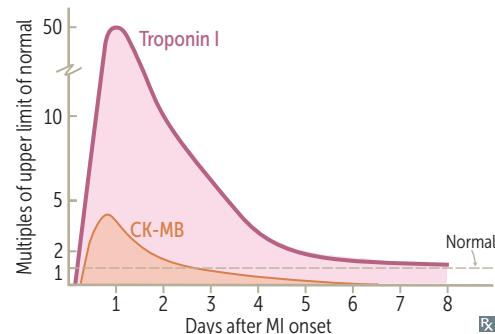
### Diagnosis of myocardial infarction

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.

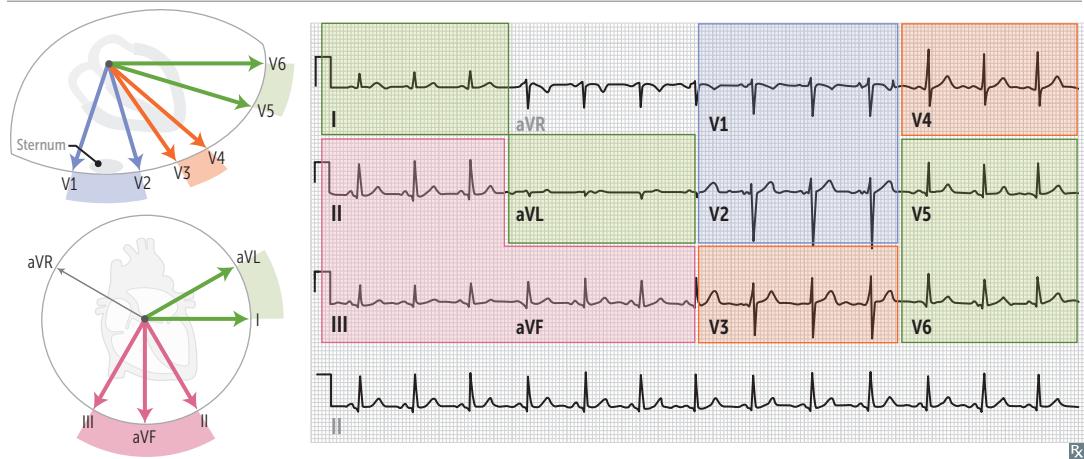
Large MIs lead to greater elevations in troponin I and CK-MB. Exact curves vary with testing procedure.

ECG changes can include ST elevation (STEMI, transmural infarct), ST depression (NSTEMI, subendocardial infarct), hyperacute (peaked) T waves, T-wave inversion, new left bundle branch block, and pathologic Q waves or poor R wave progression (evolving or old transmural infarct).



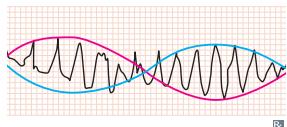
### ECG localization of STEMI

INFARCT LOCATION	LEADS WITH ST-SEGMENT ELEVATIONS OR Q WAVES
Anteroseptal (LAD)	V <sub>1</sub> –V <sub>2</sub>
Anteroapical (distal LAD)	V <sub>3</sub> –V <sub>4</sub>
Anterolateral (LAD or LCX)	V <sub>5</sub> –V <sub>6</sub>
Lateral (LCX)	I, aVL
Inferior (RCA)	II, III, aVF
Posterior (PDA)	V <sub>7</sub> –V <sub>9</sub> , ST depression in V <sub>1</sub> –V <sub>3</sub> with tall R waves



**Paroxysmal supraventricular tachycardia**

A narrow QRS complex tachycardia. Most often due to atrioventricular nodal reentrant tachycardia. Commonly presents with sudden-onset palpitations, diaphoresis, lightheadedness. Treatment: terminate re-entry by slowing AV node conduction (eg, vagal maneuvers, IV adenosine). Electrical cardioversion if hemodynamically unstable. Definitive treatment is catheter ablation of re-entry tract.

**Torsades de pointes**

Polymorphic ventricular tachycardia, characterized by shifting sinusoidal waveforms on ECG; can progress to ventricular fibrillation. Long QT interval predisposes to torsades de pointes. Caused by drugs, ↓ K<sup>+</sup>, ↓ Mg<sup>2+</sup>, ↓ Ca<sup>2+</sup>, congenital abnormalities. Treatment includes magnesium sulfate.

Drug-induced long QT (ABCDEF):

AntiArrhythmics (class IA, III)  
AntiBiotics (eg, macrolides, fluoroquinolones)  
Anti“C”yphotics (eg, haloperidol, ziprasidone)  
AntiDepressants (eg, TCAs)  
AntiEmetics (eg, ondansetron)  
AntiFungals (eg, azoles)

Torsades de pointes = twisting of the points

**Hereditary channelopathies**

Inherited mutations of cardiac ion channels → abnormal myocardial action potential → ↑ risk of ventricular tachyarrhythmias and sudden cardiac death (SCD).

**Brugada syndrome**

Autosomal dominant; most commonly due to loss of function mutation of Na<sup>+</sup> channels. ↑ prevalence in Asian males. ECG pattern of pseudo-right bundle branch block and ST-segment elevations in leads V<sub>1</sub>-V<sub>2</sub>. Prevent SCD with implantable cardioverter-defibrillator (ICD).

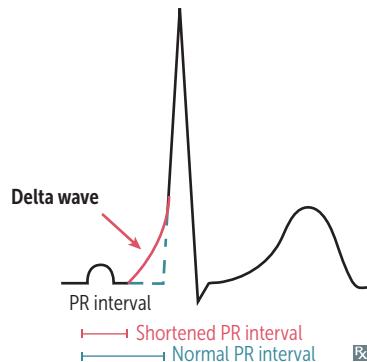
**Congenital long QT syndrome**

Most commonly due to loss of function mutation of K<sup>+</sup> channels (affects repolarization). Includes:

- Romano-Ward syndrome—autosomal dominant, pure cardiac phenotype (no deafness).
- Jervell and Lange-Nielsen syndrome—autosomal recessive, sensorineural deafness.

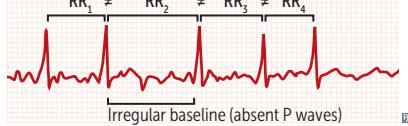
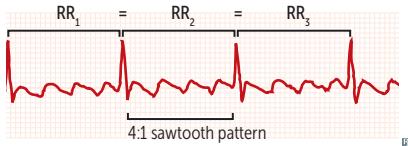
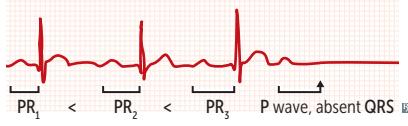
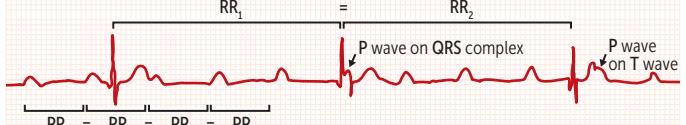
**Wolff-Parkinson-White syndrome**

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.



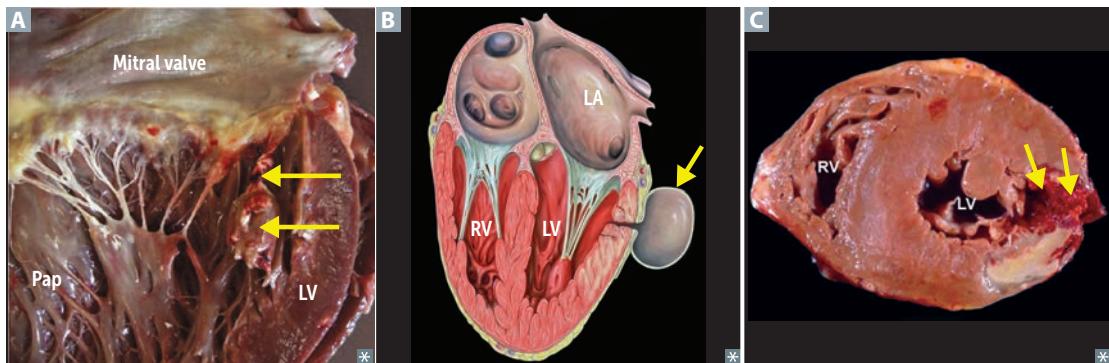
**ECG tracings**

If the R is far from P, then you have a first degree.  
 Longer, longer, longer, drop! Then you have a Wenckebach.  
 If some P's don't get through, then you have a Mobitz II.  
 If P's and Q's don't agree, then you have a third degree.

RHYTHM	DESCRIPTION	EXAMPLE
<b>Atrial fibrillation</b>	Chaotic and erratic baseline with no discrete P waves in between irregularly spaced QRS complexes. Irregularly irregular heartbeat. Most common risk factors include hypertension and coronary artery disease (CAD). Occasionally seen after episodes of excessive alcohol consumption ("holiday heart syndrome"). Can lead to thromboembolic events, particularly stroke. Treatment: anticoagulation, rate and rhythm control, cardioversion. Definitive treatment is catheter ablation.	 RR <sub>1</sub> ≠ RR <sub>2</sub> ≠ RR <sub>3</sub> ≠ RR <sub>4</sub> Irregular baseline (absent P waves)
<b>Atrial flutter</b>	A rapid succession of identical, back-to-back atrial depolarization waves. The identical appearance accounts for the "sawtooth" appearance of the flutter waves. Treat like atrial fibrillation +/- catheter ablation of region between tricuspid annulus and IVC.	 RR <sub>1</sub> = RR <sub>2</sub> = RR <sub>3</sub> 4:1 sawtooth pattern
<b>Ventricular fibrillation</b>	A completely erratic rhythm with no identifiable waves. Fatal arrhythmia without immediate CPR and defibrillation.	 No discernible rhythm
<b>AV block</b>		
<b>First-degree AV block</b>	The PR interval is prolonged (> 200 msec). Benign and asymptomatic. No treatment required.	 PR <sub>1</sub> = PR <sub>2</sub> = PR <sub>3</sub> = PR <sub>4</sub>
<b>Second-degree AV block</b>		
<b>Mobitz type I (Wenckebach)</b>	Progressive lengthening of PR interval until a beat is "dropped" (a P wave not followed by a QRS complex). Usually asymptomatic. Variable RR interval with a pattern (regularly irregular).	 PR <sub>1</sub> < PR <sub>2</sub> < PR <sub>3</sub> P wave, absent QRS
<b>Mobitz type II</b>	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.	 PR <sub>1</sub> = PR <sub>2</sub> P wave, absent QRS
<b>Third-degree (complete) AV block</b>	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 Lym <sup>3</sup> disease.	 PP <sub>1</sub> = PP <sub>2</sub> = PP <sub>3</sub> = PP <sub>4</sub> RR <sub>1</sub> = RR <sub>2</sub> P wave on QRS complex P wave on T wave

### Myocardial infarction complications

<b>Cardiac arrhythmia</b>	Occurs within the first few days after MI. Important cause of death before reaching the hospital and within the first 24 hours post-MI.
<b>Postinfarction fibrinous pericarditis</b>	1–3 days: friction rub.
<b>Papillary muscle rupture</b>	2–7 days: posteromedial papillary muscle rupture <b>A</b> ↑ risk due to single blood supply from posterior descending artery. Can result in severe mitral regurgitation.
<b>Interventricular septal rupture</b>	3–5 days: macrophage-mediated degradation → VSD → ↑ O <sub>2</sub> saturation and pressure in RV.
<b>Ventricular pseudoaneurysm formation</b>	3–14 days: free wall rupture contained by adherent pericardium or scar tissue <b>B</b> ; ↓ CO, risk of arrhythmia, embolus from mural thrombus.
<b>Ventricular free wall rupture</b>	5–14 days: free wall rupture <b>C</b> → cardiac tamponade. LV hypertrophy and previous MI protect against free wall rupture. Acute form usually leads to sudden death.
<b>True ventricular aneurysm</b>	2 weeks to several months: outward bulge with contraction (“dyskinesia”), associated with fibrosis.
<b>Dressler syndrome</b>	Several weeks: autoimmune phenomenon resulting in fibrinous pericarditis.
<b>LV failure and pulmonary edema</b>	Can occur 2° to LV infarction, VSD, free wall rupture, papillary muscle rupture with mitral regurgitation.

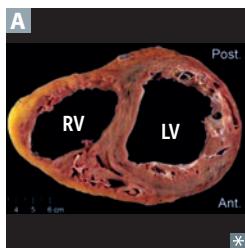


### Acute coronary syndrome treatments

<b>Unstable angina/NSTEMI</b>	—Anticoagulation (eg, heparin), antiplatelet therapy (eg, aspirin) + ADP receptor inhibitors (eg, clopidogrel), β-blockers, ACE inhibitors, statins. Symptom control with nitroglycerin +/- morphine.
<b>STEMI</b>	—In addition to above, reperfusion therapy most important (percutaneous coronary intervention preferred over fibrinolysis). If RV affected (eg, RCA occlusion), support venous return/preload to maintain cardiac output (eg, IV fluids, avoiding nitroglycerin).

## Cardiomyopathies

### Dilated cardiomyopathy



Most common cardiomyopathy (90% of cases).

Often idiopathic or familial (eg, due to mutation of *TTN* gene encoding the sarcomeric protein titin).

Other etiologies include drugs (eg, alcohol, cocaine, doxorubicin), infection (eg, coxsackie B virus, Chagas disease), ischemia (eg, CAD), systemic conditions (eg, hemochromatosis, sarcoidosis, thyrotoxicosis, wet beriberi), peripartum cardiomyopathy.

Findings: HF, S3, systolic regurgitant murmur, dilated heart on echocardiogram, balloon appearance of heart on CXR.

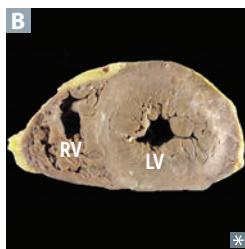
Treatment:  $\text{Na}^+$  restriction, ACE inhibitors,  $\beta$ -blockers, sacubitril, diuretics, mineralocorticoid receptor blockers (eg, spironolactone), digoxin, ICD, heart transplant.

Leads to systolic dysfunction.

Dilated cardiomyopathy **A** displays eccentric hypertrophy (sarcomeres added in series).

**Takotsubo cardiomyopathy:** broken heart syndrome—ventricular apical ballooning likely due to increased sympathetic stimulation (eg, stressful situations).

### Hypertrophic cardiomyopathy



60–70% of cases are familial, autosomal dominant (most commonly due to mutations in genes encoding sarcomeric proteins, such as myosin binding protein C and  $\beta$ -myosin heavy chain). Causes syncope during exercise and may lead to sudden death (eg, in young athletes) due to ventricular arrhythmia.

Findings: S4, systolic murmur. May see mitral regurgitation due to impaired mitral valve closure.

Treatment: cessation of high-intensity athletics, use of  $\beta$ -blocker or nondihydropyridine  $\text{Ca}^{2+}$  channel blockers (eg, verapamil). ICD if syncope occurs. Avoid drugs that decrease preload (eg, diuretics, vasodilators).

Diastolic dysfunction ensues.

Marked ventricular concentric hypertrophy (sarcomeres added in parallel) **B**, often septal predominance. Myofibrillar disarray and fibrosis.

Classified as hypertrophic obstructive cardiomyopathy when outflow from LV is obstructed. Asymmetric septal hypertrophy and systolic anterior motion of mitral valve  $\rightarrow$  outflow obstruction  $\rightarrow$  dyspnea, possible syncope.

Other causes of concentric LV hypertrophy: chronic HTN, Friedreich ataxia.

### Restrictive/infiltrative cardiomyopathy

Postradiation fibrosis, **Löffler endocarditis**, **Endocardial fibroelastosis** (thick fibroelastic tissue in endocardium of young children), **Amyloidosis**, **Sarcoidosis**, **Hemochromatosis** (**PLEASe Help!**).

Diastolic dysfunction ensues. Can have low-voltage ECG despite thick myocardium (especially in amyloidosis).

**Löffler endocarditis**—associated with hypereosinophilic syndrome; histology shows eosinophilic infiltrates in myocardium.

**Heart failure**

Clinical syndrome of cardiac pump dysfunction → congestion and low perfusion. Symptoms include dyspnea, orthopnea, fatigue; signs include S3 heart sound, rales, jugular venous distention (JVD), pitting edema **A**.

Systolic dysfunction—reduced EF, ↑ EDV; ↓ contractility often 2° to ischemia/MI or dilated cardiomyopathy.

Diastolic dysfunction—preserved EF, normal EDV; ↓ compliance (↑ EDP) often 2° to myocardial hypertrophy.

Right HF most often results from left HF. Cor pulmonale refers to isolated right HF due to pulmonary cause.

ACE inhibitors or angiotensin II receptor blockers,  $\beta$ -blockers (except in acute decompensated HF), and spironolactone ↓ mortality. Loop and thiazide diuretics are used mainly for symptomatic relief. Hydralazine with nitrate therapy improves both symptoms and mortality in select patients.

**Left heart failure****Orthopnea**

Shortness of breath when supine: ↑ 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**

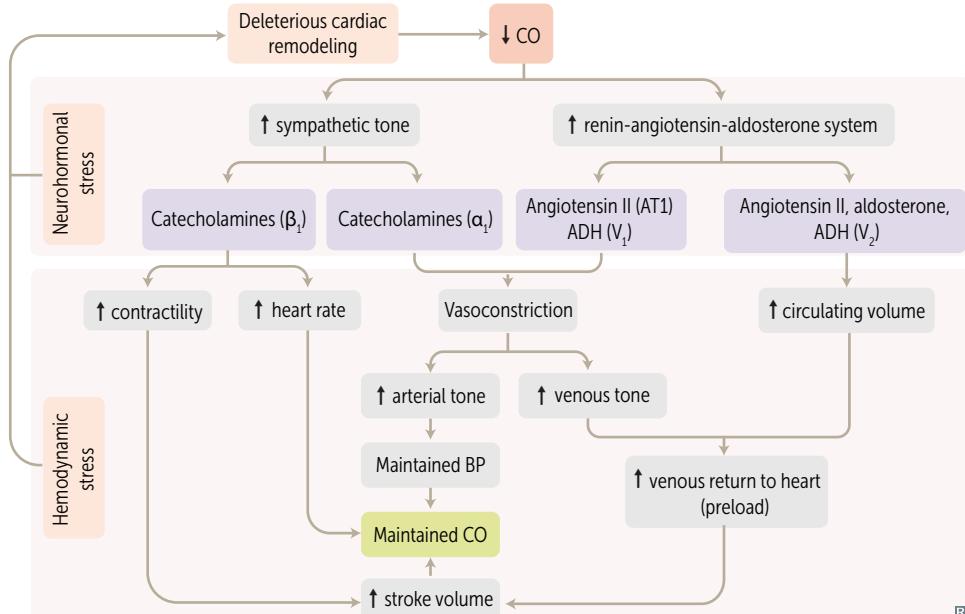
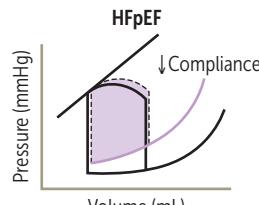
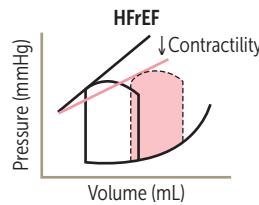
↑ central venous pressure → ↑ resistance to portal flow. Rarely, leads to “cardiac cirrhosis.” Associated with nutmeg liver (mottled appearance) on gross exam.

**Jugular venous distention**

↑ venous pressure.

**Peripheral edema**

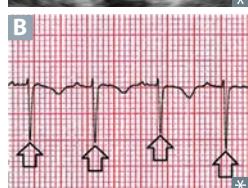
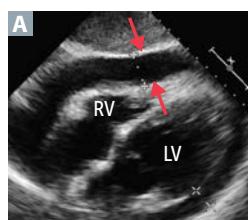
↑ venous pressure → fluid transudation.



**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
<b>Hypovolemic shock</b>	Hemorrhage, dehydration, burns	Cold, clammy	↓↓	↓	↑	IV fluids
<b>Cardiogenic shock</b>	Acute MI, HF, valvular dysfunction, arrhythmia					Inotropes, diuresis
<b>Obstructive shock</b>	Cardiac tamponade, pulmonary embolism, tension pneumothorax	Cold, clammy	↑ or ↓	↓↓	↑	Relieve obstruction
<b>Distributive shock</b>	Sepsis, anaphylaxis CNS injury	Warm Dry	↓ ↓	↑ ↓	↓↓ ↓↓	IV fluids, pressors, epinephrine (anaphylaxis)

**Cardiac tamponade**

Compression of the heart by fluid (eg, blood, effusions [arrows in A] in pericardial space) → ↓ CO. Equilibration of diastolic pressures in all 4 chambers.

Findings: Beck triad (hypotension, distended neck veins, distant heart sounds), ↑ HR, pulsus paradoxus. ECG shows low-voltage QRS and electrical alternans B (due to “swinging” movement of heart in large effusion).

Treatment: pericardiocentesis or surgical drainage.

**Pulsus paradoxus**—↓ in amplitude of systolic BP by > 10 mm Hg during inspiration. Seen in constrictive pericarditis, obstructive pulmonary disease (eg, Croup, OSA, Asthma, COPD), cardiac Tamponade (pea COAT).

**Bacterial endocarditis**

**Acute**—*S aureus* (high virulence). Large vegetations on previously normal valves **A**. Rapid onset.

**Subacute**—viridans streptococci (low virulence). Smaller vegetations on congenitally abnormal or diseased valves. Sequela of dental procedures. Gradual onset.

Symptoms: fever (most common), new murmur, Roth spots (Round white spots on Retina surrounded by hemorrhage **B**), Osler nodes (Ouchy raised lesions on finger or toe pads **C** due to immune complex deposition), Janeway lesions (small, painless, erythematous lesions on palm or sole) **D**, splinter hemorrhages **E** on nail bed.

Associated with glomerulonephritis, septic arterial or pulmonary emboli.

May be nonbacterial (marantic/thrombotic) 2° to malignancy, hypercoagulable state, or lupus.

**FROM JANE with ❤:**

Fever

Roth spots

Osler nodes

Murmur

Janeway lesions

Anemia

Nail-bed hemorrhage

Emboli

Requires multiple blood cultures for diagnosis.

If culture ⊖, most likely *Coxiella burnetii*,

*Bartonella* spp.

Mitral valve is most frequently involved.

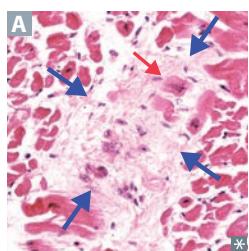
Tricuspid valve endocarditis is associated with IV drug use (don't "tri" drugs). Associated with *S aureus*, *Pseudomonas*, and *Candida*.

*S bovis (gallolyticus)* is present in colon cancer, *S epidermidis* on prosthetic valves.

Native valve endocarditis may be due to HACEK organisms (*Haemophilus*,

*Aggregatibacter* [formerly *Actinobacillus*], *Cardiobacterium*, *Eikenella*, *Kingella*).



**Rheumatic fever**

A consequence of pharyngeal infection with group A  $\beta$ -hemolytic streptococci. Late sequelae include **rheumatic heart disease**, which affects heart valves—**mitral > aortic >> tricuspid** (high-pressure valves affected most). Early lesion is mitral valve regurgitation; late lesion is mitral stenosis.

Associated with Aschoff bodies (granuloma with giant cells [blue arrows in A]), Anitschkow cells (enlarged macrophages with ovoid, wavy, rod-like nucleus [red arrow in A]), ↑ anti-streptolysin O (ASO) and ↑ anti-DNase B titers.

Immune mediated (type II hypersensitivity); not a direct effect of bacteria. Antibodies to **M** protein cross-react with self antigens, often **myosin** (**molecular mimicry**).

Treatment/prophylaxis: penicillin.

**JONES (major criteria):**

**Joint** (migratory polyarthritis)

**Heart** (carditis)

**Nodules** in skin (subcutaneous)

**Erythema marginatum** (evanescent rash with ring margin)

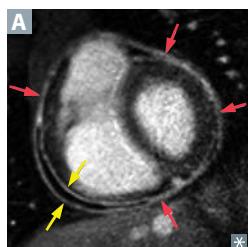
**Sydenham chorea** (involuntary irregular movements of limbs and face)

**Syphilitic heart disease**

3° syphilis disrupts the vasa vasorum of the aorta with consequent atrophy of vessel wall and dilation of aorta and valve ring.

May see calcification of aortic root, ascending aortic arch, and thoracic aorta. Leads to “tree bark” appearance of aorta.

Can result in aneurysm of ascending aorta or aortic arch, aortic insufficiency.

**Acute pericarditis**

Inflammation of the pericardium (red arrows in A). Commonly presents with sharp pain, aggravated by inspiration, and relieved by sitting up and leaning forward. Often complicated by pericardial effusion [between yellow arrows in A]. Presents with friction rub. ECG changes include widespread ST-segment elevation and/or PR depression.

Causes include idiopathic (most common; presumed viral), confirmed infection (eg, coxsackievirus B), neoplasia, autoimmune (eg, SLE, rheumatoid arthritis), uremia, cardiovascular (acute STEMI or Dressler syndrome), radiation therapy.

Treatment: NSAIDs, colchicine, glucocorticoids, dialysis (uremia).

**Myocarditis**

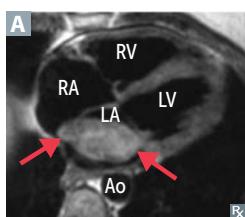
Inflammation of myocardium → global enlargement of heart and dilation of all chambers. Major cause of SCD in adults < 40 years old.

Presentation highly variable, can include dyspnea, chest pain, fever, arrhythmias (persistent tachycardia out of proportion to fever is characteristic).

Multiple causes:

- Viral (eg, adenovirus, coxsackie B, parvovirus B19, HIV, HHV-6); lymphocytic infiltrate with focal necrosis highly indicative of viral myocarditis
- Parasitic (eg, *Trypanosoma cruzi*, *Toxoplasma gondii*)
- Bacterial (eg, *Borrelia burgdorferi*, *Mycoplasma pneumoniae*, *Corynebacterium diphtheriae*)
- Toxins (eg, carbon monoxide, black widow venom)
- Rheumatic fever
- Drugs (eg, doxorubicin, cocaine)
- Autoimmune (eg, Kawasaki disease, sarcoidosis, SLE, polymyositis/dermatomyositis)

Complications include sudden death, arrhythmias, heart block, dilated cardiomyopathy, HF, mural thrombus with systemic emboli.

**Cardiac tumors****Myxomas**

Most common cardiac tumor is a metastasis (eg, melanoma).

Most common 1° cardiac tumor in **adults** (arrows in A). 90% occur in the atria (mostly left atrium). Myxomas are usually described as a “ball valve” obstruction in the left atrium (associated with multiple syncopal episodes). IL-6 production by tumor → constitutional symptoms (eg, fever, weight loss). May auscultate early diastolic “tumor plop” sound. Histology: gelatinous material, myxoma cells immersed in glycosaminoglycans.

**Adults make 6 myxed drinks.**

**Rhabdomyomas**

Most frequent 1° cardiac tumor in children (associated with tuberous sclerosis). Histology: hamartomatous growths. More common in the ventricles.

**Kussmaul sign**

Paradoxical ↑ in JVP on inspiration (normally, inspiration → negative intrathoracic pressure → ↑ venous return → ↓ JVP).

Impaired RV filling → blood backs up into vena cava → ↓ venous return as negative intrathoracic pressure is insufficient to bring blood to right heart → Kussmaul sign. May be seen with constrictive pericarditis, restrictive cardiomyopathy, right heart failure, massive pulmonary embolism, right atrial or ventricular tumors.

**Hereditary hemorrhagic telangiectasia**

Also called Osler-Weber-Rendu syndrome. Autosomal dominant disorder of blood vessels. Findings: blanching lesions (telangiectasias) on skin and mucous membranes, recurrent epistaxis, skin discolorations, arteriovenous malformations (AVMs), GI bleeding, hematuria.

## ▶ CARDIOVASCULAR—PHARMACOLOGY

**Hypertension treatment****Primary (essential) hypertension**

Thiazide diuretics, ACE inhibitors, angiotensin II receptor blockers (ARBs), dihydropyridine Ca<sup>2+</sup> channel blockers.

**Hypertension with heart failure**

Diuretics, ACE inhibitors/ARBs, β-blockers (compensated HF), aldosterone antagonists.

β-blockers must be used cautiously in decompensated HF and are contraindicated in cardiogenic shock.

In HF, ARBs may be combined with the neprilysin inhibitor sacubitril.

**Hypertension with diabetes mellitus**

ACE inhibitors/ARBs, Ca<sup>2+</sup> channel blockers, thiazide diuretics, β-blockers.

ACE inhibitors/ARBs are protective against diabetic nephropathy.

β-blockers can mask hypoglycemia symptoms.

**Hypertension in asthma**

ARBs, Ca<sup>2+</sup> channel blockers, thiazide diuretics, cardioselective β-blockers.

Avoid nonselective β-blockers to prevent β<sub>2</sub>-receptor-induced bronchoconstriction.

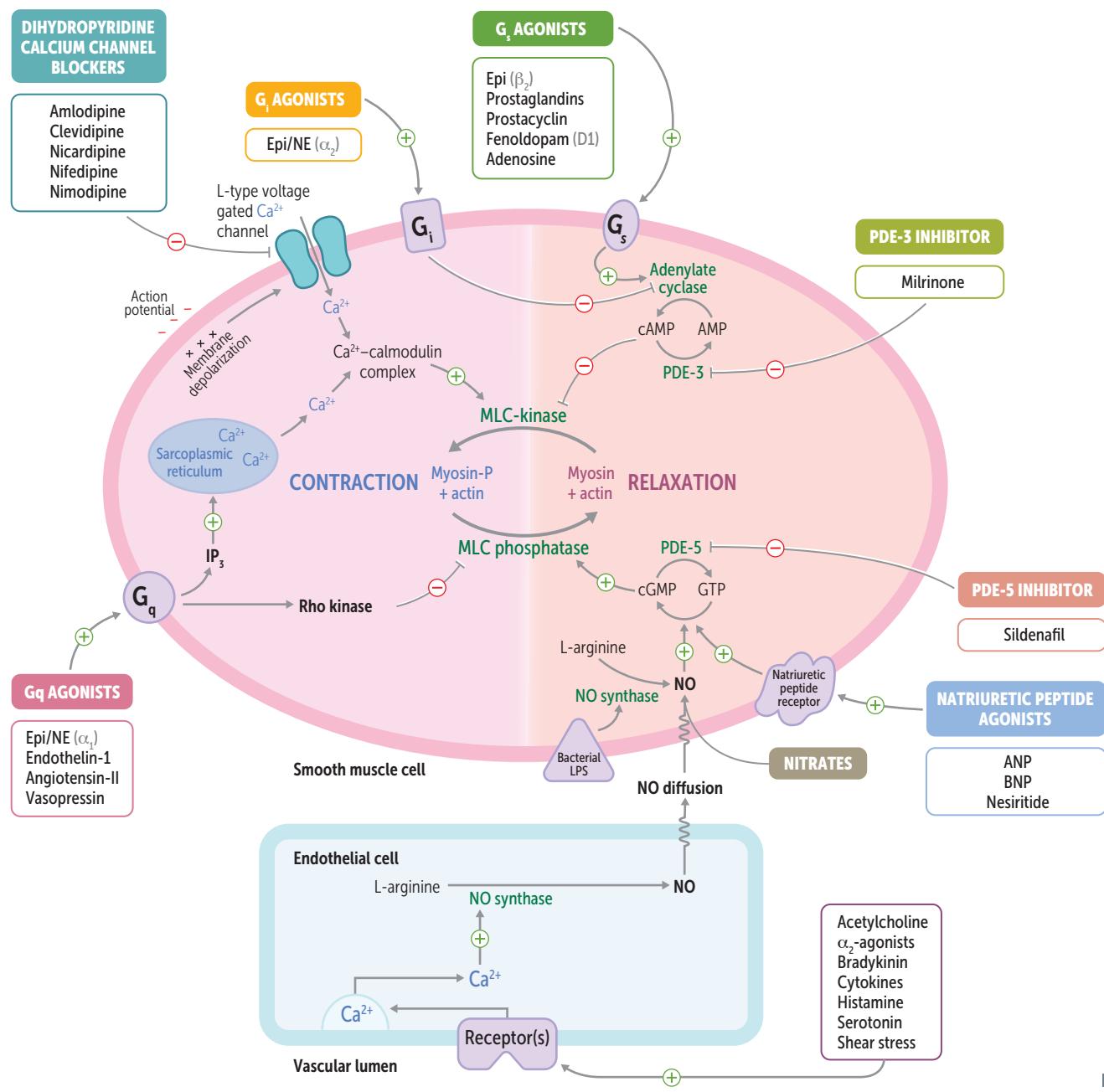
Avoid ACE inhibitors to prevent confusion between drug or asthma-related cough.

**Hypertension in pregnancy**

Nifedipine, methyldopa, labetalol, hydralazine.

New moms love hugs.

## Cardiovascular agents and molecular targets



<b>Calcium channel blockers</b>	Amlodipine, clevidipine, nicardipine, nifedipine, nimodipine (dihydropyridines, act on vascular smooth muscle); diltiazem, verapamil (nondihydropyridines, 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.
CLINICAL USE	Dihydropyridines (except nimodipine): hypertension, angina (including vasospastic type), Raynaud phenomenon. Nimodipine: subarachnoid hemorrhage (prevents cerebral vasospasm). Nicardipine, clevidipine: hypertensive urgency or emergency. Nondihydropyridines: hypertension, angina, atrial fibrillation/flutter.
ADVERSE EFFECTS	Gingival hyperplasia. Dihydropyridine: peripheral edema, flushing, dizziness. Nondihydropyridine: cardiac depression, AV block, hyperprolactinemia (verapamil), constipation.

**Hydralazine**

MECHANISM	↑ cGMP → smooth muscle relaxation. Vasodilates arterioles > veins; afterload reduction.
CLINICAL USE	Severe hypertension (particularly acute), HF (with organic nitrate). Safe to use during pregnancy. Frequently coadministered with a β-blocker to prevent reflex tachycardia.
ADVERSE EFFECTS	Compensatory tachycardia (contraindicated in angina/CAD), fluid retention, headache, angina, drug-induced lupus.

**Hypertensive emergency**

Treat with labetalol, clevidipine, fenoldopam, nicardipine, nitroprusside.

<b>Nitroprusside</b>	Short acting vasodilator (arteries = veins); ↑ cGMP via direct release of NO. Can cause cyanide toxicity (releases cyanide).
<b>Fenoldopam</b>	<b>Dopamine D<sub>1</sub></b> receptor agonist—coronary, peripheral, renal, and splanchnic vasodilation. ↓ BP, ↑ natriuresis. Also used postoperatively as an antihypertensive. Can cause hypotension, tachycardia, flushing, headache, nausea.

**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 nitrate exposure: development of tolerance for the vasodilating action during the work week and loss of tolerance over the weekend → tachycardia, dizziness, headache upon reexposure. Contraindicated in right ventricular infarction, hypertrophic cardiomyopathy, and with concurrent PDE-5 inhibitor use.

**Antianginal therapy** Goal is reduction of myocardial O<sub>2</sub> consumption (MVO<sub>2</sub>) by ↓ 1 or more of the determinants of MVO<sub>2</sub>: end-diastolic volume, BP, HR, contractility.

COMPONENT	NITRATES	β-BLOCKERS	NITRATES + β-BLOCKERS
End-diastolic volume	↓	No effect or ↑	No effect or ↓
Blood pressure	↓	↓	↓
Contractility	↑ (reflex response)	↓	Little/no effect
Heart rate	↑ (reflex response)	↓	No effect or ↓
Ejection time	↓	↑	Little/no effect
MVO <sub>2</sub>	↓	↓	↓↓

Verapamil is similar to β-blockers in effect.

Pindolol and acebutolol are partial β-agonists that should be used with caution in angina.

### Ranolazine

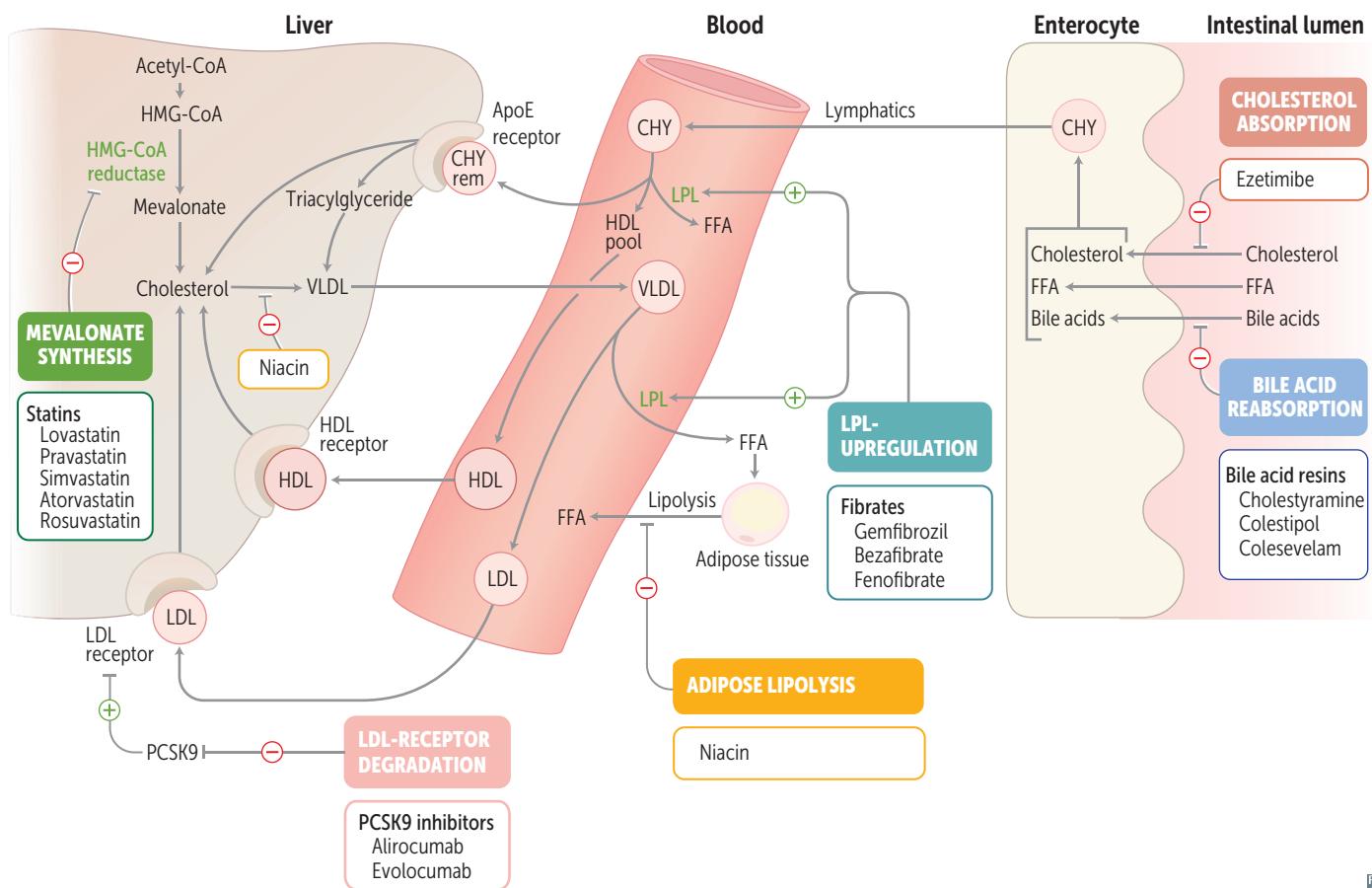
MECHANISM	Inhibits the late phase of inward sodium current thereby reducing diastolic wall tension and oxygen consumption. Does not affect heart rate or blood pressure.
CLINICAL USE	Refractory angina.
ADVERSE EFFECTS	Constipation, dizziness, headache, nausea.

### Sacubitril

MECHANISM	A neprilysin inhibitor; prevents degradation of bradykinin, natriuretic peptides, angiotensin II, and substance P → ↑ vasodilation, ↓ ECF volume.
CLINICAL USE	Used in combination with valsartan (an ARB) to treat HFrEF.
ADVERSE EFFECTS	Hypotension, hyperkalemia, cough, dizziness; contraindicated with ACE inhibitors due to angioedema (both drugs ↑ bradykinin).

**Lipid-lowering agents**

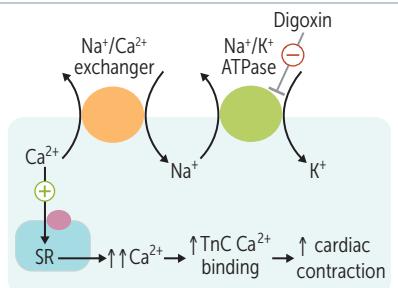
DRUG	LDL	HDL	TRIGLYCERIDES	MECHANISMS OF ACTION	ADVERSE EFFECTS/PROBLEMS
<b>HMG-CoA reductase inhibitors</b> Atorvastatin, simvastatin	↓↓↓	↑	↓	Inhibit conversion of HMG-CoA to mevalonate, a cholesterol precursor; → ↓ intrahepatic cholesterol → ↑ LDL receptor recycling → ↑ LDL catabolism ↓ in mortality in patients with CAD	Hepatotoxicity (↑ LFTs), myopathy (esp when used with fibrates or niacin)
<b>Bile acid resins</b> 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
<b>Ezetimibe</b>	↓↓	↑/—	↓/—	Prevents cholesterol absorption at small intestine brush border	Rare ↑ LFTs, diarrhea
<b>Fibrates</b> Gemfibrozil, bezafibrate, fenofibrate	↓	↑	↓↓↓	Activate PPAR-α → upregulate LPL → ↑ TG clearance Activate PPAR-α → induce HDL synthesis	Myopathy (↑ risk with statins), cholesterol gallstones (via inhibition of cholesterol 7α-hydroxylase)
<b>Niacin</b>	↓↓	↑↑	↓	Inhibits lipolysis (hormone-sensitive lipase) in adipose tissue; reduces hepatic VLDL synthesis	Flushed face (prostaglandin mediated; ↓ by NSAIDs or long-term use) Hyperglycemia Hyperuricemia
<b>PCSK9 inhibitors</b> Alirocumab, evolocumab	↓↓↓	↑	↓	Inactivation of LDL-receptor degradation → ↑ removal of LDL from bloodstream	Myalgias, delirium, dementia, other neurocognitive effects
<b>Fish oil and marine omega-3 fatty acids</b>	↑ slightly	↑ slightly	↓ at high doses	Believed to decrease FFA delivery to liver and decrease activity of TG-synthesizing enzymes	Nausea, fish-like taste

**Lipid-lowering agents (continued)****Cardiac glycosides**

Digoxin.

**MECHANISM**

Direct inhibition of  $\text{Na}^+/\text{K}^+$  ATPase  
 → indirect inhibition of  $\text{Na}^+/\text{Ca}^{2+}$  exchanger.  
 $\uparrow [\text{Ca}^{2+}]_{\text{i}}$  → positive inotropy. Stimulates vagus nerve →  $\downarrow \text{HR}$ .

**CLINICAL USE**HF ( $\uparrow$  contractility); atrial fibrillation ( $\downarrow$  conduction at AV node and depression of SA node).**ADVERSE EFFECTS**

Cholinergic effects (nausea, vomiting, diarrhea), blurry yellow vision (think van Glow), arrhythmias, AV block.

Can lead to hyperkalemia, which indicates poor prognosis.

Factors predisposing to toxicity: renal failure ( $\downarrow$  excretion), hypokalemia (permissive for digoxin binding at  $\text{K}^+$ -binding site on  $\text{Na}^+/\text{K}^+$  ATPase), drugs that displace digoxin from tissue-binding sites, and  $\downarrow$  clearance (eg, verapamil, amiodarone, quinidine).**ANTIDOTE**Slowly normalize  $\text{K}^+$ , cardiac pacer, anti-digoxin Fab fragments,  $\text{Mg}^{2+}$ .

**Antiarrhythmics—  
sodium channel  
blockers (class I)**

Slow or block conduction (especially in depolarized cells). ↓ slope of phase 0 depolarization.  
 ↑ action at **faster** HR. State dependent ↑ HR → shorter diastole,  $\text{Na}^+$  channels spend less time in resting state (drugs dissociate during this state) → less time for drug to dissociate from receptor.  
 Effect most pronounced in **IC>IA>IB** due to relative binding strength. **Fast taxi CAB.**

**Class IA**

**Quinidine, procainamide, disopyramide.**  
 “The queen proclaims **Diso’s pyramid.**”

**MECHANISM**

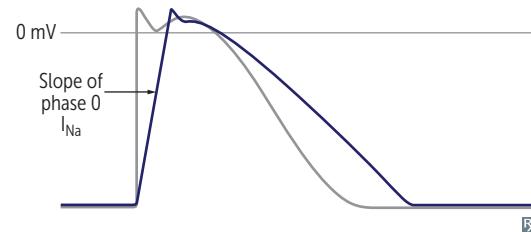
Moderate  $\text{Na}^+$  channel blockade.  
 ↑ AP duration, ↑ effective refractory period (ERP) in ventricular action potential, ↑ QT interval, some potassium channel blocking effects.

**CLINICAL USE**

Both atrial and ventricular arrhythmias, especially re-entrant and ectopic SVT and VT.

**ADVERSE EFFECTS**

Cinchonism (headache, tinnitus with quinidine), reversible SLE-like syndrome (procainamide), HF (disopyramide), thrombocytopenia, torsades de pointes due to ↑ QT interval.



**Class IB**

**Lidocaine, phenytoin, mexiletine.**  
 “I’d Buy Liddy’s phine Mexican tacos.”

**MECHANISM**

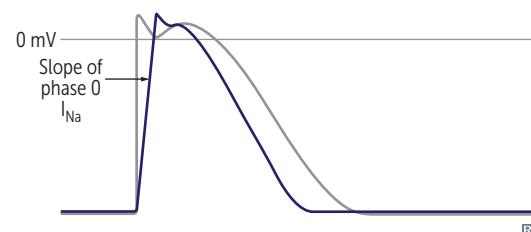
Weak  $\text{Na}^+$  channel blockade.  
 ↓ AP duration. Preferentially affect ischemic or depolarized Purkinje and ventricular tissue.

**CLINICAL USE**

Acute ventricular arrhythmias (especially post-MI), digitalis-induced arrhythmias.  
**IB** is Best post-MI.

**ADVERSE EFFECTS**

CNS stimulation/depression, cardiovascular depression.



**Class IC**

**Flecainide, propafenone.**  
 “Can I have fries, please?”

**MECHANISM**

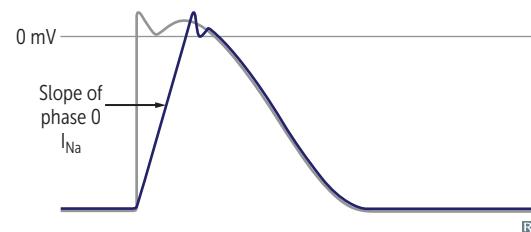
Strong  $\text{Na}^+$  channel blockade.  
 Significantly prolongs ERP in AV node and accessory bypass tracts. No effect on ERP in Purkinje and ventricular tissue.  
 Minimal effect on AP duration.

**CLINICAL USE**

SVTs, including atrial fibrillation. Only as a last resort in refractory VT.

**ADVERSE EFFECTS**

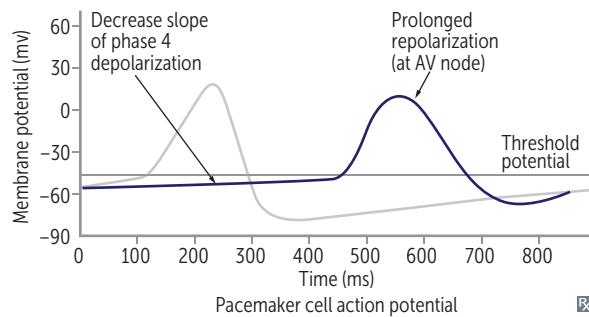
Proarrhythmic, especially post-MI (contraindicated). **IC** is Contraindicated in structural and ischemic heart disease.



**Antiarrhythmics—  
β-blockers (class II)**

Metoprolol, propranolol, esmolol, atenolol, timolol, carvedilol.

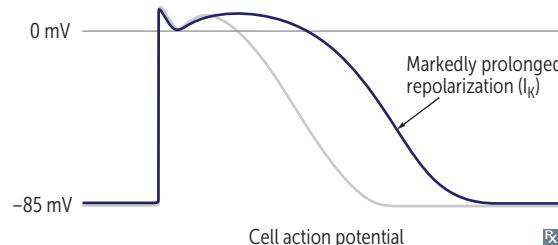
MECHANISM	Decrease SA and AV nodal activity by ↓ cAMP, ↓ Ca <sup>2+</sup> currents. Suppress abnormal pacemakers by ↓ slope of phase 4. AV node particularly sensitive—↑ PR interval. Esmolol very short acting.
CLINICAL USE	SVT, ventricular rate control for atrial fibrillation and atrial flutter.
ADVERSE EFFECTS	Impotence, exacerbation of COPD and asthma, cardiovascular effects (bradycardia, AV block, HF), CNS effects (sedation, sleep alterations). May mask the signs of hypoglycemia. Metoprolol can cause dyslipidemia. Propranolol can exacerbate vasospasm in vasospastic angina. β-blockers (except the nonselective α- and β-antagonists carvedilol and labetalol) cause unopposed α <sub>1</sub> -agonism if given alone for pheochromocytoma or for cocaine toxicity (unsubstantiated). 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 or hyperthyroidism (amiodarone is 40% iodine by weight), acts as hapten (corneal deposits, blue/gray skin deposits resulting in photodermatitis), neurologic effects, constipation, cardiovascular effects (bradycardia, heart block, HF).	Remember to check PFTs, LFTs, and TFTs when using amiodarone. Amiodarone is lipophilic and has class I, II, III, and IV effects.



**Antiarrhythmics—  
calcium channel  
blockers (class IV)**

## MECHANISM

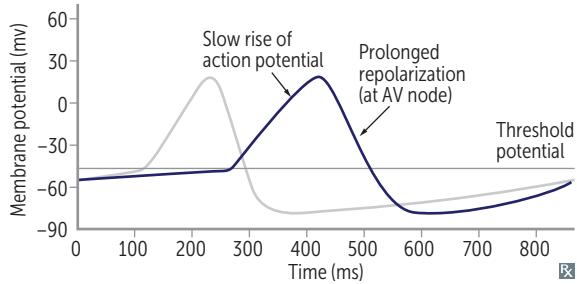
Decrease conduction velocity, ↑ ERP, ↑ PR interval.

## CLINICAL USE

Prevention of nodal arrhythmias (eg, SVT), rate control in atrial fibrillation.

## ADVERSE EFFECTS

Constipation, flushing, edema, cardiovascular effects (HF, AV block, sinus node depression).



**Other antiarrhythmics**

**Adenosine**

↑ K<sup>+</sup> out of cells → hyperpolarizing the cell and ↓ I<sub>Ca</sub>, decreasing AV node conduction. Drug of choice in diagnosing/terminating certain forms of SVT. Very short acting (~ 15 sec). Effects blunted by theophylline and caffeine (both are adenosine receptor antagonists). Adverse effects include flushing, hypotension, chest pain, sense of impending doom, bronchospasm.

**Magnesium**

Effective in torsades de pointes and digoxin toxicity.

**Ivabradine**

## MECHANISM

**IV**abradine prolongs slow depolarization (phase “IV”) by selectively inhibiting “funny” sodium channels (I<sub>f</sub>).

## CLINICAL USE

Chronic stable angina in patients who cannot take β-blockers. Chronic HFrEF.

## ADVERSE EFFECTS

Luminous phenomena/visual brightness, hypertension, bradycardia.

# Endocrine

*“If you skew the endocrine system, you lose the pathways to self.”*

—Hilary Mantel

*“Sometimes you need a little crisis to get your adrenaline flowing and help you realize your potential.”*

—Jeannette Walls, *The Glass Castle*

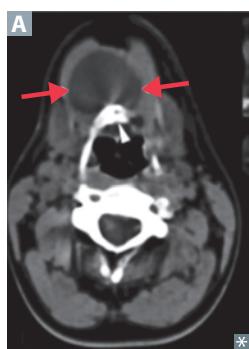
*“Chocolate causes certain endocrine glands to secrete hormones that affect your feelings and behavior by making you happy.”*

—Elaine Sherman, *Book of Divine Indulgences*

The endocrine system comprises widely distributed organs that work in a highly integrated manner to orchestrate a state of hormonal equilibrium within the body. Generally speaking, endocrine diseases can be classified either as diseases of underproduction or overproduction, or as conditions involving the development of mass lesions—which themselves may be associated with underproduction or overproduction of hormones. Therefore, study the endocrine system first by learning the glands, their hormones, and their regulation, and then by integrating disease manifestations with diagnosis and management. Take time to learn the multisystem connections.

► Embryology	334
► Anatomy	335
► Physiology	336
► Pathology	346
► Pharmacology	362

## ▶ ENDOCRINE—EMBRYOLOGY

**Thyroid development**

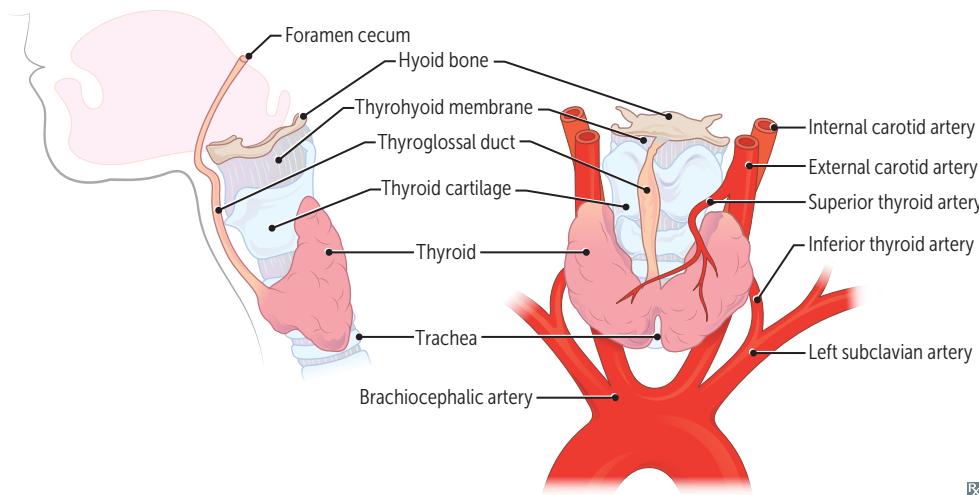
Thyroid diverticulum arises from floor of primitive pharynx and descends into neck. Connected to tongue by thyroglossal duct, which normally disappears but may persist as cysts or the pyramidal lobe of thyroid. Foramen cecum is normal remnant of thyroglossal duct.

Most common ectopic thyroid tissue site is the tongue (lingual thyroid). Removal may result in hypothyroidism if it is the only thyroid tissue present.

Thyroglossal duct cyst **A** presents as an anterior midline neck mass that moves with swallowing or protrusion of the tongue (vs persistent cervical sinus leading to pharyngeal cleft cyst in lateral neck).

Thyroid follicular cells derived from endoderm.

Parafollicular cells arise from 4th pharyngeal pouch.



## ▶ ENDOCRINE—ANATOMY

**Pituitary gland****Anterior pituitary  
(adenohypophysis)**

Secretes FSH, LH, ACTH, TSH, prolactin, GH, and  $\beta$ -endorphin. Melanotropin (MSH) secreted from intermediate lobe of pituitary. Derived from oral ectoderm (Rathke pouch).

- $\alpha$  subunit—hormone subunit common to TSH, LH, FSH, and hCG.
- $\beta$  subunit—determines hormone specificity.

Proopiomelanocortin derivatives— $\beta$ -endorphin, ACTH, and MSH. Go pro with a BAM!

**FLAT PiG:** FSH, LH, ACTH, TSH, PRL, GH.

**B-FLAT:** Basophils—FSH, LH, ACTH, TSH.

**Acid PiG:** Acidophils — PRL, GH.

**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.

**Adrenal cortex and medulla**

Adrenal cortex (derived from mesoderm) and medulla (derived from neural crest).

ANATOMY	HISTOLOGY	1° REGULATION BY	HORMONE CLASS	1° HORMONE PRODUCED
Adrenal gland	Zona Glomerulosa	Angiotensin II	Mineralocorticoids	Aldosterone
Capsule	Zona Fasciculata	ACTH, CRH	Glucocorticoids	Cortisol
Superior surface of kidney	Zona Reticularis	ACTH, CRH	Androgens	DHEA
	Chromaffin cells	Preganglionic sympathetic fibers	Catecholamines	Epi, NE

**GFR** corresponds with salt (mineralocorticoids), sugar (glucocorticoids), and sex (androgens). “The deeper you go, the sweeter it gets.”

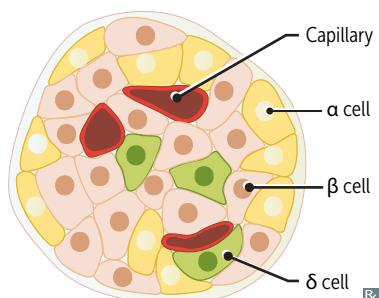
**Endocrine pancreas cell types**

Islets of Langerhans are collections of  $\alpha$ ,  $\beta$ , and  $\delta$  endocrine cells. Islets arise from pancreatic buds.

$\alpha$  = glucagon (peripheral)

$\beta$  = insulin (central)

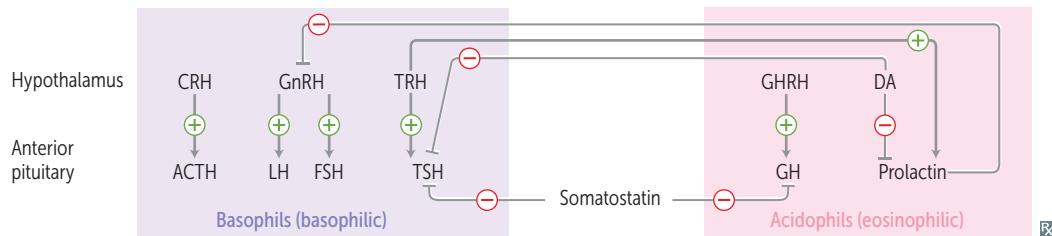
$\delta$  = somatostatin (interspersed)



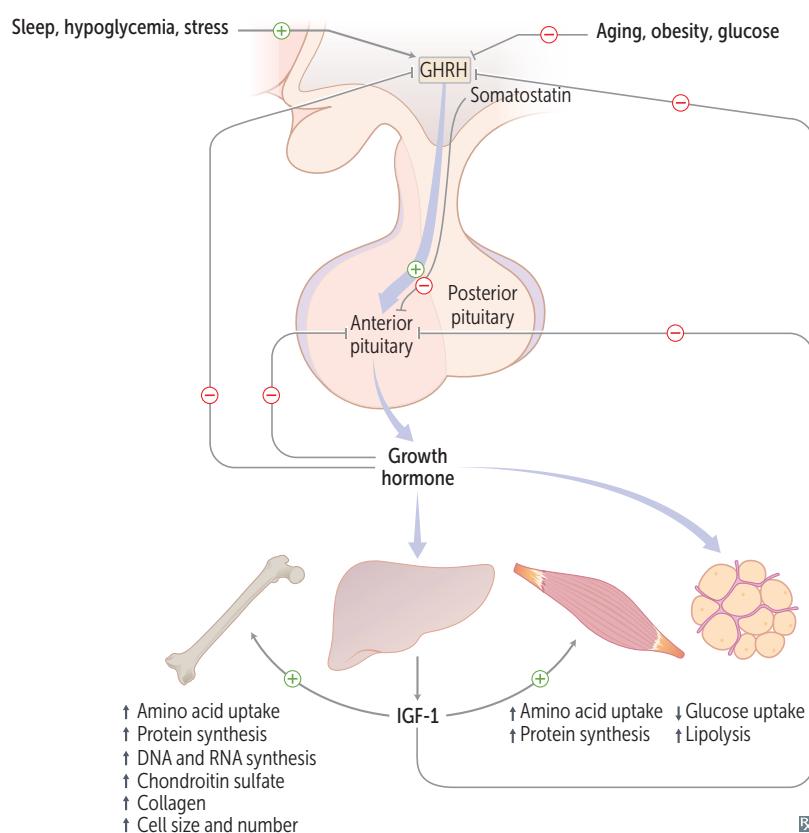
## ► ENDOCRINE—PHYSIOLOGY

**Hypothalamic-pituitary hormones**

HORMONE	FUNCTION	CLINICAL NOTES
<b>ADH</b>	↑ water permeability of distal convoluted tubule and collecting duct cells in kidney to ↑ water reabsorption	Stimulus for secretion is ↑ plasma osmolality, except in SIADH, in which ADH is elevated despite ↓ plasma osmolality
<b>CRH</b>	↑ ACTH, MSH, β-endorphin	↓ in chronic exogenous steroid use
<b>Dopamine</b>	↓ prolactin, TSH	Also called prolactin-inhibiting factor Dopamine antagonists (eg, antipsychotics) can cause galactorrhea due to hyperprolactinemia
<b>GHRH</b>	↑ GH	Analog (tesamorelin) used to treat HIV-associated lipodystrophy
<b>GnRH</b>	↑ FSH, LH	Suppressed by hyperprolactinemia Tonic GnRH analog (eg, leuprolide) suppresses hypothalamic–pituitary–gonadal axis. Pulsatile GnRH leads to puberty, fertility
<b>MSH</b>	↑ melanogenesis by melanocytes	Causes hyperpigmentation in Cushing disease, as MSH and ACTH share the same precursor molecule, proopiomelanocortin
<b>Oxytocin</b>	Causes uterine contractions during labor. Responsible for milk letdown reflex in response to suckling.	Modulates fear, anxiety, social bonding, mood, and depression
<b>Prolactin</b>	↓ GnRH Stimulates lactogenesis.	Pituitary prolactinoma → amenorrhea, osteoporosis, hypogonadism, galactorrhea Breastfeeding → ↑ prolactin → ↓ GnRH → delayed postpartum ovulation (natural contraception)
<b>Somatostatin</b>	↓ GH, TSH	Also called growth hormone inhibiting hormone (GHIH) Analog used to treat acromegaly
<b>TRH</b>	↑ TSH, prolactin	↑ TRH (eg, in 1°/2° hypothyroidism) may increase prolactin secretion → galactorrhea



## Growth hormone



Also called somatotropin. Secreted by anterior pituitary.

Stimulates linear growth and muscle mass through IGF-1 (somatomedin C) secretion by liver. ↑ insulin resistance (diabetogenic).

Released in pulses in response to growth hormone-releasing hormone (GHRH).

Secretion ↑ during exercise, deep sleep, puberty, hypoglycemia.

Secretion ↓ by glucose, somatostatin, somatomedin (regulatory molecule secreted by liver in response to GH acting on target tissues).

Excess secretion of GH (eg, pituitary adenoma) may cause acromegaly (adults) or gigantism (children). Treatment: somatostatin analogs (eg, octreotide) or surgery.

## Antidiuretic hormone

Also called vasopressin.

### SOURCE

Synthesized in hypothalamus (supraoptic and paraventricular nuclei), stored and secreted by posterior pituitary.

### FUNCTION

Regulates blood pressure ( $V_1$ -receptors) and serum osmolality ( $V_2$ -receptors). Primary function is serum osmolality regulation (ADH ↓ serum osmolality, ↑ urine osmolality) via regulation of aquaporin channel insertion in principal cells of renal collecting duct.

### REGULATION

Plasma osmolality (↑); hypovolemia.

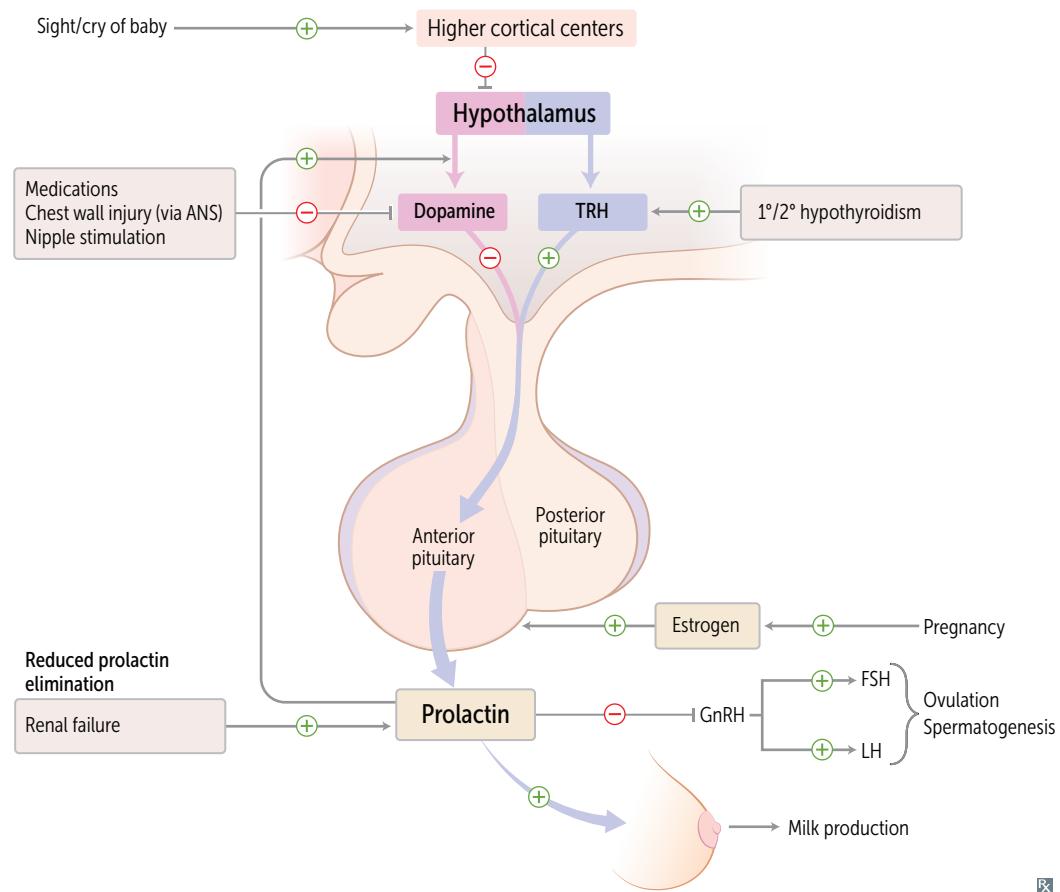
ADH level is ↓ in central diabetes insipidus (DI), normal or ↑ in nephrogenic DI.

Nephrogenic DI can be caused by mutation in  $V_2$ -receptor.

Desmopressin (ADH analog) is a treatment for central DI and nocturnal enuresis.

**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 tuberoinfundibular pathway of hypothalamus. Prolactin in turn inhibits its own secretion by ↑ dopamine synthesis and secretion from hypothalamus. TRH ↑ prolactin secretion (eg, in 1° or 2° hypothyroidism).	Dopamine agonists (eg, bromocriptine) inhibit prolactin secretion and can be used in treatment of prolactinoma. Dopamine antagonists (eg, most antipsychotics, metoclopramide) and estrogens (eg, OCPs, pregnancy) stimulate prolactin secretion.



**Thyroid hormones**

Thyroid produces triiodothyronine ( $T_3$ ) and thyroxine ( $T_4$ ), iodine-containing hormones that control the body's metabolic rate.

## SOURCE

Follicles of thyroid.  $5'$ -deiodinase converts  $T_4$  (the major thyroid product) to  $T_3$  in peripheral tissue (5, 4, 3). Peripheral conversion is inhibited by glucocorticoids,  $\beta$ -blockers, and propylthiouracil (PTU). Reverse  $T_3$  ( $rT_3$ ) is a metabolically inactive byproduct of the peripheral conversion of  $T_4$  and its production is increased by growth hormone and glucocorticoids. Functions of thyroid peroxidase include oxidation, organification of iodine, and coupling of monoiodotyrosine (MIT) and diiodotyrosine (DIT). Inhibited by PTU and methimazole.  $DIT + DIT = T_4$ .  $DIT + MIT = T_3$ . Wolff-Chaikoff effect—protective autoregulation; sudden exposure to excess iodine temporarily turns off thyroid peroxidase  $\rightarrow \downarrow T_3/T_4$  production.

## FUNCTION

Only free hormone is active.  $T_3$  binds nuclear receptor with greater affinity than  $T_4$ .  $T_3$  functions  $\sim 7$  B's:

- Brain maturation
- Bone growth (synergism with GH)
- $\beta$ -adrenergic effects.  $\uparrow \beta_1$  receptors in heart  $\rightarrow \uparrow CO, HR, SV$ , contractility;  $\beta$ -blockers alleviate adrenergic symptoms in thyrotoxicosis
- Basal metabolic rate  $\uparrow$  (via  $\uparrow Na^+/K^+$ -ATPase  $\rightarrow \uparrow O_2$  consumption, RR, body temperature)
- Blood sugar ( $\uparrow$  glycogenolysis, gluconeogenesis)
- Break down lipids ( $\uparrow$  lipolysis)
- Stimulates surfactant synthesis in Babies

## REGULATION

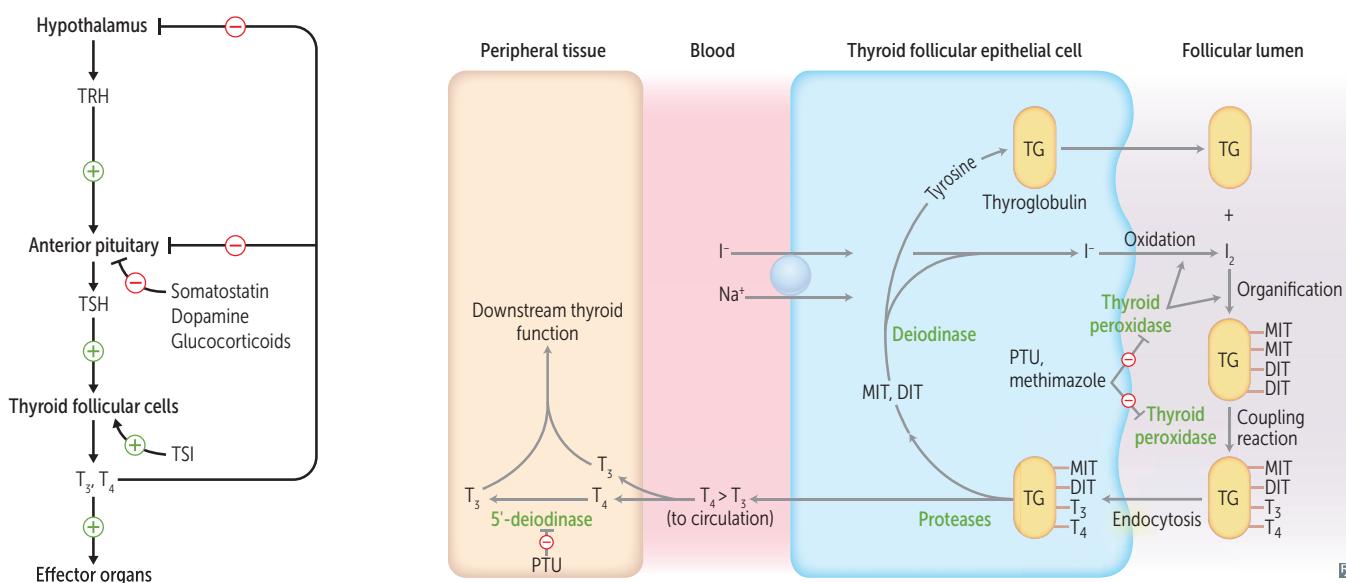
TRH  $\rightarrow \oplus$  TSH release  $\rightarrow \oplus$  follicular cells. Thyroid-stimulating immunoglobulin (TSI) may  $\oplus$  follicular cells in Graves disease.

Negative feedback primarily by free  $T_3/T_4$ :

- Anterior pituitary  $\rightarrow \downarrow$  sensitivity to TRH
- Hypothalamus  $\rightarrow \downarrow$  TRH secretion

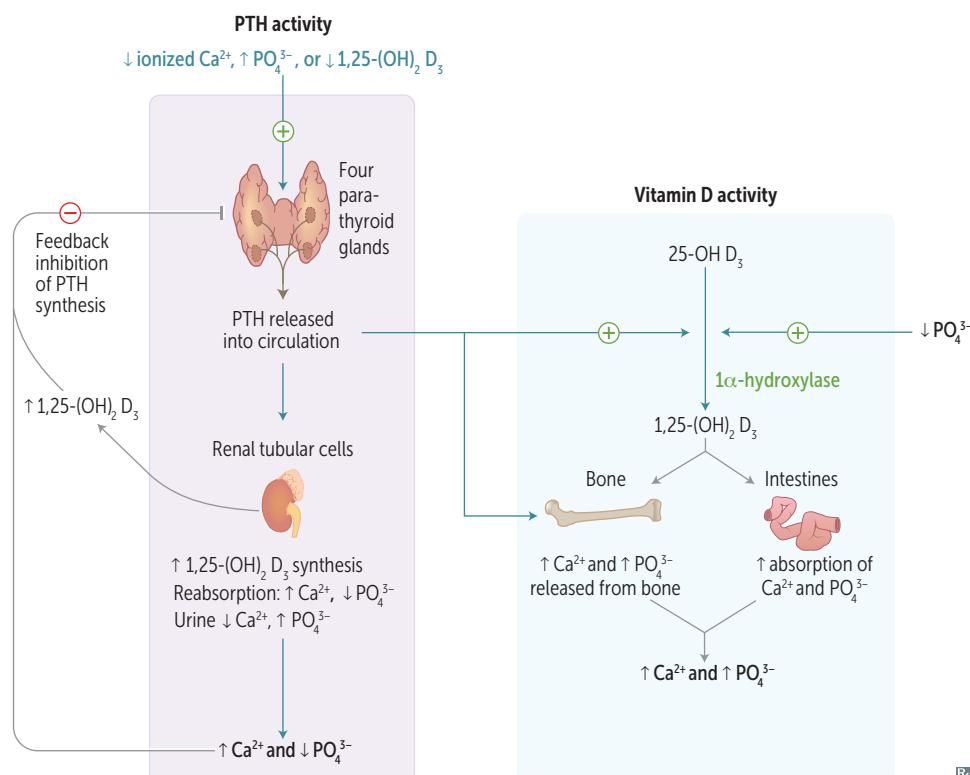
Thyroxine-binding globulin (TBG) binds most  $T_3/T_4$  in blood. Bound  $T_3/T_4$  = inactive.

- $\uparrow$  TBG in pregnancy, OCP use (estrogen  $\rightarrow \uparrow$  TBG)  $\rightarrow \uparrow$  total  $T_3/T_4$
- $\downarrow$  TBG in steroid use, nephrotic syndrome



### Parathyroid hormone

SOURCE	Chief cells of parathyroid	
FUNCTION	<ul style="list-style-type: none"> <li>↑ free <math>\text{Ca}^{2+}</math> in the blood (1° function)</li> <li>↑ <math>\text{Ca}^{2+}</math> and <math>\text{PO}_4^{3-}</math> absorption in GI system</li> <li>↑ <math>\text{Ca}^{2+}</math> and <math>\text{PO}_4^{3-}</math> from bone resorption</li> <li>↑ <math>\text{Ca}^{2+}</math> reabsorption from DCT</li> <li>↓ <math>\text{PO}_4^{3-}</math> reabsorption in PCT</li> <li>↑ <math>1,25-(\text{OH})_2\text{D}_3</math> (calcitriol) production by activating <math>\text{l}\alpha</math>-hydroxylase in <b>PCT</b> (tri to make <math>\text{D}_3</math> in the <b>PCT</b>)</li> </ul>	<ul style="list-style-type: none"> <li>PTH ↑ serum <math>\text{Ca}^{2+}</math>, ↓ serum <math>\text{PO}_4^{3-}</math>, ↑ urine <math>\text{PO}_4^{3-}</math>, ↑ urine cAMP</li> <li>↑ RANK-L (receptor activator of NF-κB ligand) secreted by osteoblasts and osteocytes; binds RANK (receptor) on osteoclasts and their precursors to stimulate osteoclasts and ↑ <math>\text{Ca}^{2+}</math> → bone resorption (intermittent PTH release can also stimulate bone formation)</li> </ul> <p><b>PTH = Phosphate-Trashing Hormone</b></p> <p>PTH-related peptide (PTHRP) functions like PTH and is commonly increased in malignancies (eg, squamous cell carcinoma of the lung, renal cell carcinoma)</p>
REGULATION	<ul style="list-style-type: none"> <li>↓ serum <math>\text{Ca}^{2+}</math> → ↑ PTH secretion</li> <li>↑ serum <math>\text{PO}_4^{3-}</math> → ↑ PTH secretion</li> <li>↓ serum <math>\text{Mg}^{2+}</math> → ↑ PTH secretion</li> <li>↓↓ serum <math>\text{Mg}^{2+}</math> → ↓ PTH secretion</li> </ul> <p>Common causes of ↓ <math>\text{Mg}^{2+}</math> include diarrhea, aminoglycosides, diuretics, alcohol use disorder</p>	



**Calcium homeostasis**

Plasma  $\text{Ca}^{2+}$  exists in three forms:

- Ionized/free (~ 45%, active form)
- Bound to albumin (~ 40%)
- Bound to anions (~ 15%)

↑ pH (less  $\text{H}^+$ ) → albumin binds more  $\text{Ca}^{2+}$  → ↓ ionized  $\text{Ca}^{2+}$  (eg, cramps, pain, paresthesias, carpopedal spasm) → ↑ PTH

↓ pH (more  $\text{H}^+$ ) → albumin binds less  $\text{Ca}^{2+}$  → ↑ ionized  $\text{Ca}^{2+}$  → ↓ PTH

Ionized/free  $\text{Ca}^{2+}$  is 1° regulator of PTH; changes in pH alter PTH secretion, whereas changes in albumin concentration do not

**Calcitonin**

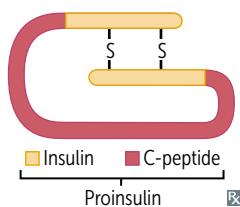
SOURCE	Parafollicular cells (C cells) of thyroid.	Calcitonin opposes actions of PTH. Not important in normal $\text{Ca}^{2+}$ homeostasis Calcitonin tones down serum $\text{Ca}^{2+}$ levels and keeps it in bones
FUNCTION	↓ bone resorption.	
REGULATION	↑ serum $\text{Ca}^{2+}$ → ↑ calcitonin secretion.	

**Glucagon**

SOURCE	Made by $\alpha$ cells of pancreas.
FUNCTION	Promotes glycogenolysis, gluconeogenesis, lipolysis, ketogenesis. Elevates blood sugar levels to maintain homeostasis when bloodstream glucose levels fall too low (ie, fasting state).
REGULATION	Secreted in response to hypoglycemia. Inhibited by insulin, amylin, somatostatin, hyperglycemia.

## Insulin

### SYNTHESIS



Preproinsulin (synthesized in RER of pancreatic  $\beta$  cells)  $\rightarrow$  cleavage of “presignal”  $\rightarrow$  proinsulin (stored in secretory granules)  $\rightarrow$  cleavage of proinsulin  $\rightarrow$  exocytosis of insulin and C-peptide equally. Insulin and C-peptide are  $\uparrow$  in insulinoma and sulfonylurea use, whereas exogenous insulin lacks C-peptide.

### FUNCTION

Binds insulin receptors (tyrosine kinase activity ①), inducing glucose uptake (carrier-mediated transport) into insulin-dependent tissue ② and gene transcription.

Anabolic effects of insulin:

- $\uparrow$  glucose transport in skeletal muscle and adipose tissue
- $\uparrow$  glycogen synthesis and storage
- $\uparrow$  triglyceride synthesis
- $\uparrow$   $\text{Na}^+$  retention (kidneys)
- $\uparrow$  protein synthesis (muscles)
- $\uparrow$  cellular uptake of  $\text{K}^+$  and amino acids
- $\downarrow$  glucagon release
- $\downarrow$  lipolysis in adipose tissue

Unlike glucose, insulin does not cross placenta.

Insulin-dependent glucose transporters:

- GLUT4: adipose tissue, striated muscle (exercise can also  $\uparrow$  GLUT4 expression)

Insulin-independent transporters:

- GLUT1: RBCs, brain, cornea, placenta
- GLUT2 (bidirectional):  $\beta$  islet cells, liver, kidney, GI tract (think 2-way street)
- GLUT3: brain, placenta
- GLUT5 (fructose): spermatocytes, GI tract
- SGLT1/SGLT2 ( $\text{Na}^+$ -glucose cotransporters): kidney, small intestine

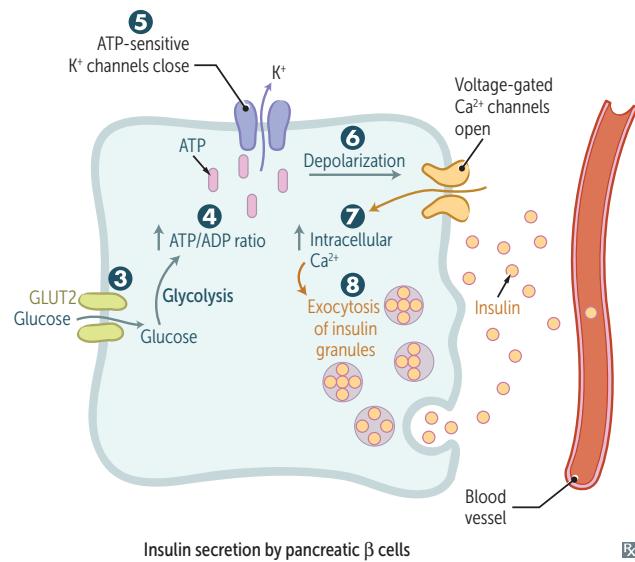
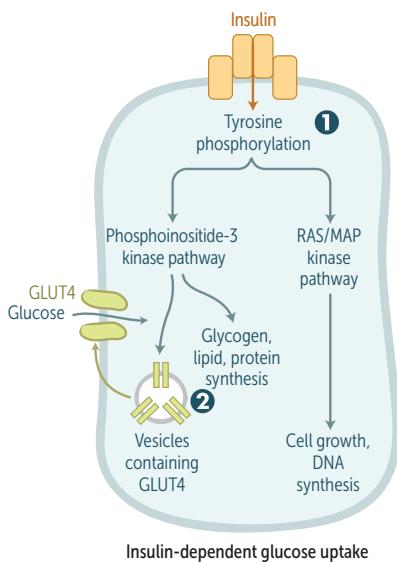
Brain prefers glucose, but may use ketone bodies during starvation. RBCs utilize glucose, as they lack mitochondria for aerobic metabolism.

**BRICK LIPS** (insulin-independent glucose uptake): Brain, RBCs, Intestine, Cornea, Kidney, Liver, Islet ( $\beta$ ) cells, Placenta, Spermatocytes.

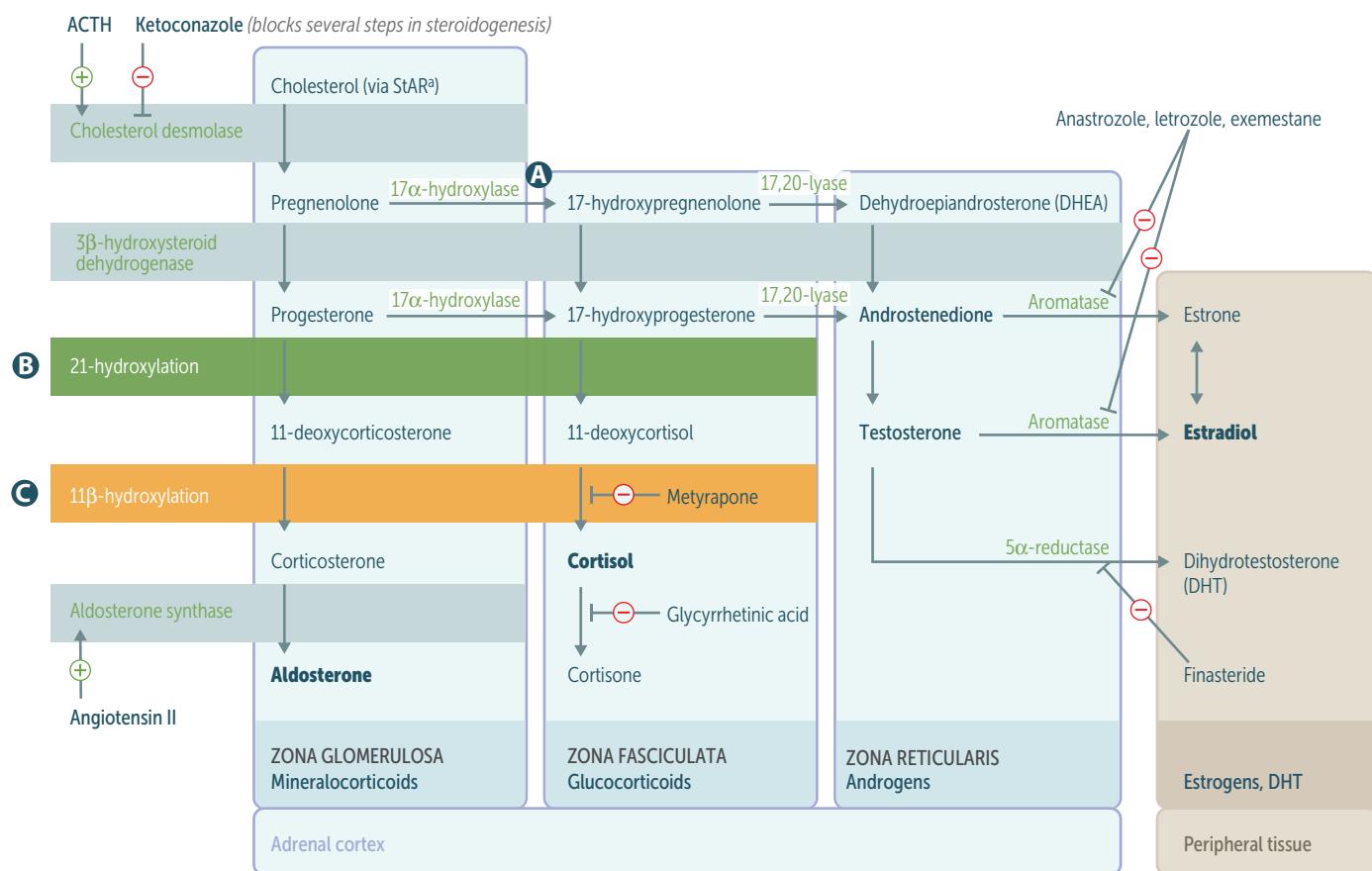
### REGULATION

Glucose is the major regulator of insulin release.  $\uparrow$  insulin response with oral vs IV glucose due to incretins (eg, glucagon-like peptide 1 [GLP-1], glucose-dependent insulinotropic polypeptide [GIP]), which are released after meals and  $\uparrow$   $\beta$  cell sensitivity to glucose. Release  $\downarrow$  by  $\alpha_2$ ,  $\uparrow$  by  $\beta_2$  stimulation (2 = regulates insulin).

Glucose enters  $\beta$  cells ③  $\rightarrow$   $\uparrow$  ATP generated from glucose metabolism ④ closes  $\text{K}^+$  channels (target of sulfonylureas) ⑤ and depolarizes  $\beta$  cell membrane ⑥. Voltage-gated  $\text{Ca}^{2+}$  channels open  $\rightarrow$   $\text{Ca}^{2+}$  influx ⑦ and stimulation of insulin exocytosis ⑧.



### Adrenal steroids and congenital adrenal hyperplasias



<sup>a</sup>Rate-limiting step.

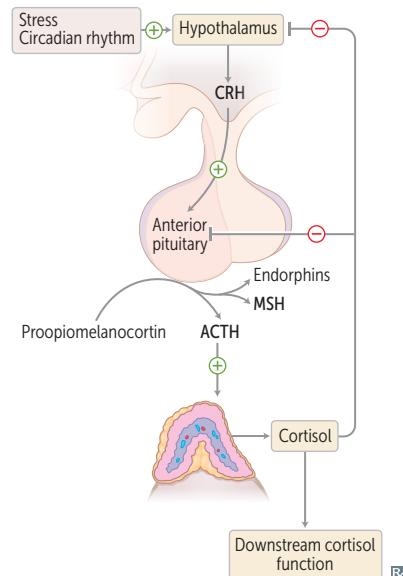
ENZYME DEFICIENCY	MINERALOCORTICOIDS	[K <sup>+</sup> ]	BP	CORTISOL	SEX HORMONES	LABS	PRESENTATION
<b>A 17<math>\alpha</math>-hydroxylase<sup>a</sup></b>	↑		↓	↑	↓	↓ androstenedione	XY: ambiguous genitalia, undescended testes XX: lacks 2 <sup>o</sup> sexual development
<b>B 21-hydroxylase<sup>a</sup></b>	↓		↑	↓	↓	↑ renin activity ↑ 17-hydroxyprogesterone	Most common Presents in infancy (salt wasting) or childhood (precocious puberty) XX: virilization
<b>C 11<math>\beta</math>-hydroxylase<sup>a</sup></b>	↓ aldosterone ↑ 11-deoxycorticosterone (results in ↑ BP)	↓	↑	↓	↑	↓ renin activity	Presents in infancy (severe hypertension) or childhood (precocious puberty) XX: virilization

<sup>a</sup>All congenital adrenal enzyme deficiencies are autosomal recessive disorders and most are characterized by skin hyperpigmentation (due to ↑ MSH production, which is coproduced and secreted with ACTH) and bilateral adrenal gland enlargement (due to ↑ ACTH stimulation).

If deficient enzyme starts with 1, it causes hypertension; if deficient enzyme ends with 1, it causes virilization in females.

**Cortisol**

SOURCE	Adrenal zona fasciculata.	Bound to corticosteroid-binding globulin.
FUNCTION	<ul style="list-style-type: none"> <li>↑ Appetite</li> <li>↑ Blood pressure:           <ul style="list-style-type: none"> <li>▪ Upregulates <math>\alpha_1</math>-receptors on arterioles → ↑ sensitivity to norepinephrine and epinephrine (permissive action)</li> <li>▪ At high concentrations, can bind to mineralocorticoid (aldosterone) receptors</li> </ul> </li> <li>↑ Insulin resistance (diabetogenic)</li> <li>↑ Gluconeogenesis, lipolysis, and proteolysis (↓ glucose utilization)</li> <li>↓ Fibroblast activity (poor wound healing, ↓ collagen synthesis, ↑ striae)</li> <li>↓ Inflammatory and Immune responses:           <ul style="list-style-type: none"> <li>▪ Inhibits production of leukotrienes and prostaglandins</li> <li>▪ Inhibits WBC adhesion → neutrophilia</li> <li>▪ Blocks histamine release from mast cells</li> <li>▪ Eosinopenia, lymphopenia</li> <li>▪ Blocks IL-2 production</li> </ul> </li> <li>↓ Bone formation (↓ osteoblast activity)</li> </ul>	Cortisol is <b>A BIG FIB</b> . Exogenous corticosteroids can cause reactivation of TB and candidiasis (blocks IL-2 production).
REGULATION	CRH (hypothalamus) stimulates ACTH release (pituitary) → cortisol production in adrenal zona fasciculata. Excess cortisol ↓ CRH, ACTH, and cortisol secretion.	Chronic stress may induce prolonged cortisol secretion, cortisol resistance, impaired immunocompetency, and dysregulation of HPA axis.

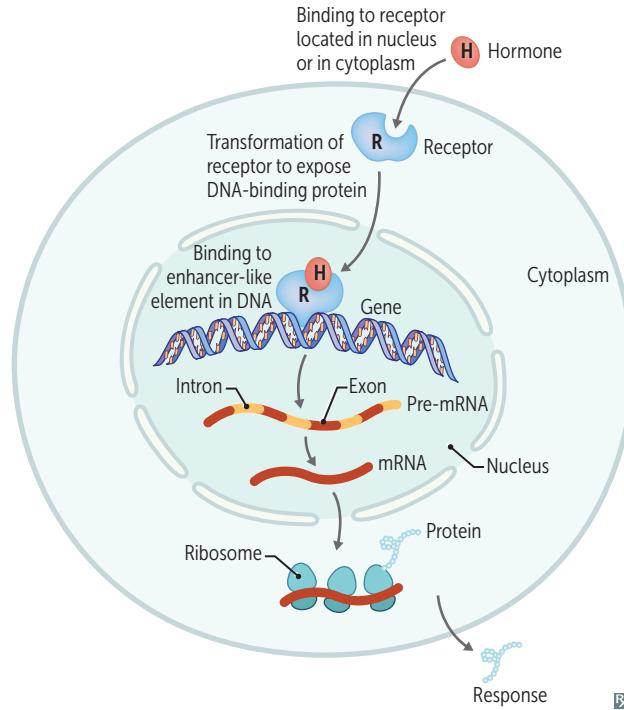
**Appetite regulation**

Ghrelin	<p>Stimulates hunger (orexigenic effect) and GH release (via GH secretagog receptor). Produced by stomach. Sleep deprivation, fasting, or Prader-Willi syndrome → ↑ ghrelin production.</p> <p><b>Ghrelin makes you <i>ghrow hungry</i>.</b> Acts on lateral area of hypothalamus (hunger center) to ↑ appetite.</p>
Leptin	<p>Satiety hormone. Produced by adipose tissue. Mutation of leptin gene → severe obesity. Obese people have ↑ leptin due to ↑ adipose tissue but are tolerant or resistant to leptin's anorexigenic effect. Sleep deprivation or starvation → ↓ leptin production.</p> <p><b>Leptin keeps you <i>thin</i>.</b> Acts on ventromedial area of hypothalamus (satiety center) to ↓ appetite.</p>
Endocannabinoids	<p>Act at cannabinoid receptors in hypothalamus and nucleus accumbens, two key brain areas for the homeostatic and hedonic control of food intake → ↑ appetite.</p> <p>Exogenous cannabinoids cause “the munchies.”</p>

### Signaling pathways of endocrine hormones

cAMP	FSH, LH, ACTH, TSH, CRH, hCG, ADH (V <sub>2</sub> -receptor), MSH, PTH, Calcitonin, Histamine (H <sub>2</sub> -receptor), Glucagon, GHRH	FLAT ChAMPs CHuGG
cGMP	BNP, ANP, EDRF (NO)	BAD GraMPa Think vasodilation and diuresis
IP <sub>3</sub>	GnRH, Oxytocin, ADH (V <sub>1</sub> -receptor), TRH, Histamine (H <sub>1</sub> -receptor), Angiotensin II, Gastrin	GOAT HAG
Intracellular receptor	Progesterone, Estrogen, Testosterone, Cortisol, Aldosterone, T <sub>3</sub> /T <sub>4</sub> , Vitamin D	PET CAT in TV
Receptor tyrosine kinase	IGF-1, FGF, PDGF, EGF, Insulin	MAP kinase pathway Get Found In the MAP
Serine/threonine kinase receptor	TGF-β	
Nonreceptor tyrosine kinase	G-CSF, Erythropoietin, Thrombopoietin Prolactin, Immunomodulators (eg, cytokines IL-2, IL-6, IFN), GH	JAK/STAT pathway Think acidophils and cytokines GET a JAKed PIG

### Signaling pathways of steroid hormones



Steroid hormones are lipophilic and therefore must circulate bound to specific binding globulins, which ↑ their solubility.  
 In males, ↑ sex hormone–binding globulin (SHBG) lowers free testosterone → gynecomastia.  
 In females, ↓ SHBG raises free testosterone → hirsutism.  
 ↑ estrogen (eg, OCPs, pregnancy) → ↑ SHBG.

## ▶ ENDOCRINE—PATHOLOGY

**Syndrome of inappropriate antidiuretic hormone secretion**

Characterized by:

- Excessive free water retention
- Euvolemic hyponatremia with continued urinary  $\text{Na}^+$  excretion
- Urine osmolality > serum osmolality

Body responds to water retention with ↓ aldosterone and ↑ ANP and BNP → ↑ urinary  $\text{Na}^+$  secretion → normalization of extracellular fluid volume → euvoemic hyponatremia. Very low serum  $\text{Na}^+$  levels can lead to cerebral edema, seizures. Correct slowly to prevent osmotic demyelination syndrome (formerly called central pontine myelinolysis).

SIADH causes include (HELD-up water):

- Head trauma/CNS disorders
- Ectopic ADH (eg, small cell lung cancer)
- Lung disease
- Drugs (eg, SSRIs, carbamazepine, cyclophosphamide)

Treatment: fluid restriction (first line), salt tablets, IV hypertonic saline, diuretics, ADH antagonists (eg, conivaptan, tolvaptan, demeclocycline).

**Primary polydipsia and diabetes insipidus**

Characterized by the production of large amounts of dilute urine +/- thirst. Urine specific gravity <1.006. Urine osmolality usually <300 mOsm/kg. Diabetes insipidus (DI) is classified as central or nephrogenic depending on etiology.

	<b>Primary polydipsia</b>	<b>Central DI</b>	<b>Nephrogenic DI</b>
<b>DEFINITION</b>	Excessive water intake	↓ ADH release	ADH resistance
<b>CAUSES</b>	Psychiatric illnesses, hypothalamic lesions affecting thirst center	Idiopathic, tumors (eg, pituitary), infiltrative diseases (eg, sarcoidosis), trauma, surgery, hypoxic encephalopathy	Hereditary (ADH receptor mutation), drugs (eg, lithium, demeclocycline), hypercalcemia, hypokalemia
<b>SERUM OSMOLALITY</b>	↓	↑	↑
<b>ADH LEVEL</b>	↓ or normal	↓	Normal or ↑
<b>WATER RESTRICTION<sup>a</sup></b>	Significant ↑ in urine osmolality (>700 mOsm/kg)	No change or slight ↑ in urine osmolality	No change or slight ↑ in urine osmolality
<b>DESMOPRESSIN ADMINISTRATION<sup>b</sup></b>	—	Significant ↑ in urine osmolality (>50%)	Minimal change in urine osmolality
<b>TREATMENT</b>	Water restriction	Desmopressin	Manage the underlying cause. Low-solute diet, HCTZ, amiloride, indomethacin

<sup>a</sup>No water intake for 2-3 hours followed by hourly measurements of urine volume and osmolality as well as plasma  $\text{Na}^+$  concentration and osmolality.

<sup>b</sup>Desmopressin (ADH analog) is administered if serum osmolality >295-300 mOsm/kg, plasma  $\text{Na}^+ \geq 145$  mEq/L, or urine osmolality does not rise despite ↑ plasma osmolality.

**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 females; associated with idiopathic intracranial hypertension
- **Pituitary apoplexy**—sudden hemorrhage of pituitary gland, often in the presence of an existing pituitary adenoma. Usually presents with sudden onset severe headache, visual impairment (eg, bitemporal hemianopia, diplopia due to CN III palsy), and features of hypopituitarism
- Brain injury
- Radiation

Treatment: hormone replacement therapy (corticosteroids, thyroxine, sex steroids, human growth hormone)

**Acromegaly**

Excess GH in adults. Typically caused by pituitary adenoma.

**FINDINGS**

Large tongue with deep furrows, deep voice, large hands and feet, coarsening of facial features with aging **A**, frontal bossing, diaphoresis (excessive sweating), impaired glucose tolerance (insulin resistance), hypertension. ↑ risk of colorectal polyps and cancer.

↑ GH in children → gigantism (↑ 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), pegvisomant (GH receptor antagonist), or dopamine agonists (eg, cabergoline).

**Hypothyroidism vs hyperthyroidism**

	<b>Hypothyroidism</b>	<b>Hyperthyroidism</b>
METABOLIC	Cold intolerance, ↓ sweating, weight gain (↓ basal metabolic rate → ↓ calorigenesis), hyponatremia (↓ free water clearance)	Heat intolerance, ↑ sweating, weight loss (↑ synthesis of Na <sup>+</sup> -K <sup>+</sup> ATPase → ↑ basal metabolic rate → ↑ calorigenesis)
SKIN/HAIR	Dry, cool skin (due to ↓ blood flow); coarse, brittle hair; diffuse alopecia; brittle nails; puffy facies and generalized nonpitting edema (myxedema <b>A</b> ) due to ↑ GAGs in interstitial spaces → ↑ osmotic pressure → water retention	Warm, moist skin (due to vasodilation); fine hair; onycholysis ( <b>B</b> ); pretibial myxedema in Graves disease
OCULAR	Periorbital edema <b>C</b>	Ophthalmopathy in Graves disease (including periorbital edema, exophthalmos), lid lag/retraction (↑ sympathetic stimulation of levator palpebrae superioris and superior tarsal muscle)
GASTROINTESTINAL	Constipation (↓ GI motility), ↓ appetite	Hyperdefecation/diarrhea (↑ GI motility), ↑ appetite
MUSCULOSKELETAL	Hypothyroid myopathy (proximal weakness, ↑ CK), carpal tunnel syndrome, myoedema (small lump rising on the surface of a muscle when struck with a hammer)	Thyrotoxic myopathy (proximal weakness, normal CK), osteoporosis/↑ fracture rate (T <sub>3</sub> directly stimulates bone resorption)
REPRODUCTIVE	Abnormal uterine bleeding, ↓ libido, infertility	Abnormal uterine bleeding, gynecomastia, ↓ libido, infertility
NEUROPSYCHIATRIC	Hypoactivity, lethargy, fatigue, weakness, depressed mood, ↓ reflexes (delayed/slow relaxing)	Hyperactivity, restlessness, anxiety, insomnia, fine tremors (due to ↑ β-adrenergic activity), ↑ reflexes (brisk)
CARDIOVASCULAR	Bradycardia, dyspnea on exertion (↓ cardiac output)	Tachycardia, palpitations, dyspnea, arrhythmias (eg, atrial fibrillation), chest pain and systolic HTN due to ↑ number and sensitivity of β-adrenergic receptors, ↑ expression of cardiac sarcolemmal ATPase and ↓ expression of phospholamban
LABS	↑ TSH (if 1°) ↓ free T <sub>3</sub> and T <sub>4</sub> Hypercholesterolemia (due to ↓ LDL receptor expression)	↓ TSH (if 1°) ↑ free T <sub>3</sub> and T <sub>4</sub> ↓ LDL, HDL, and total cholesterol



## Hypothyroidism

### Hashimoto thyroiditis

Also called chronic autoimmune thyroiditis. Most common cause of hypothyroidism in iodine-sufficient regions. Associated with HLA-DR3, ↑ risk of primary thyroid lymphoma (typically diffuse large B-cell lymphoma).

Findings: moderately enlarged, **nontender** thyroid. May be preceded by transient hyperthyroid state (“Hashitoxicosis”) due to follicular rupture and thyroid hormone release.

Serology: + antithyroid peroxidase (antimicrosomal) and antithyroglobulin antibodies.

Histology: Hurthle cells **A**, lymphoid aggregates with germinal centers **B**.

**Postpartum thyroiditis**—mild, self-limited variant of Hashimoto thyroiditis arising < 1 year after delivery.

### Subacute granulomatous thyroiditis

Also called de Quervain thyroiditis. Usually, a self-limited disease. Natural history: transient hyperthyroidism → euthyroid state → hypothyroidism. Often preceded by viral infection.

Findings: ↑ ESR, jaw pain, very **tender** thyroid (de Quervain is associated with **pain**).

Histology: granulomatous inflammation **C**.

### Riedel thyroiditis

Also called invasive fibrous thyroiditis. May be part of IgG<sub>4</sub>-related disease (eg, autoimmune pancreatitis, retroperitoneal fibrosis, noninfectious aortitis). Hypothyroidism occurs in ½ of patients.

Fibrosis may extend to local structures (eg, trachea, esophagus), mimicking anaplastic carcinoma.

Findings: slowly enlarging, hard (rock-like), fixed, **nontender** thyroid.

Histology: thyroid replaced by fibrous tissue and inflammatory infiltrate **D**.

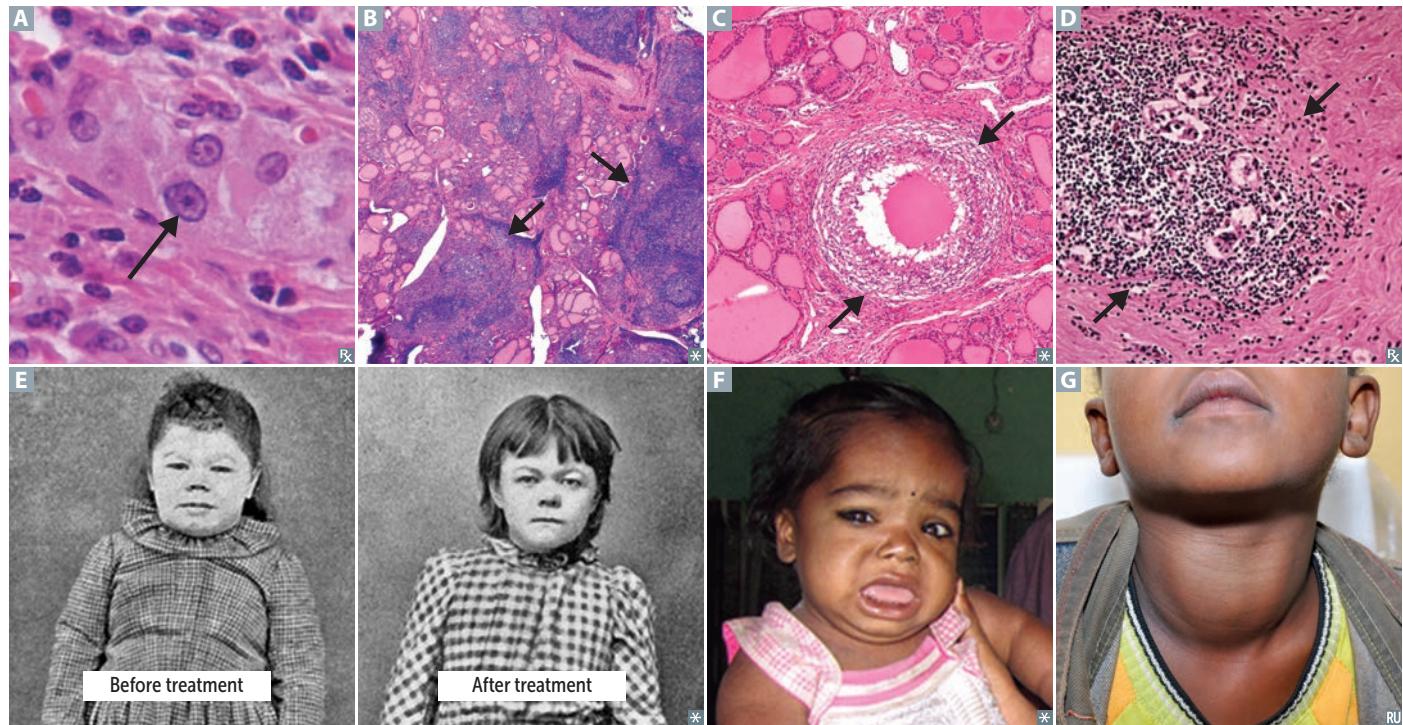
### Congenital hypothyroidism

Formerly called cretinism. Most commonly caused by thyroid dysgenesis (abnormal thyroid gland development; eg, agenesis, hypoplasia, ectopy) or dyshormonogenesis (abnormal thyroid hormone synthesis; eg, mutations in thyroid peroxidase) in iodine-sufficient regions.

Findings (**6 P's**): **pot-bellied**, **pale**, **puffy-faced** child **E** with protruding umbilicus, protuberant tongue **F**, and poor brain development.

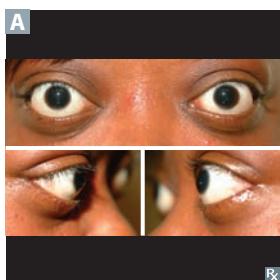
### Other causes

Iodine deficiency (most common cause worldwide; typically presents with goiter **G**), iodine excess (Wolff-Chaikoff effect), drugs (eg, amiodarone, lithium), nonthyroidal illness syndrome (also called euthyroid sick syndrome; ↓ T<sub>3</sub> with normal/↓ T<sub>4</sub> and TSH in critically ill patients).



## Hyperthyroidism

### Graves disease



Most common cause of hyperthyroidism. Thyroid-stimulating immunoglobulin (IgG, can cause transient neonatal hyperthyroidism; type II hypersensitivity) stimulates TSH receptors on thyroid (hyperthyroidism, diffuse goiter), dermal fibroblasts (pretibial myxedema), and orbital fibroblasts (Graves orbitopathy). Activation of T-cells → lymphocytic infiltration of retroorbital space → ↑ cytokines (eg, TNF- $\alpha$ , IFN- $\gamma$ ) → ↑ fibroblast secretion of hydrophilic GAGs → ↑ osmotic muscle swelling, muscle inflammation, and adipocyte count → exophthalmos **A**. Often presents during stress (eg, pregnancy). Associated with HLA-DR3 and HLA-B8. Histology: tall, crowded follicular epithelial cells; scalloped colloid.

### Toxic multinodular goiter

Focal patches of hyperfunctioning follicular cells distended with colloid working independently of TSH (due to TSH receptor mutations in 60% of cases). ↑ release of T<sub>3</sub> and T<sub>4</sub>. Hot nodules are rarely malignant.

### Thyroid storm

Uncommon but serious complication that occurs when hyperthyroidism is incompletely treated/untreated and then significantly worsens in the setting of acute stress such as infection, trauma, surgery. Presents with agitation, delirium, fever, diarrhea, coma, and tachyarrhythmia (cause of death). May see ↑ LFTs. Treat with the **4 P's**:  $\beta$ -blockers (eg, propranolol), propylthiouracil, corticosteroids (eg, prednisolone), potassium iodide (Lugol iodine). Iodide load → ↓ T<sub>4</sub> synthesis → Wolff-Chaikoff effect.

### Jod-Basedow phenomenon

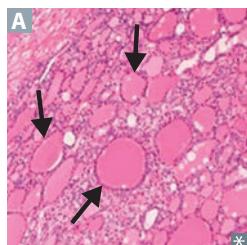
Iodine-induced hyperthyroidism. Occurs when a patient with iodine deficiency and partially autonomous thyroid tissue (eg, autonomous nodule) is made iodine replete. Can happen after iodine IV contrast or amiodarone use. Opposite to Wolff-Chaikoff effect.

### Causes of goiter

Smooth/diffuse: Graves disease, Hashimoto thyroiditis, iodine deficiency, TSH-secreting pituitary adenoma.

Nodular: toxic multinodular goiter, thyroid adenoma, thyroid cancer, thyroid cyst.

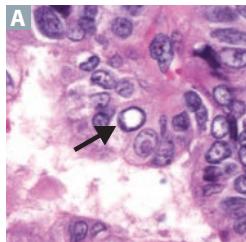
## Thyroid adenoma



Benign solitary growth of the thyroid. Most are nonfunctional (“cold”), can rarely cause hyperthyroidism via autonomous thyroid hormone production (“hot” or “toxic”). Most common histology is follicular (arrows in **A**); absence of capsular or vascular invasion (unlike follicular carcinoma).

**Thyroid cancer**

Typically diagnosed with fine needle aspiration; treated with thyroidectomy. Complications of surgery include hypocalcemia (due to removal of parathyroid glands), transection of recurrent laryngeal nerve during ligation of inferior thyroid artery (leads to dysphagia and dysphonia [hoarseness]), and injury to the external branch of the superior laryngeal nerve during ligation of superior thyroid vascular pedicle (may lead to loss of tenor usually noticeable in professional voice users).

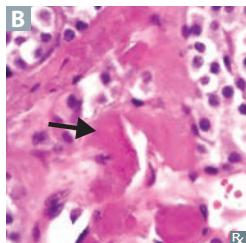
**Papillary carcinoma**

Most common. Empty-appearing nuclei with central clearing (“**Orphan Annie**” eyes) **A**, psamMoma bodies, nuclear grooves (**Papi** and **Moma** adopted **Orphan Annie**). ↑ risk with RET/PTC rearrangements and BRAF mutations, childhood irradiation.

Papillary carcinoma: most prevalent, palpable lymph nodes. Good prognosis.

**Follicular carcinoma**

Good prognosis. Invades thyroid capsule and vasculature (unlike follicular adenoma), uniform follicles; hematogenous spread is common. Associated with RAS mutation and PAX8-PPAR-γ translocations. Fine needle aspiration cytology may not be able to distinguish between follicular adenoma and carcinoma.

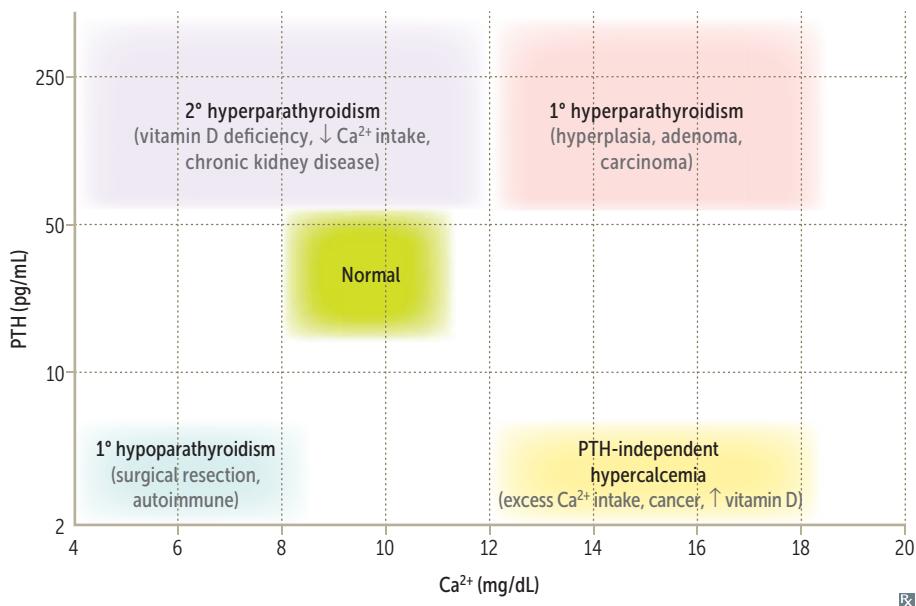
**Medullary carcinoma**

From parafollicular “**C** cells”; produces calcitonin, sheets of polygonal cells in an amyloid stroma **B** (stains with Congo red). Associated with MEN 2A and 2B (RET mutations).

**Undifferentiated/anaplastic carcinoma**

Older patients; presents with rapidly enlarging neck mass → compressive symptoms (eg, dyspnea, dysphagia, hoarseness); very poor prognosis. Associated with TP53 mutation.

### Diagnosing parathyroid disease



### Hypoparathyroidism



Due to injury to parathyroid glands or their blood supply (usually during surgery), autoimmune destruction, or DiGeorge syndrome. Findings: tetany, hypocalcemia, hyperphosphatemia.

**Chvostek sign**—tapping of facial nerve (tap the **Cheek**) → contraction of facial muscles.

**Trousseau sign**—occlusion of brachial artery with BP cuff (cuff the **Triceps**) → carpal spasm.

**Pseudohypoparathyroidism type 1A**—autosomal dominant, maternally transmitted mutations (imprinted GNAS gene). GNAS1-inactivating mutation (coupled to PTH receptor) that encodes the  $G_s$  protein  $\alpha$  subunit → inactivation of adenylate cyclase when PTH binds to its receptor → end-organ resistance (kidney and bone) to PTH.

Physical findings: Albright hereditary osteodystrophy (shortened 4th/5th digits **A**, short stature, round face, subcutaneous calcifications, developmental delay).

Labs:  $\uparrow$  PTH,  $\downarrow \text{Ca}^{2+}$ ,  $\uparrow \text{PO}_4^{3-}$ .

**Pseudopseudohypoparathyroidism**—autosomal dominant, paternally transmitted mutations (imprinted GNAS gene) but without end-organ resistance to PTH due to normal maternal allele maintaining renal responsiveness to PTH.

Physical findings: same as Albright hereditary osteodystrophy.

Labs: normal PTH,  $\text{Ca}^{2+}$ ,  $\text{PO}_4^{3-}$ .

### Lab values in hypocalcemia

DISORDER	$\text{Ca}^{2+}$	$\text{PO}_4^{3-}$	PTH
Vitamin D deficiency	↓	↓	↑
Hypoparathyroidism	↓	↑	↓
2° hyperparathyroidism (CKD)	↓	↑	↑
Pseudohypo-parathyroidism	↓	↑	↑
Hyperphosphatemia	↓	↑	↑

## Hyperparathyroidism

### Primary hyperparathyroidism



Usually due to parathyroid adenoma or hyperplasia. **Hypercalcemia**, hypercalciuria (renal **stones**), polyuria (**thrones**), hypophosphatemia, ↑ PTH, ↑ ALP, ↑ urinary cAMP. Most often asymptomatic. May present with **bone** pain, weakness, constipation (“**groans**”), abdominal/flank pain (kidney stones, acute pancreatitis), neuropsychiatric disturbances (“**psychiatric overtones**”).

### Secondary hyperparathyroidism

2° hyperplasia due to ↓ Ca<sup>2+</sup> absorption and/or ↑ PO<sub>4</sub><sup>3-</sup>, most often in chronic kidney disease (causes hypovitaminosis D and hyperphosphatemia → ↓ Ca<sup>2+</sup>). **Hypocalcemia**, hyperphosphatemia in chronic kidney disease (vs hypophosphatemia with most other causes), ↑ ALP, ↑ PTH.

### Tertiary hyperparathyroidism

Refractory (autonomous) hyperparathyroidism resulting from chronic kidney disease.  
↑↑ PTH, ↑ Ca<sup>2+</sup>.

### Familial hypocalciuric hypercalcemia

Defective G-coupled Ca<sup>2+</sup>-sensing receptors in multiple tissues (eg, parathyroids, kidneys). Higher than normal Ca<sup>2+</sup> levels required to suppress PTH. Excessive renal Ca<sup>2+</sup> reabsorption → mild hypercalcemia and hypocalciuria with normal to ↑ PTH levels.

**Osteitis fibrosa cystica**—cystic **bone** spaces filled with brown fibrous tissue **A** (“brown tumor” consisting of osteoclasts and deposited hemosiderin from hemorrhages; causes bone pain). Due to ↑ PTH, classically associated with 1° (but also seen with 2°) hyperparathyroidism.

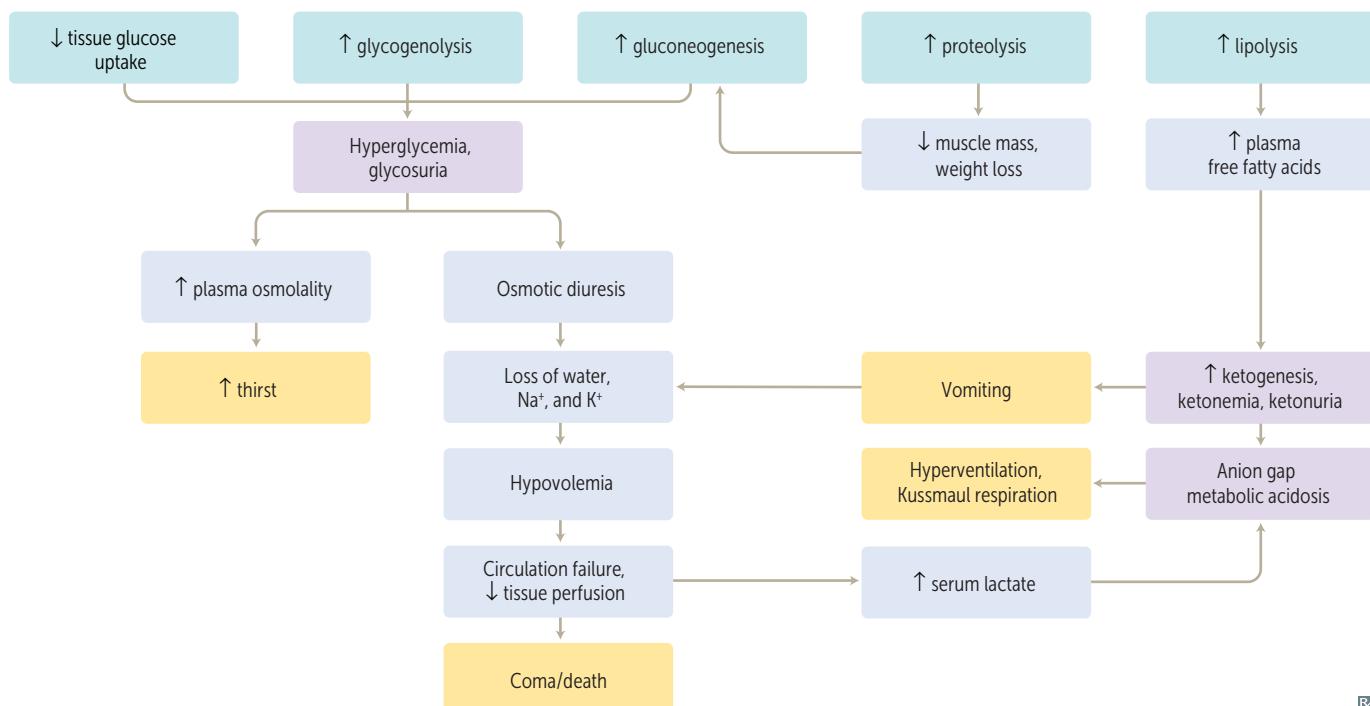
“**Stones, thrones, bones, groans, and psychiatric overtones.**”

**Renal osteodystrophy**—renal disease → 2° and 3° hyperparathyroidism → bone lesions.

### Diabetes mellitus

ACUTE MANIFESTATIONS	<p>Polydipsia, polyuria, polyphagia, weight loss, DKA (type 1), hyperosmolar hyperglycemic state (type 2).</p> <p>Rarely, can be caused by unopposed secretion of GH and epinephrine. Also seen in patients on glucocorticoid therapy (steroid diabetes).</p>		
CHRONIC COMPLICATIONS	<p>Nonenzymatic glycation:</p> <ul style="list-style-type: none"> <li>Small vessel disease (diffuse thickening of basement membrane) → retinopathy (hemorrhage, exudates, microaneurysms, vessel proliferation), glaucoma, nephropathy. Nodular glomerulosclerosis → progressive proteinuria (initially microalbuminuria; ACE inhibitors and ARBs are renoprotective). Arteriolosclerosis (causing hypertension) → chronic kidney disease.</li> <li>Large vessel atherosclerosis, CAD, peripheral vascular occlusive disease, gangrene → limb loss, cerebrovascular disease. MI most common cause of death.</li> </ul> <p>Osmotic damage (sorbitol accumulation in organs with aldose reductase and ↓ or absent sorbitol dehydrogenase):</p> <ul style="list-style-type: none"> <li>Neuropathy: motor, sensory (glove and stocking distribution), autonomic degeneration (eg, GERD, gastroparesis, diabetic diarrhea).</li> <li>Cataracts.</li> </ul>		
DIAGNOSIS	TEST HbA <sub>1c</sub>	DIAGNOSTIC CUTOFF ≥ 6.5%	NOTES Reflects average blood glucose over prior 3 months (influenced by RBC turnover)
	Fasting plasma glucose	≥ 126 mg/dL	Fasting for > 8 hours
	2-hour oral glucose tolerance test	≥ 200 mg/dL	2 hours after consumption of 75 g of glucose in water
	Random plasma glucose	≥ 200 mg/dL	Presence of hyperglycemic symptoms is required

### Insulin deficiency or severe insulin insensitivity



**Type 1 vs type 2 diabetes mellitus**

	Type 1	Type 2
1° DEFECT	Autoimmune T-cell-mediated destruction of β cells (eg, due to presence of glutamic acid decarboxylase antibodies)	↑ resistance to insulin, progressive pancreatic β-cell failure
INSULIN NECESSARY IN TREATMENT	Always	Sometimes
AGE (EXCEPTIONS COMMON)	< 30 yr	> 40 yr
ASSOCIATION WITH OBESITY	No	Yes
GENETIC PREDISPOSITION	Relatively weak (50% concordance in identical twins), polygenic	Relatively strong (90% concordance in identical twins), polygenic
ASSOCIATION WITH HLA SYSTEM	Yes, HLA-DR4 and -DR3 (4 – 3 = type 1)	No
GLUCOSE INTOLERANCE	Severe	Mild to moderate
INSULIN SENSITIVITY	High	Low
KETOACIDOSIS	Common	Rare
β-CELL NUMBERS IN THE ISLETS	↓	Variable (with amyloid deposits)
SERUM INSULIN LEVEL	↓	↑ initially, but ↓ in advanced disease
CLASSIC SYMPTOMS OF POLYURIA, POLYDIPSIA, POLYPHAGIA, WEIGHT LOSS	Common	Sometimes
HISTOLOGY	Islet leukocytic infiltrate	Islet amyloid polypeptide (IAPP) deposits

**Hyperglycemic emergencies**

	Diabetic ketoacidosis	Hyperosmolar hyperglycemic state
PATHOGENESIS	Insulin noncompliance or ↑ requirements due to ↑ stress (eg, infection) → excess lipolysis and ↑ ketogenesis from ↑ free fatty acids → ketone bodies (β-hydroxybutyrate > acetoacetate). <b>Insulin deficient, ketones present.</b>	Profound hyperglycemia → excessive osmotic diuresis → dehydration and ↑ serum osmolality → HHS. Classically seen in elderly patients with type 2 DM and limited ability to drink. <b>Insulin present, ketones absent.</b>
SIGNS/SYMPTOMS	<b>DKA is Deadly:</b> Delirium/psychosis, Kussmaul respirations (rapid, deep breathing), Abdominal pain/nausea/vomiting, Dehydration. Fruity breath odor due to exhaled acetone.	Thirst, polyuria, lethargy, focal neurologic deficits, seizures.
LABS	Hyperglycemia, ↑ H <sup>+</sup> , ↓ HCO <sub>3</sub> <sup>-</sup> (↑ anion gap metabolic acidosis), ↑ urine and blood ketone levels, leukocytosis. Normal/↑ serum K <sup>+</sup> , but depleted intracellular K <sup>+</sup> due to transcellular shift from ↓ insulin and acidosis. Osmotic diuresis → ↑ K <sup>+</sup> loss in urine → total body K <sup>+</sup> depletion.	Hyperglycemia (often > 600 mg/dL), ↑ serum osmolality (> 320 mOsm/kg), normal pH (no acidosis), no ketones. Normal/↑ serum K <sup>+</sup> , ↓ intracellular K <sup>+</sup> .
COMPLICATIONS	Life-threatening mucormycosis, cerebral edema, cardiac arrhythmias.	Can progress to coma and death if untreated.
TREATMENT	IV fluids, IV insulin, and K <sup>+</sup> (to replete intracellular stores). Glucose may be required to prevent hypoglycemia from insulin therapy.	

### Hypoglycemia in diabetes mellitus

- Usually occurs in patients treated with insulin or insulin secretagogues (eg, sulfonylureas, meglitinides) in the setting of high-dose treatment, inadequate food intake, and/or exercise.
- Neurogenic/autonomic symptoms: diaphoresis, tachycardia, tremor, anxiety, hunger. May allow perception of ↓ glucose (hypoglycemia awareness).
  - Neuroglycopenic symptoms: altered mental status, seizures, death due to insufficient glucose in CNS.
- Treatment: simple carbohydrates (eg, glucose tablets, fruit juice), IM glucagon, IV dextrose.

### Cushing syndrome

#### Etiology

↑ cortisol due to a variety of causes:

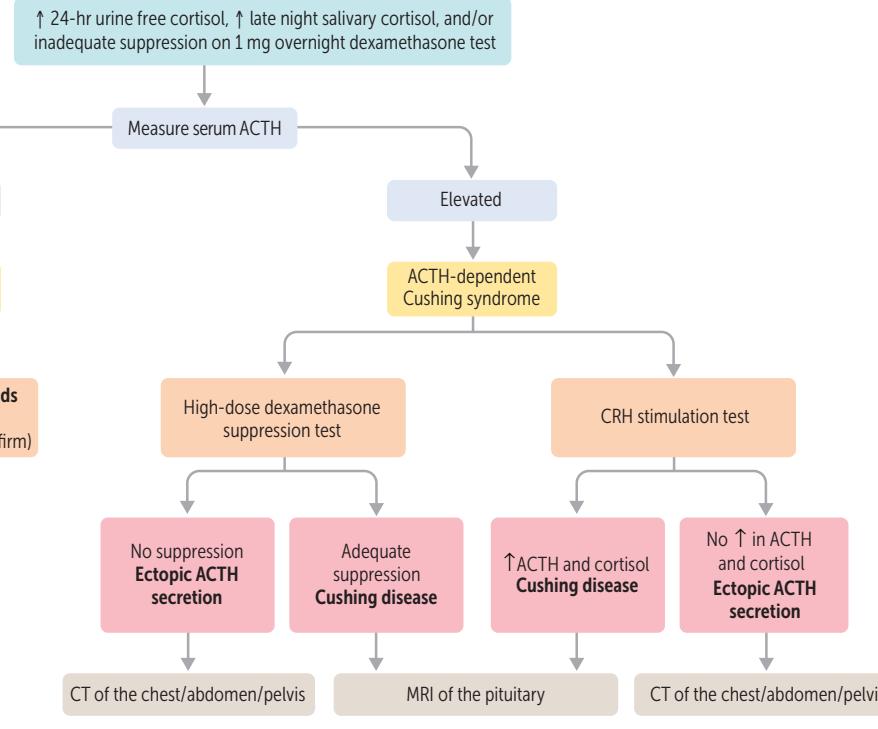
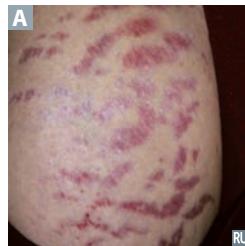
- Exogenous corticosteroids → ↓ ACTH → bilateral adrenal atrophy. Most common cause.
- Primary adrenal adenoma, hyperplasia, or carcinoma → ↓ ACTH → atrophy of uninvolved adrenal gland.
- ACTH-secreting pituitary adenoma (Cushing disease); paraneoplastic ACTH secretion (eg, small cell lung cancer, bronchial carcinoids) → bilateral adrenal hyperplasia. Cushing disease is responsible for the majority of endogenous cases of Cushing syndrome.

#### Findings

**CUSHING Syndrome:** ↑ Cholesterol, ↑ Urinary free cortisol, Skin changes (thinning, striae **A**), Hypertension, Immunosuppression, Neoplasm (a cause, not a finding), Growth restriction (in children), ↑ Sugar (hyperglycemia, insulin resistance). Also, amenorrhea, moon facies **B**, buffalo hump, osteoporosis, ↑ weight (truncal obesity), hirsutism.

#### Diagnosis

Screening tests include: ↑ free cortisol on 24-hr urinalysis, ↑ late night salivary cortisol, and no suppression with overnight low-dose dexamethasone test.



**Nelson syndrome**

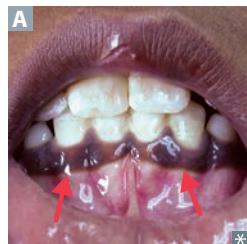
Enlargement of pre-existing ACTH–secreting pituitary adenoma after bilateral adrenalectomy for refractory Cushing disease → ↑ ACTH (hyperpigmentation), mass effect (headaches, bitemporal hemianopia).

Treatment: transsphenoidal resection, postoperative pituitary irradiation for residual tumor.

**Adrenal insufficiency**

Inability of adrenal glands to generate enough glucocorticoids +/- mineralocorticoids for the body's needs. Can be acute or chronic. Symptoms include weakness, fatigue, orthostatic hypotension, muscle aches, weight loss, GI disturbances, sugar and/or salt cravings.

Treatment: glucocorticoid +/- mineralocorticoid replacement.

**Primary adrenal insufficiency**

↓ gland function → ↓ cortisol, ↓ aldosterone → hypotension (hyponatremic volume contraction), hyperkalemia, metabolic acidosis, skin/mucosal hyperpigmentation **A** (↑ melanin synthesis due to ↑ MSH, a byproduct of POMC cleavage). Primary pigments the skin/mucosa.

**Addison disease**—chronic 1° adrenal insufficiency; caused by adrenal atrophy or destruction. Most commonly due to autoimmune adrenalitis (developed world) or TB (developing world).

**Secondary and tertiary adrenal insufficiency**

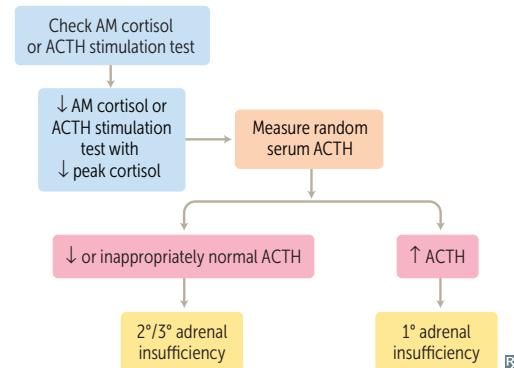
↓ pituitary ACTH secretion (secondary) or ↓ hypothalamic CRH secretion (tertiary). No hyperkalemia (aldosterone synthesis preserved due to functioning adrenal gland, intact RAAS), no hyperpigmentation.

2° adrenal insufficiency is due to pituitary pathologies, 3° adrenal insufficiency is most commonly due to abrupt cessation of chronic steroid therapy (HPA suppression). **Tertiary** from **ter**mination.

**Acute adrenal insufficiency**

Also called adrenal (addisonian) crisis; often precipitated by acute stressors that ↑ steroid requirements (eg, infection) in patients with pre-existing adrenal insufficiency or on steroid therapy. May present with acute abdomen, nausea, vomiting, altered mental status, shock.

**Waterhouse-Friderichsen syndrome**—bilateral adrenal hemorrhage often due to meningococcemia. May present with acute adrenal insufficiency, fever, petechiae, sepsis.



**Hyperaldosteronism**

Increased secretion of aldosterone from adrenal gland. Clinical features include hypertension, ↓ or normal K<sup>+</sup>, metabolic alkalosis. 1° hyperaldosteronism does not directly cause edema due to aldosterone escape mechanism. However, certain 2° causes of hyperaldosteronism (eg, heart failure) impair the aldosterone escape mechanism, leading to worsening of edema.

**Primary hyperaldosteronism**

Seen in patients with bilateral adrenal hyperplasia or adrenal adenoma (Conn syndrome). ↑ aldosterone, ↓ renin. Leads to treatment-resistant hypertension.

**Secondary hyperaldosteronism**

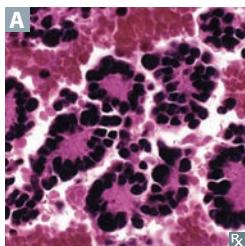
Seen in patients with renovascular hypertension, juxtaglomerular cell tumors (renin-producing), and edema (eg, cirrhosis, heart failure, nephrotic syndrome).

**Neuroendocrine tumors**

Heterogeneous group of neoplasms originating from neuroendocrine cells (which have traits similar to nerve cells and hormone-producing cells).

Most neoplasms occur in the GI system (eg, carcinoid, gastrinoma), pancreas (eg, insulinoma, glucagonoma), and lungs (eg, small cell carcinoma). Also in thyroid (eg, medullary carcinoma) and adrenals (eg, pheochromocytoma).

Neuroendocrine cells (eg, pancreatic β cells, enterochromaffin cells) share a common biologic function through amine precursor uptake decarboxylase (APUD) despite differences in embryologic origin, anatomic site, and secretory products (eg, chromogranin A, neuron-specific enolase [NSE], synaptophysin, serotonin, histamine, calcitonin). Treatment: surgical resection, somatostatin analogs.

**Neuroblastoma**

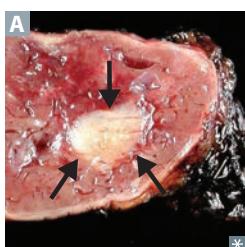
Most common tumor of the adrenal medulla in **children**, usually < 4 years old. Originates from neural crest cells. Occurs anywhere along the sympathetic chain.

Most common presentation is abdominal distension and a firm, irregular mass that can cross the midline (vs Wilms tumor, which is smooth and unilateral). Less likely to develop hypertension than with pheochromocytoma (neuroblastoma is normotensive). Can also present with opsoclonus-myoclonus syndrome ("dancing eyes-dancing feet").

↑ HVA and VMA (catecholamine metabolites) in urine. Homer-Wright rosettes (neuroblasts surrounding a central lumen **A**) characteristic of neuroblastoma and medulloblastoma. Bombesin and NSE  $\oplus$ . Associated with amplification of **N-myc** oncogene.

## Pheochromocytoma

### Etiology



Most common tumor of the adrenal medulla in adults **A**. Derived from chromaffin cells (arise from neural crest).

May be associated with germline mutations (eg, NF-1, VHL, RET [MEN 2A, 2B]).

### Rule of 10's:

**10%** malignant

**10%** bilateral

**10%** extra-adrenal (eg, bladder wall, organ of Zuckerkandl)

**10%** calcify

**10%** kids

### Symptoms

Most tumors secrete epinephrine, norepinephrine, and dopamine, which can cause episodic hypertension. May also secrete EPO → polycythemia.

Symptoms occur in “spells”—relapse and remit.

Episodic hyperadrenergic symptoms (**5 P's**):

**P**ressure ( $\uparrow$  BP)

**P**ain (headache)

**P**erspiration

**P**alpitations (tachycardia)

**P**allor

### Findings

$\uparrow$  catecholamines and metanephrenes (eg, homovanillic acid, vanillylmandelic acid) in urine and plasma.

Chromogranin, synaptophysin and NSE  $\oplus$ .

### Treatment

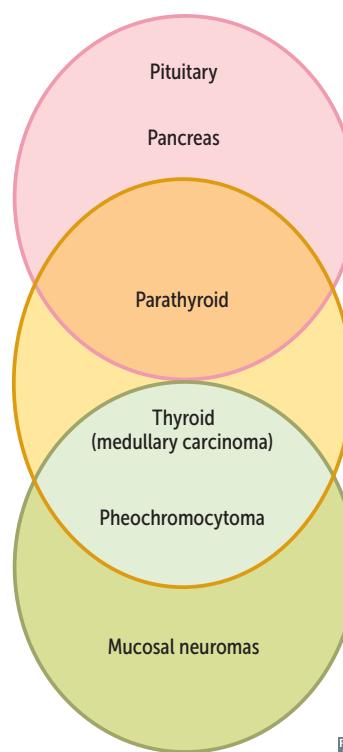
Irreversible  $\alpha$ -antagonists (eg, phenoxybenzamine) followed by  $\beta$ -blockers prior to tumor resection.  $\alpha$ -blockade must be achieved before giving  $\beta$ -blockers to avoid a hypertensive crisis. **A** before **B**.

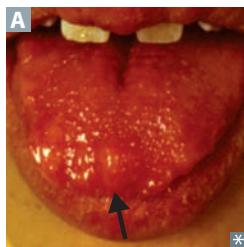
**Phe**noxybenzamine for **phe**ochromocytoma.

**Multiple endocrine neoplasias**

All **MEN** syndromes have autosomal **dominant** inheritance.

The **X-MEN** are **dominant** over villains.

SUBTYPE	CHARACTERISTICS	COMMENTS
<b>MEN 1</b>	<ul style="list-style-type: none"> <li>Pituitary tumors (prolactin or GH)</li> <li>Pancreatic endocrine tumors—Zollinger-Ellison syndrome, insulinomas, VIPomas, glucagonomas (rare)</li> <li>Parathyroid adenomas</li> </ul> <p>Associated with mutation of <i>MEN1</i> (menin, a tumor suppressor, chromosome 11), angiofibromas, collagenomas, meningiomas</p>	
<b>MEN 2A</b>	<ul style="list-style-type: none"> <li>Parathyroid hyperplasia</li> <li>Medullary thyroid carcinoma—neoplasm of parafollicular C cells; secretes calcitonin; prophylactic thyroidectomy required</li> <li>Pheochromocytoma (secretes catecholamines)</li> </ul> <p>Associated with mutation in <i>RET</i> (codes for receptor tyrosine kinase)</p>	
<b>MEN 2B</b>	<ul style="list-style-type: none"> <li>Medullary thyroid carcinoma</li> <li>Pheochromocytoma</li> <li>Mucosal neuromas <b>A</b> (oral/intestinal ganglioneuromatosis)</li> </ul> <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:** parathyroid and pheochromocytoma

**MEN 2B = 1 P:** pheochromocytoma

### Pancreatic islet cell tumors

#### Insulinoma

Tumor of pancreatic  $\beta$  cells  $\rightarrow$  overproduction of insulin  $\rightarrow$  hypoglycemia. May see Whipple triad: low blood glucose, symptoms of hypoglycemia (eg, lethargy, syncope, diplopia), and resolution of symptoms after normalization of plasma glucose levels. Symptomatic patients have  $\downarrow$  blood glucose and  $\uparrow$  C-peptide levels (vs exogenous insulin use).  $\sim 10\%$  of cases associated with MEN 1 syndrome.

Treatment: surgical resection.

#### Glucagonoma

Tumor of pancreatic  $\alpha$  cells  $\rightarrow$  overproduction of glucagon. Presents with **6 D's**: dermatitis (necrolytic migratory erythema), diabetes (hyperglycemia), DVT, declining weight, depression, diarrhea.

Treatment: octreotide, surgical resection.

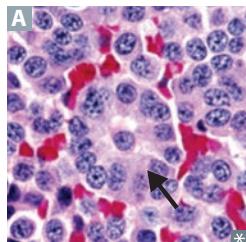
#### Somatostatinoma

Tumor of pancreatic  $\delta$  cells  $\rightarrow$  overproduction of somatostatin  $\rightarrow$   $\downarrow$  secretion of secretin, cholecystokinin, glucagon, insulin, gastrin, gastric inhibitory peptide (GIP).

May present with diabetes/glucose intolerance, steatorrhea, gallstones, achlorhydria.

Treatment: surgical resection; somatostatin analogs (eg, octreotide) for symptom control.

### Carcinoid tumors



Carcinoid tumors arise from neuroendocrine cells, most commonly in the intestine or lung.

Neuroendocrine cells secrete 5-HT, which undergoes hepatic first-pass metabolism and enzymatic breakdown by MAO in the lung. If 5-HT reaches the systemic circulation (eg, after liver metastasis), carcinoid tumor may present with **carcinoid syndrome**—episodic flushing, diarrhea, wheezing, right-sided valvular heart disease (eg, tricuspid regurgitation, pulmonic stenosis), niacin deficiency (pellagra).

Histology: prominent rosettes (arrow in A), chromogranin A  $\oplus$ , synaptophysin  $\oplus$ .

Treatment: surgical resection, somatostatin analog (eg, octreotide) or tryptophan hydroxylase inhibitor (eg, telotristat) for symptom control.

#### Rule of thirds:

**1/3** metastasize

**1/3** present with 2nd malignancy

**1/3** are multiple

### Zollinger-Ellison syndrome

Gastrin-secreting tumor (gastrinoma) of duodenum or pancreas. Acid hypersecretion causes recurrent ulcers in duodenum and jejunum. Presents with abdominal pain (peptic ulcer disease, distal ulcers), diarrhea (malabsorption). Positive secretin stimulation test:  $\uparrow$  gastrin levels after administration of secretin, which normally inhibits gastrin release. May be associated with MEN 1.

## ► ENDOCRINE—PHARMACOLOGY

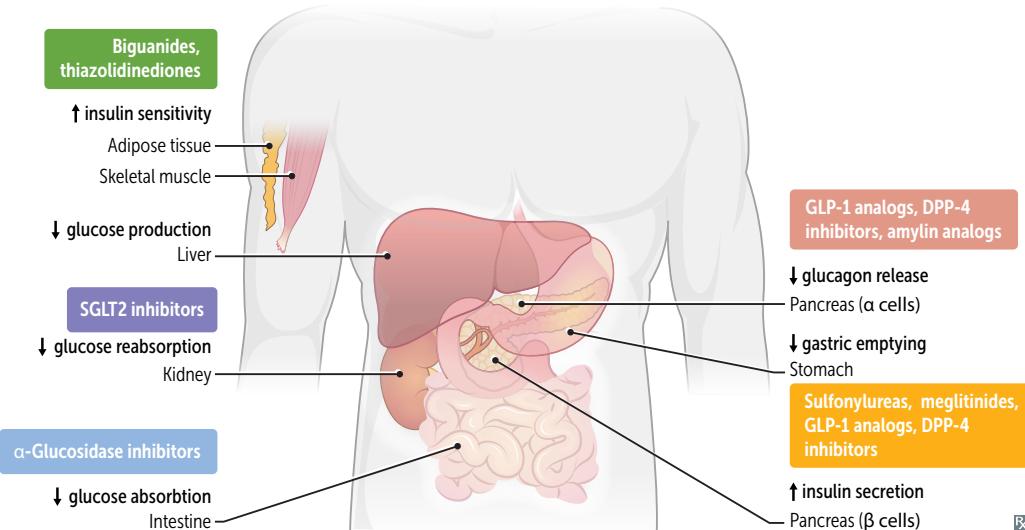
**Diabetes mellitus therapy**

All patients with diabetes mellitus should receive education on diet, exercise, blood glucose monitoring, and complication management. Treatment differs based on the type of diabetes and glycemic control:

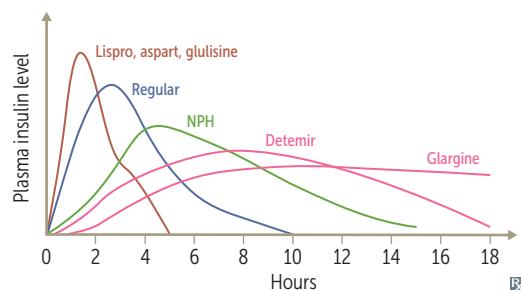
- Type 1 DM—insulin replacement
- Type 2 DM—oral agents (metformin is first line), non-insulin injectables, insulin replacement; weight loss particularly helpful in lowering blood glucose
- Gestational DM—insulin replacement if nutrition therapy and exercise alone fail

Regular (short-acting) insulin is preferred for DKA (IV), hyperkalemia (+ glucose), stress hyperglycemia.

These drugs help **To normalize pancreatic function** (-glits, -glins, -glips, -glifs).



DRUG CLASS	MECHANISM	ADVERSE EFFECTS
<b>Insulin preparations</b>		
Rapid acting (1-hr peak): Lispro, Aspart, Glulisine (no LAG)	Bind insulin receptor (tyrosine kinase activity) Liver: ↑ glucose storage as glycogen Muscle: ↑ glycogen, protein synthesis Fat: ↑ TG storage Cell membrane: ↑ K <sup>+</sup> uptake	Hypoglycemia, lipodystrophy, hypersensitivity reactions (rare), weight gain
Short acting (2–3 hr peak): regular		
Intermediate acting (4–10 hr peak): NPH		
Long acting (no real peak): detemir, glargine		



**Diabetes mellitus therapy (continued)**

DRUG CLASS	MECHANISM	ADVERSE EFFECTS
<b>Increase insulin sensitivity</b>		
<b>Biguanides</b>	Inhibit mGPD → inhibition of hepatic gluconeogenesis and the action of glucagon.	GI upset, lactic acidosis (use with caution in renal insufficiency), vitamin B <sub>12</sub> deficiency.
<b>Metformin</b>	↑ glycolysis, peripheral glucose uptake (↑ insulin sensitivity).	Weight loss (often desired).
<b>Thiazolidinediones</b>		
"-glits"	Activate PPAR-γ (a nuclear receptor) → ↑ insulin sensitivity and levels of adiponectin	Weight gain, edema, HF, ↑ risk of fractures.
<b>Pioglitazone, rosiglitazone</b>	→ regulation of glucose metabolism and fatty acid storage.	Delayed onset of action (several weeks). Rosiglitazone: ↑ risk of MI, cardiovascular death.
<b>Increase insulin secretion</b>		
<b>Sulfonylureas (1st gen)</b>		Disulfiram-like reaction with first-generation sulfonylureas only (rarely used).
Chlorpropamide, tolbutamide		
<b>Sulfonylureas (2nd gen)</b>	Close K <sup>+</sup> channels in pancreatic B cell membrane → cell depolarizes → insulin release via ↑ Ca <sup>2+</sup> influx.	Hypoglycemia (↑ risk in renal insufficiency), weight gain.
<b>Meglitinides</b>		
"-glins"		
<b>Nateglinide, repaglinide</b>		
<b>Increase glucose-induced insulin secretion</b>		
<b>GLP-1 analogs</b>	↓ glucagon release, ↓ gastric emptying, ↑ glucose-dependent insulin release.	Nausea, vomiting, pancreatitis. Weight loss (often desired). ↑ satiety (often desired).
Exenatide, liraglutide		
<b>DPP-4 inhibitors</b>	Inhibit DPP-4 enzyme that deactivates GLP-1 → ↓ glucagon release, ↓ gastric emptying.	Respiratory and urinary infections, weight neutral.
"-glips"		
<b>Linagliptin, saxagliptin, sitagliptin</b>	↑ glucose-dependent insulin release.	↑ satiety (often desired).
<b>Decrease glucose absorption</b>		
<b>Sodium-glucose co-transporter 2 inhibitors</b>	Block reabsorption of glucose in proximal convoluted tubule.	Glucosuria (UTIs, vulvovaginal candidiasis), dehydration (orthostatic hypotension), weight loss. Use with caution in renal insufficiency (↓ efficacy with ↓ GFR).
"-glifs"		
<b>Canagliflozin, dapagliflozin, empagliflozin</b>		
<b>α-glucosidase inhibitors</b>	Inhibit intestinal brush-border α-glucosidases → delayed carbohydrate hydrolysis and glucose absorption → ↓ postprandial hyperglycemia.	GI upset, bloating. Not recommended in renal insufficiency.
Acarbose, miglitol		
<b>Others</b>		
<b>Amylin analogs</b>	↓ glucagon release, ↓ gastric emptying.	Hypoglycemia, nausea. ↑ satiety (often desired).
<b>Pramlintide</b>		

**Thionamides**

Propylthiouracil, methimazole.

**MECHANISM**

Block thyroid peroxidase, inhibiting the oxidation of iodide as well as the organification and coupling of iodine → inhibition of thyroid hormone synthesis. PTU also blocks 5'-deiodinase → ↓ Peripheral conversion of T<sub>4</sub> to T<sub>3</sub>.

**CLINICAL USE**

Hyperthyroidism. PTU used in Primary (first) trimester of pregnancy (due to methimazole teratogenicity); methimazole used in second and third trimesters of pregnancy (due to risk of PTU-induced hepatotoxicity). Not used to treat Graves ophthalmopathy (treated with corticosteroids).

**ADVERSE EFFECTS**

Skin rash, agranulocytosis (rare), aplastic anemia, hepatotoxicity.  
PTU use has been associated with ANCA-positive vasculitis.  
Methimazole is a possible teratogen (can cause aplasia cutis).

**Levothyroxine, liothyronine****MECHANISM**Hormone replacement for T<sub>4</sub> (levothyroxine) or T<sub>3</sub> (liothyronine).**CLINICAL USE**

Hypothyroidism, myxedema. May be abused for weight loss. Distinguish exogenous hyperthyroidism from endogenous hyperthyroidism by using a combination of TSH receptor antibodies, radioactive iodine uptake, and/or measurement of thyroid blood flow on ultrasound.

**ADVERSE EFFECTS**

Tachycardia, heat intolerance, tremors, arrhythmias.

**Hypothalamic/pituitary drugs**

DRUG	CLINICAL USE
Conivaptan, tolvaptan	ADH antagonists SIADH (block action of ADH at V <sub>2</sub> -receptor)
Demeclocycline	Interferes with ADH signaling, a tetracycline SIADH
Desmopressin	ADH analog Central DI, von Willebrand disease, sleep enuresis, hemophilia A
GH	GH deficiency, Turner syndrome
Oxytocin	Induction of labor (stimulates uterine contractions), control uterine hemorrhage
Somatostatin (octreotide)	Acromegaly, carcinoid syndrome, gastrinoma, glucagonoma, esophageal varices

**Fludrocortisone****MECHANISM**

Synthetic analog of aldosterone with glucocorticoid effects. Fludrocortisone retains fluid.

**CLINICAL USE**

Mineralocorticoid replacement in 1° adrenal insufficiency.

**ADVERSE EFFECTS**

Similar to glucocorticoids; also edema, exacerbation of heart failure, hyperpigmentation.

**Cinacalcet**

MECHANISM	Sensitizes calcium-sensing receptor (CaSR) in parathyroid gland to circulating $\text{Ca}^{2+}$ $\rightarrow \downarrow \text{PTH}$ . Pronounce “Senacalcet.”
CLINICAL USE	2° hyperparathyroidism in patients with CKD receiving hemodialysis, hypercalcemia in 1° hyperparathyroidism (if parathyroidectomy fails), or in parathyroid carcinoma.
ADVERSE EFFECTS	Hypocalcemia.

**Sevelamer**

MECHANISM	Nonabsorbable phosphate binder that prevents phosphate absorption from the GI tract.
CLINICAL USE	Hyperphosphatemia in CKD.
ADVERSE EFFECTS	Hypophosphatemia, GI upset.

**Cation exchange resins** Patiromer, sodium polystyrene sulfonate, zirconium cyclosilicate.

MECHANISM	Bind $\text{K}^+$ in colon in exchange for other cations (eg, $\text{Na}^+$ , $\text{Ca}^{2+}$ ) $\rightarrow \text{K}^+$ excreted in feces.
CLINICAL USE	Hyperkalemia.
ADVERSE EFFECTS	Hypokalemia, GI upset.

## ► NOTES

# Gastrointestinal

*“A good set of bowels is worth more to a man than any quantity of brains.”*  
—Josh Billings

*“Man should strive to have his intestines relaxed all the days of his life.”*  
—Moses Maimonides

*“All right, let’s not panic. I’ll make the money by selling one of my livers. I can get by with one.”*  
—Homer Simpson, *The Simpsons*

*“The truth does not change according to our ability to stomach it emotionally.”*  
—Flannery O’Connor

When studying the gastrointestinal system, be sure to understand the normal embryology, anatomy, and physiology and how the system is affected by various pathologies. Study not only disease pathophysiology, but also its specific findings, so that you can differentiate between two similar diseases. For example, what specifically makes ulcerative colitis different from Crohn disease? Also, be comfortable with basic interpretation of abdominal x-rays, CT scans, and endoscopic images.

► Embryology	368
► Anatomy	370
► Physiology	381
► Pathology	386
► Pharmacology	408

## ► GASTROINTESTINAL—EMBRYOLOGY

**Normal  
gastrointestinal  
embryology**

Foregut—esophagus to duodenum at level of pancreatic duct and common bile duct insertion (ampulla of Vater).

Midgut—lower duodenum to proximal 2/3 of transverse colon.

Hindgut—distal 1/3 of transverse colon to anal canal above pectinate line.

Midgut:

- 6th week of development—physiologic herniation of midgut through umbilical ring
- 10th week of development—returns to abdominal cavity + rotates around superior mesenteric artery (SMA), total 270° counterclockwise

**Ventral wall defects**

Developmental defects due to failure of rostral fold closure (eg, sternal defects [ectopia cordis]), lateral fold closure (eg, omphalocele, gastroschisis), or caudal fold closure (eg, bladder exstrophy).

**Gastroschisis**

## ETIOLOGY

Extrusion of abdominal contents through abdominal folds (typically right of umbilicus)

## COVERAGE

Not covered by peritoneum or amnion **A**; “the guts come out of the gap (**schism**) in the letter **G**”

## ASSOCIATIONS

Not associated with chromosome abnormalities; favorable prognosis

**Omphalocele**

Failure of lateral walls to migrate at umbilical ring → persistent midline herniation of abdominal contents into umbilical cord

Covered by peritoneum and amnion **B** (light gray shiny sac); “abdominal contents are **sealed** in the letter **O**”

Associated with congenital anomalies (eg, trisomies 13 and 18, Beckwith-Wiedemann syndrome) and other structural abnormalities (eg, cardiac, GU, neural tube)

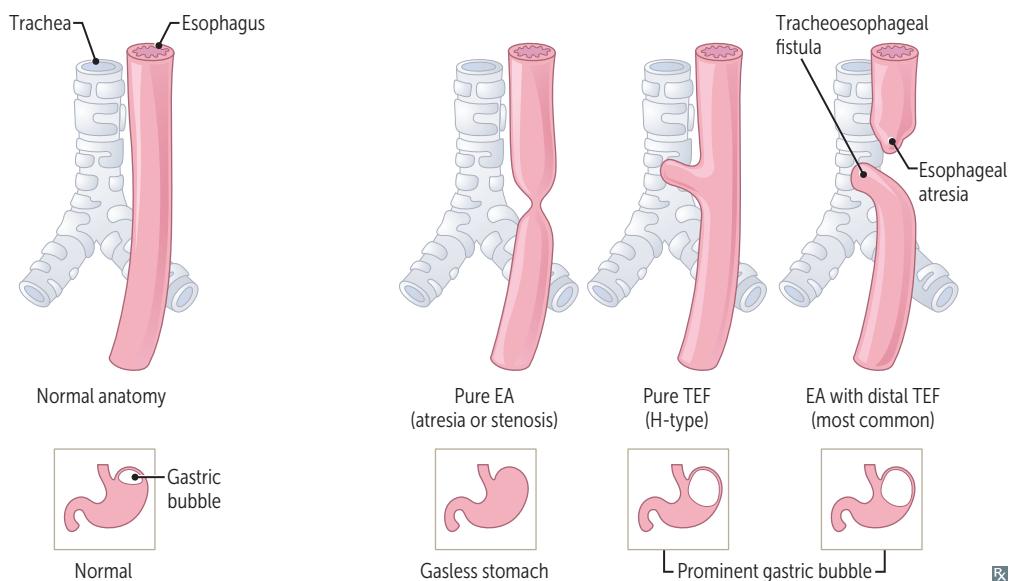
**Congenital umbilical  
hernia**

Failure of umbilical ring to close after physiologic herniation of midgut. Covered by skin **C**. Protrudes with ↑ intra-abdominal pressure (eg, crying). May be associated with congenital disorders (eg, Down syndrome, congenital hypothyroidism). Small defects usually close spontaneously.

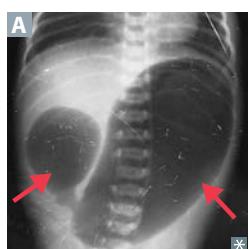
### Tracheoesophageal anomalies

Esophageal atresia (EA) with distal tracheoesophageal fistula (TEF) is the most common (85%) and often presents as polyhydramnios in utero (due to inability of fetus to swallow amniotic fluid). Neonates drool, choke, and vomit with first feeding. TEFs allow air to enter stomach (visible on CXR). Cyanosis is 2° to laryngospasm (to avoid reflux-related aspiration). Clinical test: failure to pass nasogastric tube into stomach.

In H-type, the fistula resembles the letter **H**. In pure EA, CXR shows gasless abdomen.



### Intestinal atresia

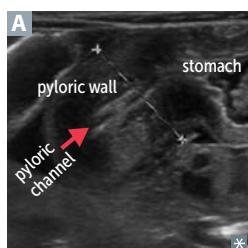


Presents with bilious vomiting and abdominal distension within first 1–2 days of life.

**Duodenal atresia**—failure to recanalize. X-ray **A** shows “double bubble” (dilated stomach, proximal duodenum). Associated with **Down syndrome**.

**Jejunal and ileal atresia**—disruption of mesenteric vessels (typically SMA) → ischemic necrosis of fetal intestine → segmental resorption: bowel becomes discontinuous. X-ray may show “triple bubble” (dilated stomach, duodenum, proximal jejunum) and gasless colon.

### Hypertrophic pyloric stenosis



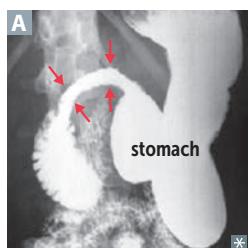
Most common cause of gastric outlet obstruction in infants (1:600). Palpable olive-shaped mass in epigastric region, visible peristaltic waves, and nonbilious projectile vomiting at ~ 2–6 weeks old. More common in firstborn males; associated with exposure to macrolides.

Results in hypokalemic hypochloremic metabolic alkalosis (2° to vomiting of gastric acid and subsequent volume contraction).

Ultrasound shows thickened and lengthened pylorus **A**.

Treatment: surgical incision of pyloric muscles (pyloromyotomy).

### Pancreas and spleen embryology



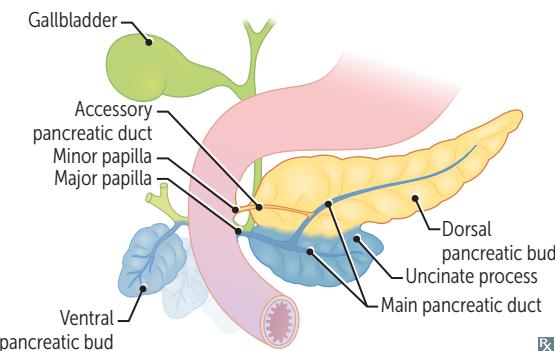
Pancreas—derived from foregut. Ventral pancreatic bud contributes to uncinate process and main pancreatic duct. The dorsal pancreatic bud alone becomes the body, tail, isthmus, and accessory pancreatic duct. Both the ventral and dorsal buds contribute to pancreatic head.

**Annular pancreas**—abnormal rotation of ventral pancreatic bud forms a ring of pancreatic tissue → encircles 2nd part of duodenum; may cause duodenal narrowing (arrows in A) and vomiting.

**Pancreas divisum**—ventral and dorsal parts fail to fuse at 7 weeks of development. Common

anomaly; mostly asymptomatic, but may cause chronic abdominal pain and/or pancreatitis.

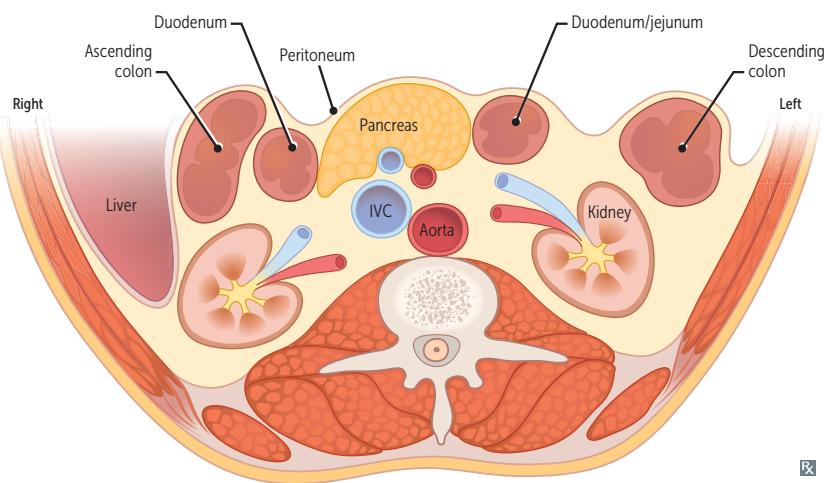
Spleen—arises in mesentery of stomach (hence is mesodermal) but has foregut supply (celiac trunk → splenic artery).



### ► GASTROINTESTINAL—ANATOMY

#### Retroperitoneal structures

Retroperitoneal structures A are posterior to (and outside of) the peritoneal cavity. Injuries to retroperitoneal structures can cause blood or gas accumulation in retroperitoneal space.



#### SAD PUCKER:

Suprarenal (adrenal) glands [not shown]

Aorta and IVC

Duodenum (2nd through 4th parts)

Pancreas (except tail)

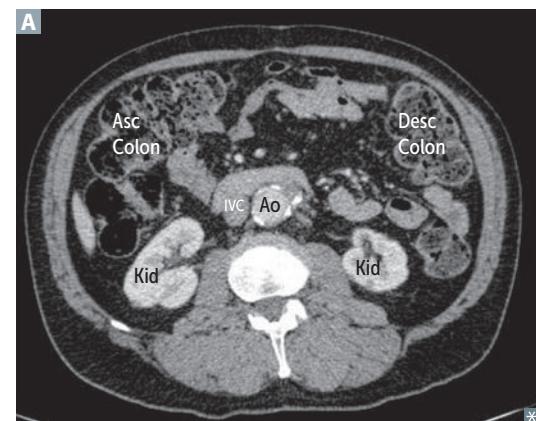
Ureters [not shown]

Colon (descending and ascending)

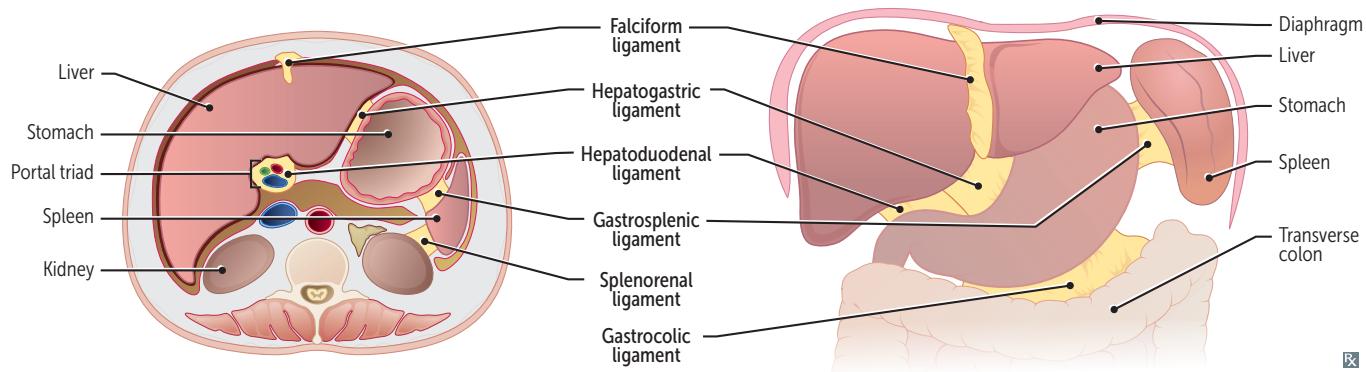
Kidneys

Esophagus (thoracic portion) [not shown]

Rectum (partially) [not shown]



### Important gastrointestinal ligaments



LIGAMENT	CONNECTS	STRUCTURES CONTAINED	NOTES
<b>Falciform ligament</b>	Liver to anterior abdominal wall	Ligamentum teres hepatitis (derivative of fetal umbilical vein), patent paraumbilical veins	Derivative of ventral mesentery
<b>Hepatoduodenal ligament</b>	Liver to duodenum	Portal triad: proper hepatic artery, portal vein, common bile duct	Derivative of ventral mesentery Pringle maneuver—ligament is compressed manually or with a vascular clamp in omental foramen to control bleeding from hepatic inflow source Borders the omental foramen, which connects the greater and lesser sacs Part of lesser omentum
<b>Hepatogastric ligament</b>	Liver to lesser curvature of stomach	Gastric vessels	Derivative of ventral mesentery Separates greater and lesser sacs on the right May be cut during surgery to access lesser sac Part of lesser omentum
<b>Gastrocolic ligament</b>	Greater curvature and transverse colon	Gastroepiploic arteries	Derivative of dorsal mesentery Part of greater omentum
<b>Gastrosplenic ligament</b>	Greater curvature and spleen	Short gastrics, left gastroepiploic vessels	Derivative of dorsal mesentery Separates greater and lesser sacs on the left Part of greater omentum
<b>Splenorenal ligament</b>	Spleen to left pararenal space	Splenic artery and vein, tail of pancreas	Derivative of dorsal mesentery

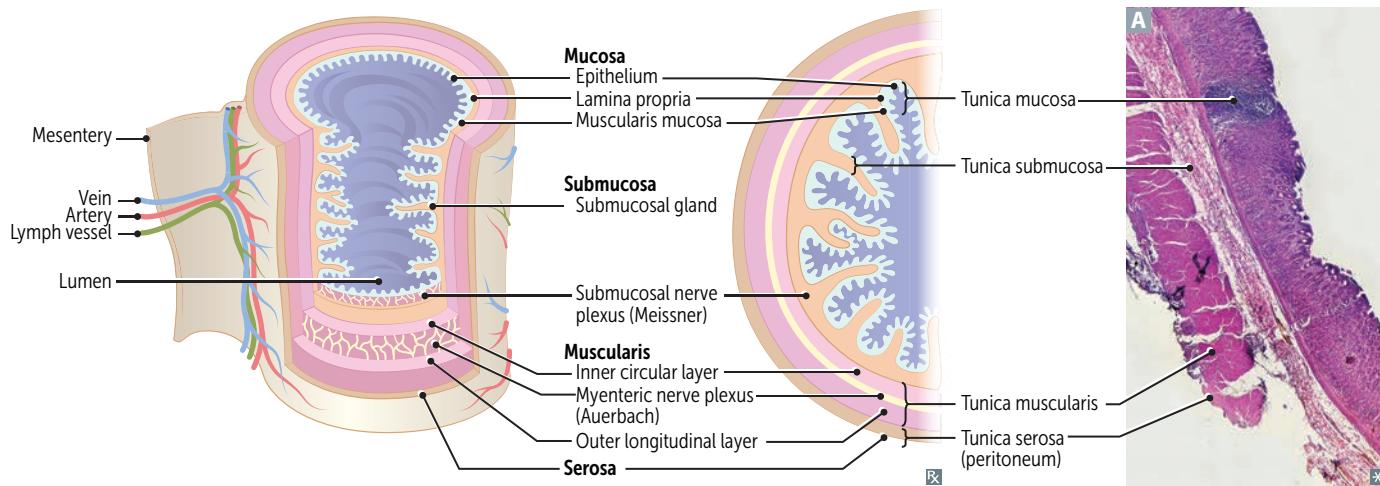
### Digestive tract anatomy

Layers of gut wall **A** (inside to outside—MSMS):

- **Mucosa**—epithelium, lamina propria, muscularis mucosa
- **Submucosa**—includes submucosal nerve plexus (Meissner), secretes fluid
- **Muscularis externa**—includes myenteric nerve plexus (Auerbach), motility
- **Serosa** (when intraperitoneal), adventitia (when retroperitoneal)

Ulcers can extend into submucosa, inner or outer muscular layer. Erosions are in mucosa only.

Frequency of basal electric rhythm (slow waves), which originate in the interstitial cells of Cajal: duodenum > ileum > stomach.



### Digestive tract histology

#### Esophagus

Nonkeratinized stratified squamous epithelium. Upper 1/3, striated muscle; middle and lower 2/3 smooth muscle, with some overlap at the transition.

#### Stomach

Gastric glands **A**. Parietal cells are eosinophilic (pink, red arrow in **B**), chief cells are basophilic (black arrow in **B**).

#### Duodenum

Villi and microvilli ↑ absorptive surface. Brunner glands (**b** bicarbonate-secreting cells of submucosa) and crypts of Lieberkühn (contain stem cells that replace enterocytes/goblet cells and Paneth cells that secrete defensins, lysozyme, and TNF).

#### Jejunum

Villi **C**, crypts of Lieberkühn, and plicae circulares (also present in distal duodenum).

#### Ileum

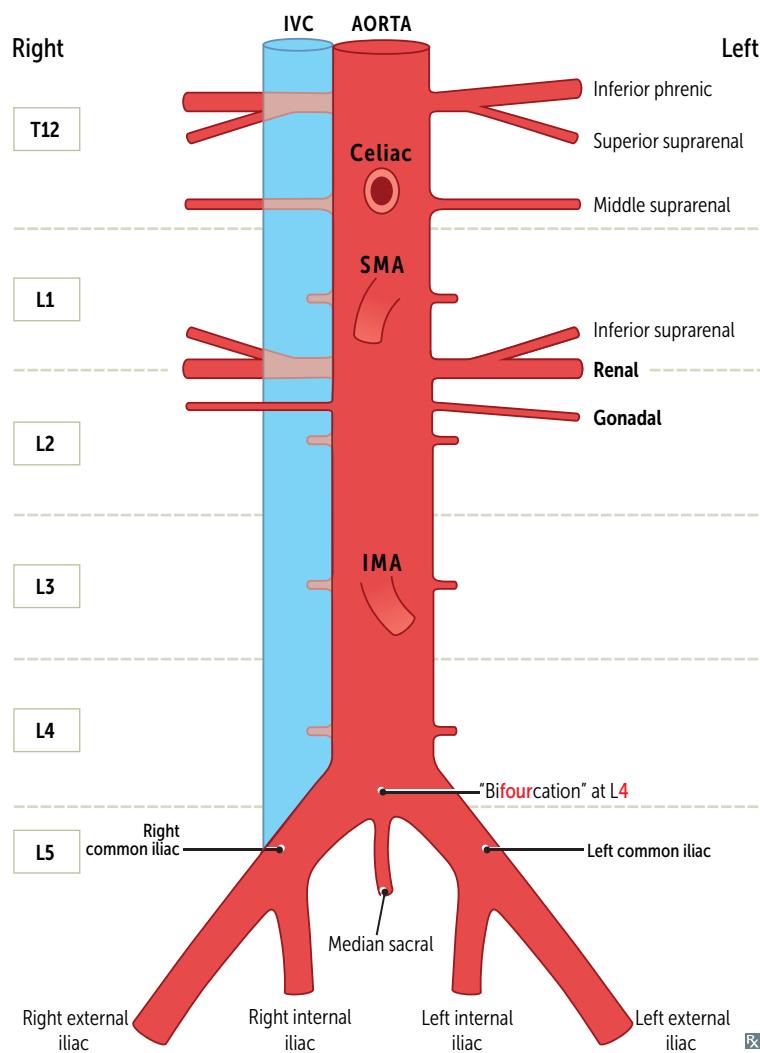
Villi, Peyer patches (arrow in **D**; lymphoid aggregates in lamina propria, submucosa), plicae circulares (proximal ileum), and crypts of Lieberkühn. Largest number of goblet cells in the small intestine.

#### Colon

Crypts of Lieberkühn with abundant goblet cells, but no villi **E**.



### Abdominal aorta and branches



Arteries supplying GI structures are single and branch anteriorly.

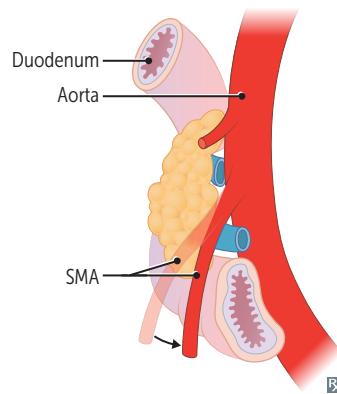
Arteries supplying non-GI structures are paired and branch laterally and posteriorly.

Two areas of the colon have dual blood supply from distal arterial branches (“watershed regions”) → susceptible in colonic ischemia:

- Splenic flexure—SMA and IMA
- Rectosigmoid junction—the last sigmoid arterial branch from the IMA and superior rectal artery

**Nutcracker syndrome**—compression of left renal vein between superior mesenteric artery and aorta. May cause abdominal (flank) pain, gross hematuria (from rupture of thin-walled renal varicosities), left-sided varicocele.

**Superior mesenteric artery syndrome**—characterized by intermittent intestinal obstruction symptoms (primarily postprandial pain) when SMA and aorta compress transverse (third) portion of duodenum. Typically occurs in conditions associated with diminished mesenteric fat (eg, low body weight/malnutrition).



**Gastrointestinal blood supply and innervation**

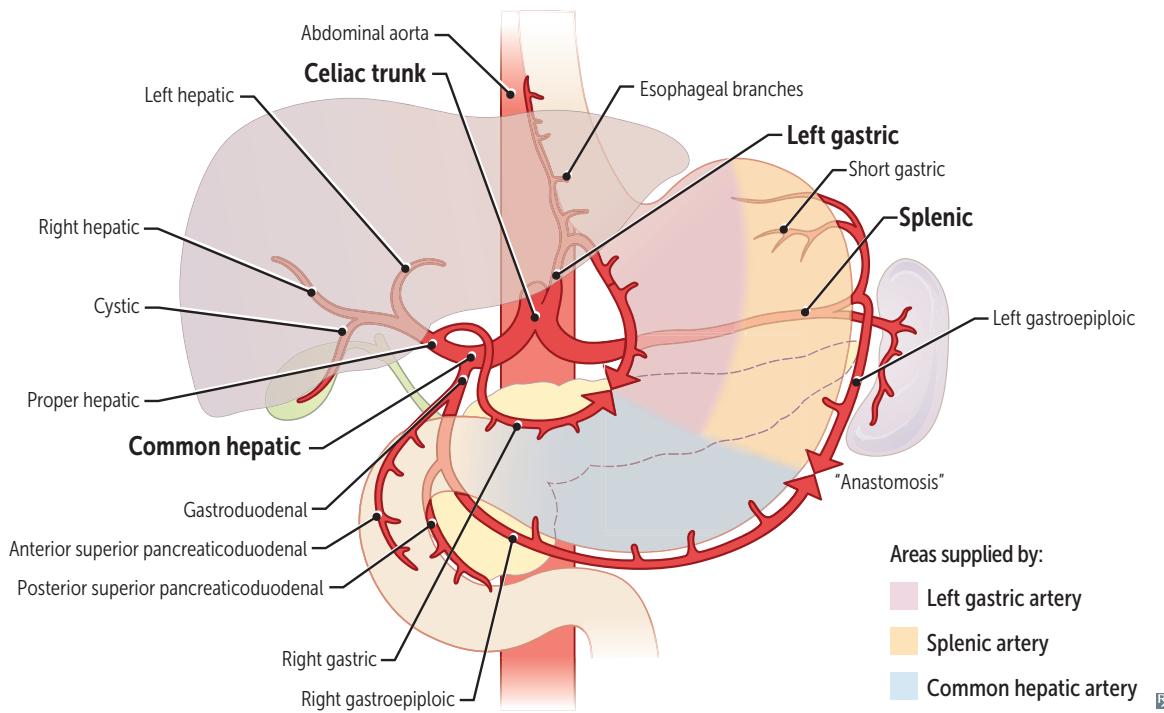
EMBRYONIC GUT REGION	ARTERY	PARASYMPATHETIC INNERVATION	VERTEBRAL LEVEL	STRUCTURES SUPPLIED
<b>Foregut</b>	Celiac	Vagus	T12/L1	Pharynx (vagus nerve only) and lower esophagus (celiac artery only) to proximal duodenum; liver, gallbladder, pancreas, spleen (mesoderm)
<b>Midgut</b>	SMA	Vagus	L1	Distal duodenum to proximal 2/3 of transverse colon
<b>Hindgut</b>	IMA	Pelvic	L3	Distal 1/3 of transverse colon to upper portion of anal canal

**Celiac trunk**

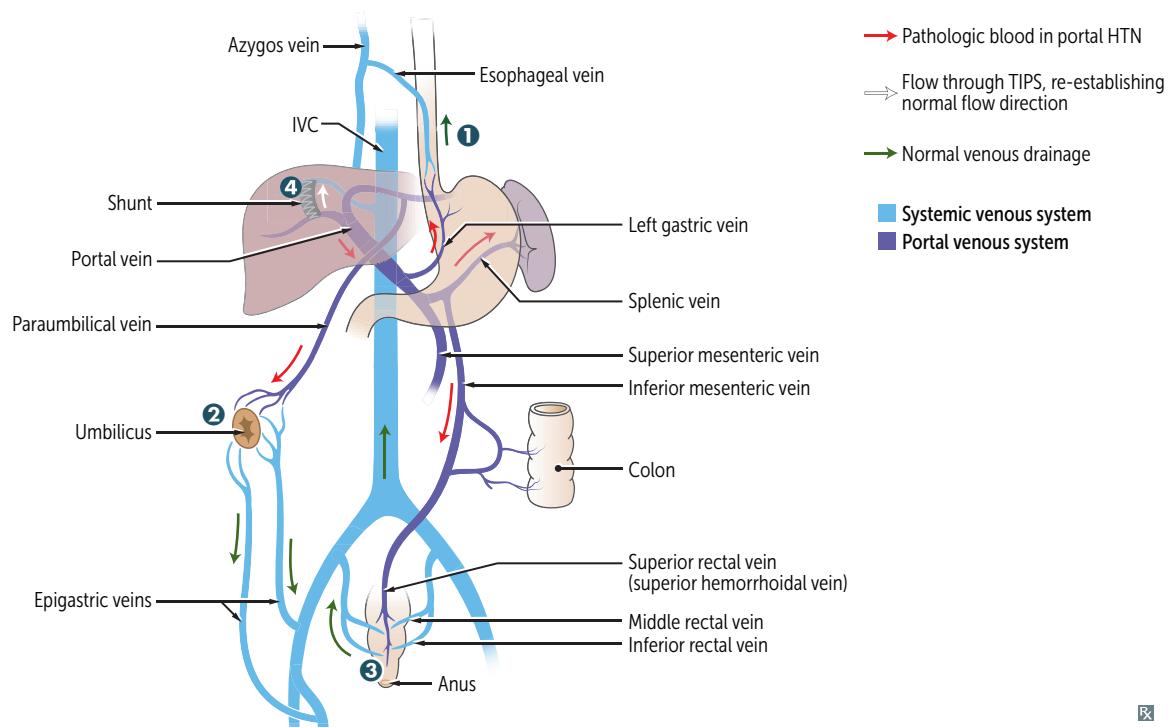
Branches of celiac trunk: common hepatic, splenic, and left gastric. These constitute the main blood supply of the foregut.

Strong anastomoses exist between:

- Left and right gastroepiploics
- Left and right gastrics



## Portosystemic anastomoses



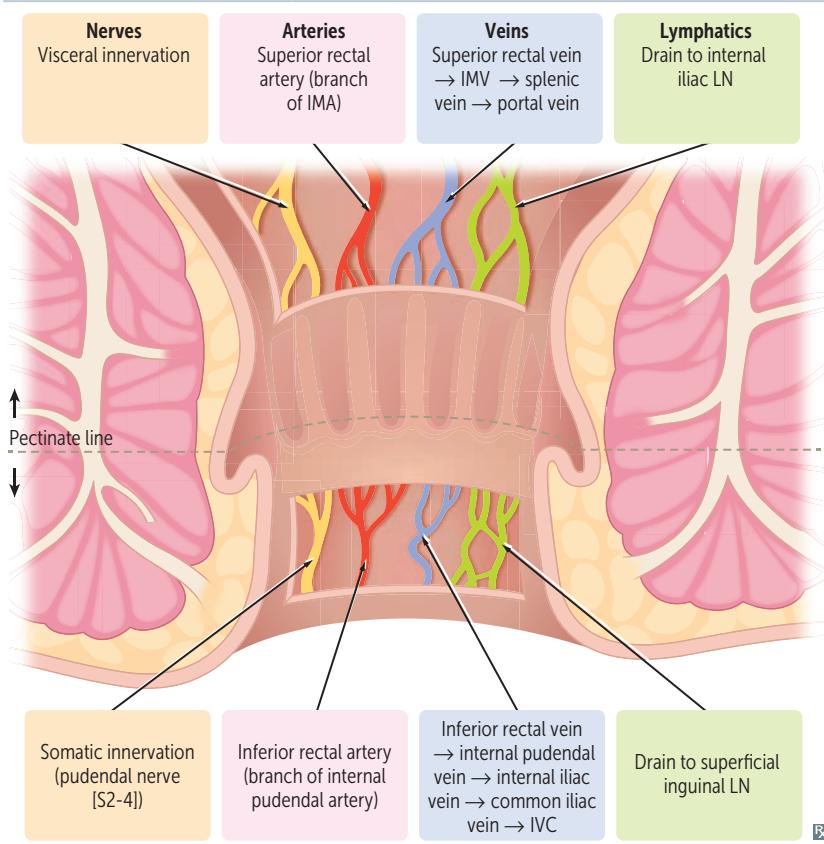
SITE OF ANASTOMOSIS	CLINICAL SIGN	PORTAL ↔ SYSTEMIC
<b>① Esophagus</b>	Esophageal varices	Left gastric ↔ esophageal (drains into azygos)
<b>② Umbilicus</b>	<b>Caput medusae</b>	Paraumbilical ↔ small epigastric veins of the anterior abdominal wall.
<b>③ Rectum</b>	Anorectal varices	Superior rectal ↔ middle and inferior rectal

Varices of **gut**, **butt**, and **caput** (medusae) are commonly seen with portal hypertension.

- ④** Treatment with a **Transjugular Intrahepatic Portosystemic Shunt (TIPS)** between the portal vein and hepatic vein relieves portal hypertension by shunting blood to the systemic circulation, bypassing the liver. TIPS can precipitate hepatic encephalopathy due to ↓ clearance of ammonia from shunting.

**Pectinate line**

Also called dentate line. Formed where endoderm (hindgut) meets ectoderm.



**Above pectinate line:** internal hemorrhoids, adenocarcinoma.

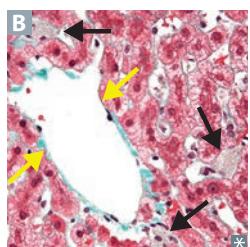
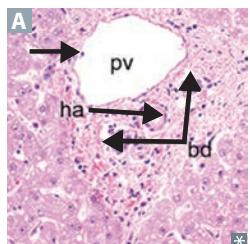
Internal hemorrhoids receive visceral innervation and are therefore **not painful**.

**Below pectinate line:** external hemorrhoids, anal fissures, squamous cell carcinoma.

External hemorrhoids receive somatic innervation (inferior rectal branch of pudendal nerve) and are therefore **painful** if thrombosed.

**Anal fissure**—tear in anoderm below pectinate line. **Pain while pooping; blood on toilet paper.** Located in the posterior midline because this area is **poorly perfused**. Associated with low-fiber diets and constipation.

### Liver tissue architecture



The functional unit of the liver is made up of hexagonally arranged lobules surrounding the central vein with portal triads on the edges (consisting of a portal vein, hepatic artery, bile ducts, as well as lymphatics) **A**.

Apical surface of hepatocytes faces bile canaliculi. Basolateral surface faces sinusoids. Kupffer cells (specialized macrophages) located in sinusoids (black arrows in **B**; yellow arrows show central vein) clear bacteria and damaged or senescent RBCs.

Hepatic stellate (Ito) cells in space of Disse store vitamin A (when quiescent) and produce extracellular matrix (when activated).

Responsible for hepatic fibrosis.

**Zone I**—periportal zone:

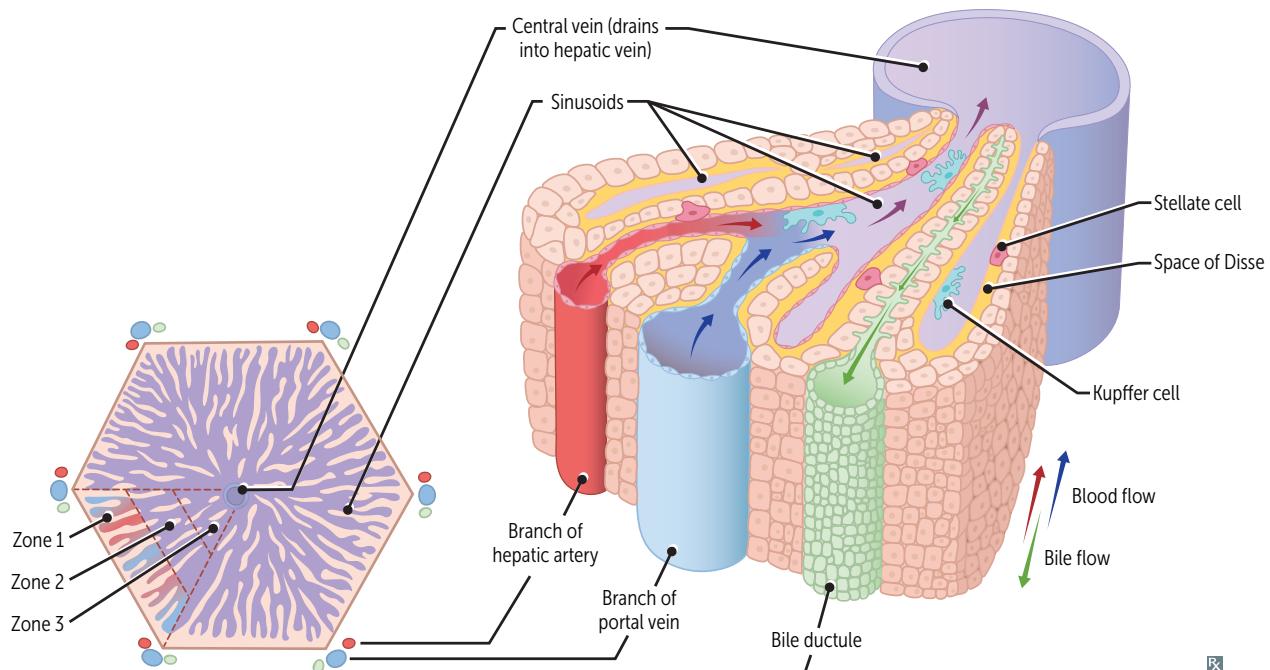
- Affected 1st by viral hepatitis
- Best oxygenated, most resistant to circulatory compromise
- Ingested toxins (eg, cocaine)

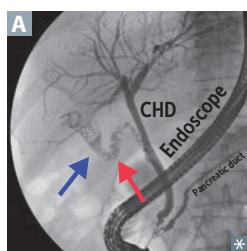
**Zone II**—intermediate zone:

- Yellow fever

**Zone III**—pericentral (centrilobular) zone:

- Affected 1st by ischemia (least oxygenated)
- High concentration of cytochrome P-450
- Most sensitive to metabolic toxins (eg, ethanol, CCl<sub>4</sub>, halothane, rifampin, acetaminophen)
- Site of alcoholic hepatitis

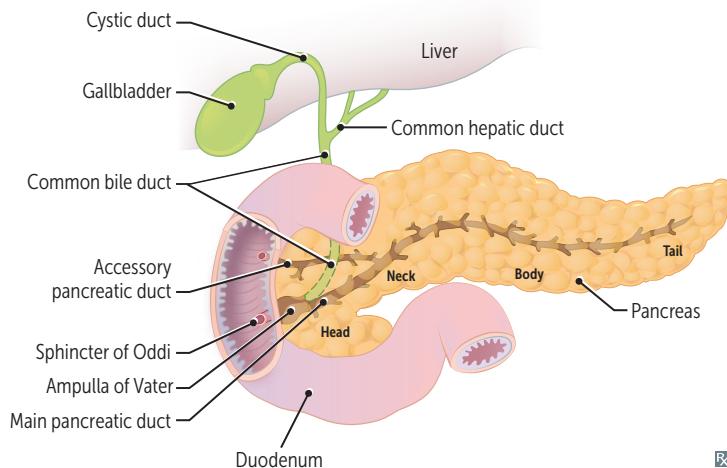


**Biliary structures**

Cholangiography shows filling defects in gallbladder (blue arrow in A) and cystic duct (red arrow in A).

Gallstones that reach the confluence of the common bile and pancreatic ducts at the ampulla of Vater can block both the common bile and pancreatic ducts (double duct sign), causing both cholangitis and pancreatitis, respectively.

Tumors that arise in head of pancreas (usually ductal adenocarcinoma) can cause obstruction of common bile duct → enlarged gallbladder with painless jaundice (Courvoisier sign).

**Femoral region****ORGANIZATION**

**Lateral to medial:** nerve-artery-vein-lymphatics.

You go from **lateral to medial** to find your **navel**.

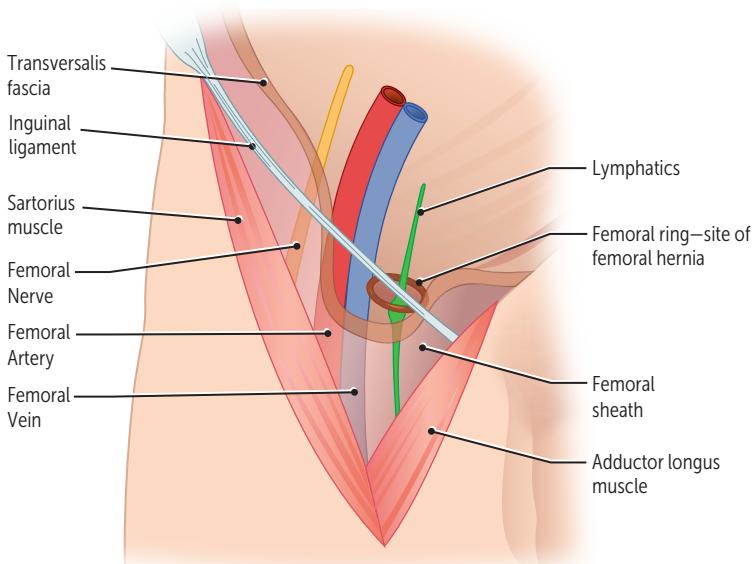
**Femoral triangle**

Contains femoral nerve, artery, vein.

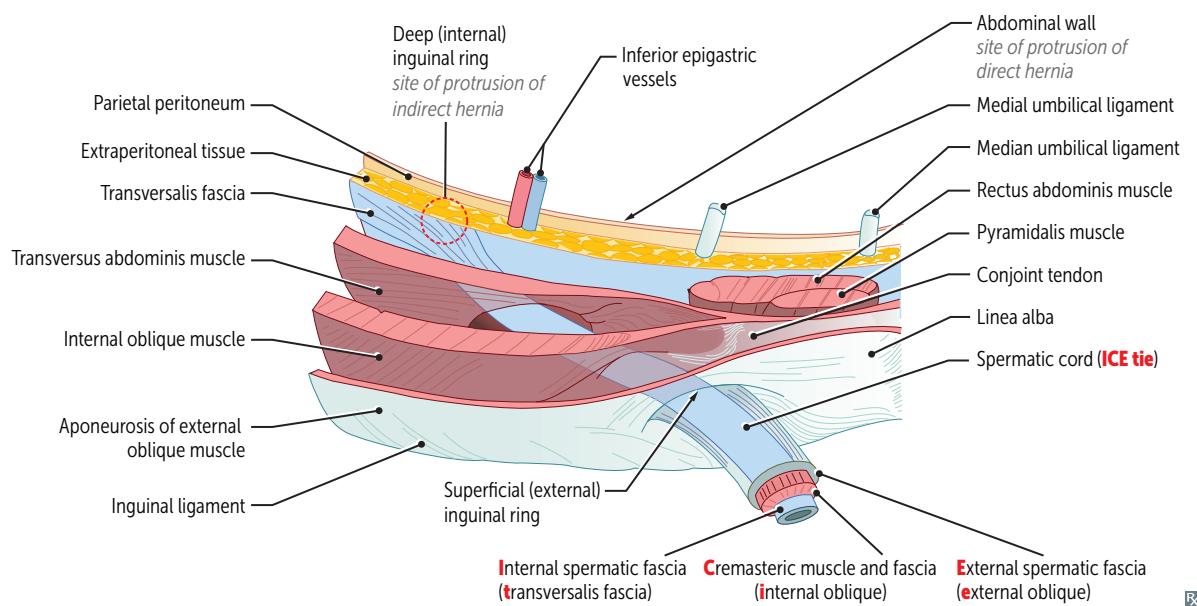
**Venous** near the penis.

**Femoral sheath**

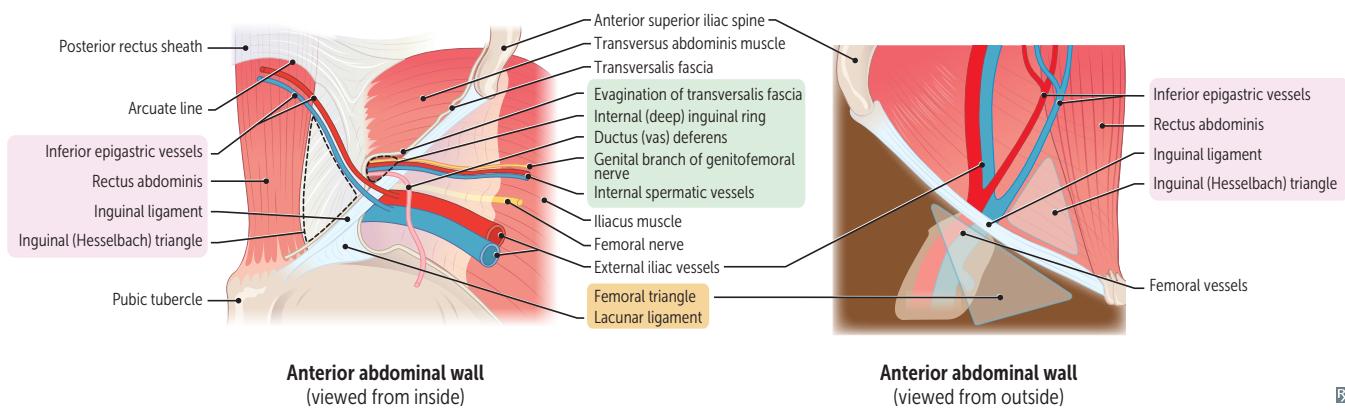
Fascial tube 3–4 cm below inguinal ligament.  
Contains femoral vein, artery, and canal (deep inguinal lymph nodes) but not femoral nerve.



### Inguinal canal

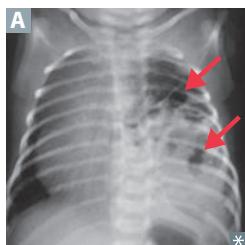


### Abdominal wall



**Hernias**

Protrusion of peritoneum through an opening, usually at a site of weakness. Contents may be at risk for incarceration (not reducible back into abdomen/pelvis) and strangulation (ischemia and necrosis). Complicated hernias can present with tenderness, erythema, fever.

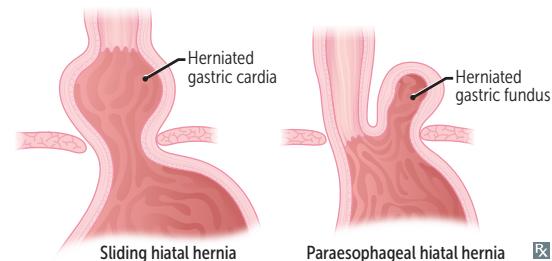
**Diaphragmatic hernia**

Abdominal structures enter the thorax. Most common causes:

- Infants—congenital defect of pleuroperitoneal membrane → left-sided herniation (right hemidiaphragm is relatively protected by liver) **A**.
- Adults—laxity/defect of phrenoesophageal membrane → **hiatal hernia** (herniation of stomach through esophageal hiatus).

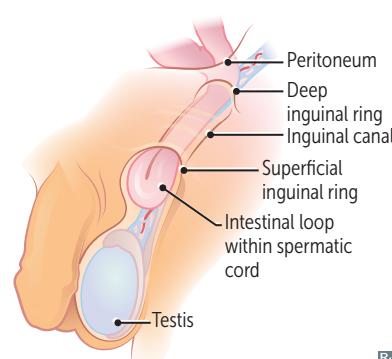
**Sliding hiatal hernia**—gastroesophageal junction is displaced upward as gastric cardia slides into hiatus; “hourglass stomach.” Most common type. Associated with GERD.

**Paraesophageal hiatal hernia**—gastroesophageal junction is usually normal but gastric fundus protrudes into the thorax.

**Indirect inguinal hernia**

Goes through the internal (deep) inguinal ring, external (superficial) inguinal ring, and into the groin. Enters internal inguinal ring lateral to inferior epigastric vessels. Caused by failure of processus vaginalis to close (can form hydrocele). May be noticed in infants or discovered in adulthood. Much more common in males **B**.

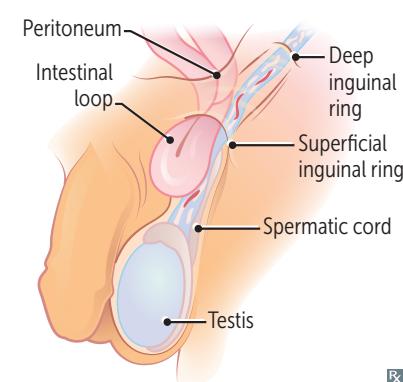
Follows the pathway of testicular descent.  
Covered by all 3 layers of spermatic fascia.

**Direct inguinal hernia**

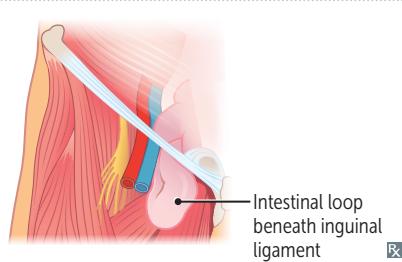
Protrudes through inguinal (Hesselbach) triangle. Bulges directly through parietal peritoneum medial to the inferior epigastric vessels but lateral to the rectus abdominis. Goes through external (superficial) inguinal ring only. Covered by external spermatic fascia. Usually occurs in older males due to acquired weakness of transversalis fascia.

**MDs don't lie:**

- Medial to inferior epigastric vessels = **Direct hernia**.
- Lateral to inferior epigastric vessels = **indirect hernia**.

**Femoral hernia**

Protrudes below inguinal ligament through femoral canal below and lateral to pubic tubercle. More common in **females**, but overall inguinal hernias are the most common. More likely to present with incarceration or strangulation (vs inguinal hernia).



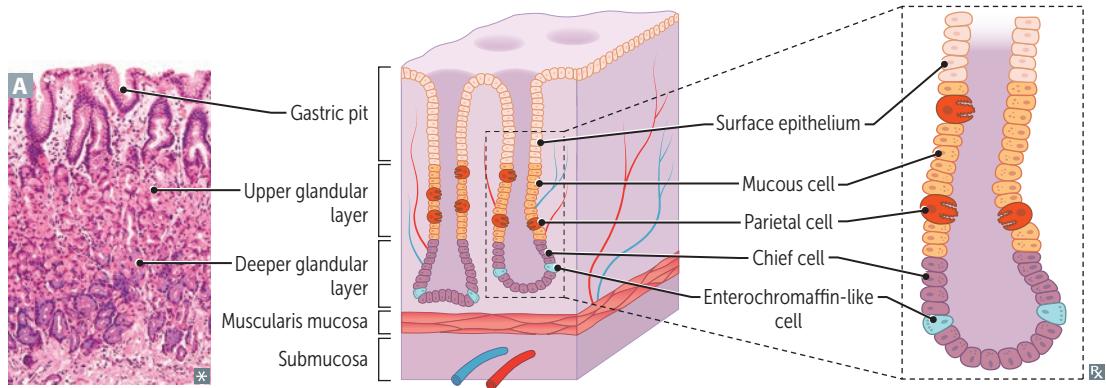
## ► GASTROINTESTINAL—PHYSIOLOGY

**Gastrointestinal regulatory substances**

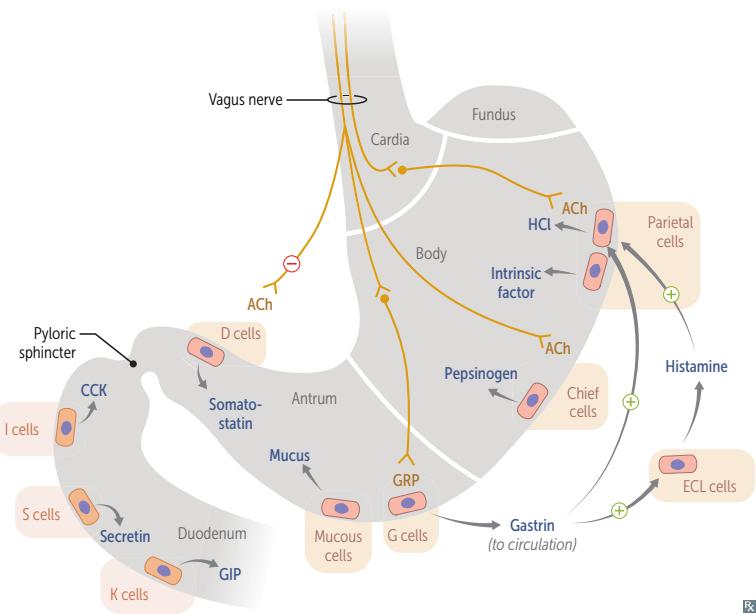
REGULATORY SUBSTANCE	SOURCE	ACTION	REGULATION	NOTES
<b>Gastrin</b>	G cells (antrum of stomach, duodenum)	↑ gastric H <sup>+</sup> secretion ↑ growth of gastric mucosa ↑ gastric motility	↑ by stomach distention/ alkalinization, amino acids, peptides, vagal stimulation via gastrin-releasing peptide (GRP) ↓ by pH < 1.5	↑ by chronic PPI use ↑ in chronic atrophic gastritis (eg, <i>H pylori</i> ) ↑↑ in Zollinger-Ellison syndrome (gastrinoma)
<b>Somatostatin</b>	D cells (pancreatic islets, GI mucosa)	↓ gastric acid and pepsinogen secretion ↓ pancreatic and small intestine fluid secretion ↓ gallbladder contraction ↓ insulin and glucagon release	↑ by acid ↓ by vagal stimulation	Inhibits secretion of various hormones (encourages somato-stasis) Octreotide is an analog used to treat acromegaly, carcinoid syndrome, VIPoma, and variceal bleeding
<b>Cholecystokinin</b>	I cells (duodenum, jejunum)	↑ pancreatic secretion ↑ gallbladder contraction ↓ gastric emptying ↑ sphincter of Oddi relaxation	↑ by fatty acids, amino acids	Acts on neural muscarinic pathways to cause pancreatic secretion
<b>Secretin</b>	S cells (duodenum)	↑ pancreatic HCO <sub>3</sub> <sup>-</sup> secretion ↓ gastric acid secretion ↑ bile secretion	↑ by acid, fatty acids in lumen of duodenum	↑ HCO <sub>3</sub> <sup>-</sup> neutralizes gastric acid in duodenum, allowing pancreatic enzymes to function
<b>Glucose-dependent insulinotropic peptide</b>	K cells (duodenum, jejunum)	Exocrine: ↓ gastric H <sup>+</sup> secretion Endocrine: ↑ insulin release	↑ by fatty acids, amino acids, oral glucose	Also called gastric inhibitory peptide (GIP) Oral glucose load ↑ insulin compared to IV equivalent due to GIP secretion
<b>Motilin</b>	Small intestine	Produces migrating motor complexes (MMCs)	↑ in fasting state	Motilin receptor agonists (eg, erythromycin) are used to stimulate intestinal peristalsis.
<b>Vasoactive intestinal polypeptide</b>	Parasympathetic ganglia in sphincters, gallbladder, small intestine	↑ intestinal water and electrolyte secretion ↑ relaxation of intestinal smooth muscle and sphincters	↑ by distention and vagal stimulation ↓ by adrenergic input	<b>VIPoma</b> —non-α, non-β islet cell pancreatic tumor that secretes VIP; associated with <b>Watery Diarrhea, Hypokalemia, Achlorhydria (WDHA syndrome)</b>
<b>Nitric oxide</b>		↑ smooth muscle relaxation, including lower esophageal sphincter (LES)		Loss of NO secretion is implicated in ↑ LES tone of achalasia
<b>Ghrelin</b>	Stomach	↑ appetite (“ghrowlin’ stomach”)	↑ in fasting state ↓ by food	↑ in Prader-Willi syndrome ↓ after gastric bypass surgery

**Gastrointestinal secretory products**

PRODUCT	SOURCE	ACTION	REGULATION	NOTES
<b>Intrinsic factor</b>	Parietal cells (stomach <b>A</b> )	Vitamin B <sub>12</sub> –binding protein (required for B <sub>12</sub> uptake in terminal ileum)		Autoimmune destruction of parietal cells → chronic gastritis and pernicious anemia
<b>Gastric acid</b>	Parietal cells (stomach)	↓ stomach pH	↑ by histamine, vagal stimulation (ACh), gastrin ↓ by somatostatin, GIP, prostaglandin, secretin	
<b>Pepsin</b>	Chief cells (stomach)	Protein digestion	↑ by vagal stimulation (ACh), local acid	Pepsinogen (inactive) is converted to pepsin (active) in the presence of H <sup>+</sup>
<b>Bicarbonate</b>	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

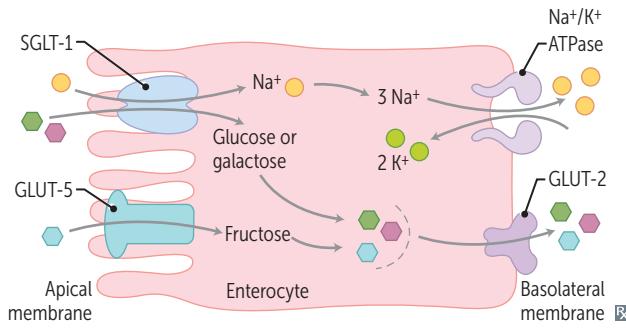


Gastrin ↑ acid secretion primarily through its effects on enterochromaffin-like (ECL) cells (leading to histamine release) rather than through its direct effect on parietal cells.

**Pancreatic secretions** Isotonic fluid; low flow → high  $\text{Cl}^-$ , high flow → high  $\text{HCO}_3^-$ .

ENZYME	ROLE	NOTES
$\alpha$ -amylase	Starch digestion	Secreted in active form
Lipases	Fat digestion	
Proteases	Protein digestion	Includes trypsin, chymotrypsin, elastase, carboxypeptidases Secreted as proenzymes also called 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



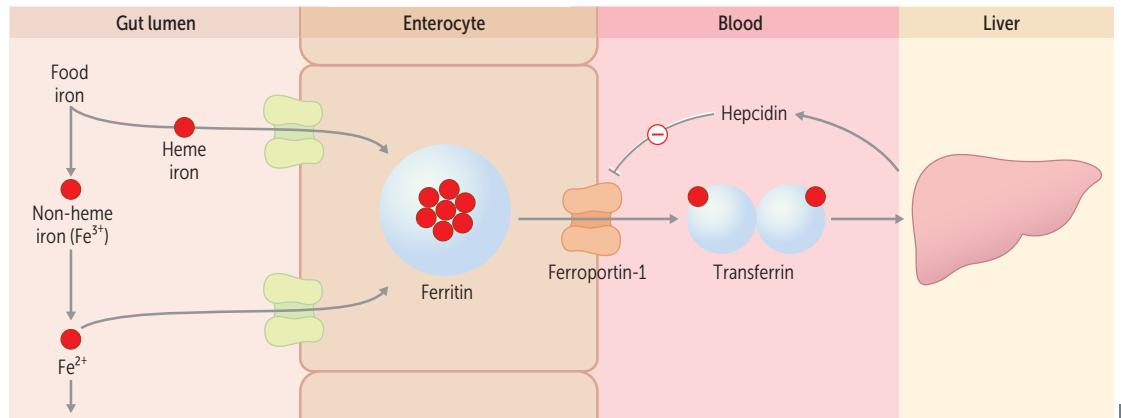
Only monosaccharides (glucose, galactose, fructose) are absorbed by enterocytes. Glucose and galactose are taken up by SGLT1 ( $\text{Na}^+$  dependent). Fructose is taken up via facilitated diffusion by GLUT5. All are transported to blood by GLUT2.  
D-xylose test: simple sugar that is passively absorbed in proximal small intestine; blood and urine levels ↓ with mucosal damage, normal in pancreatic insufficiency.

### Vitamin and mineral absorption

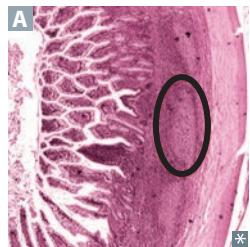
Iron absorbed as  $\text{Fe}^{2+}$  in duodenum.  
 Folate absorbed in small bowel.  
 Vitamin  $\text{B}_{12}$  absorbed in terminal ileum along with bile salts, requires intrinsic factor.

### Iron fist, Bro

Vitamin and mineral deficiencies may develop in patients with small bowel disease or after resection (eg, vitamin  $\text{B}_{12}$  deficiency after terminal ileum resection).



### Peyer patches



Unencapsulated lymphoid tissue **A** found in lamina propria and submucosa of ileum.  
 Contain specialized **M** cells that sample and present antigens to **iM**mune cells.  
**B** cells stimulated in germinal centers of Peyer patches differentiate into IgA-secreting plasma cells, which ultimately reside in lamina propria. IgA receives protective secretory component and is then transported across the epithelium to the gut to deal with intraluminal antigen.

Think of **IgA**, the **Intra-gut Antibody**

### Bile

Composed of bile salts (bile acids conjugated to glycine or taurine, making them water soluble), phospholipids, cholesterol, bilirubin, water, and ions. Cholesterol  $7\alpha$ -hydroxylase catalyzes rate-limiting step of bile acid synthesis.

Functions:

- Digestion and absorption of lipids and fat-soluble vitamins
- Bilirubin and cholesterol excretion (body's 1° means of elimination)
- Antimicrobial activity (via membrane disruption)

↓ absorption of enteric bile salts at distal ileum (as in short bowel syndrome, Crohn disease) prevents normal fat absorption and may cause bile acid diarrhea.

Calcium, which normally binds oxalate, binds fat instead, so free oxalate is absorbed by gut  
 → ↑ frequency of calcium oxalate kidney stones.

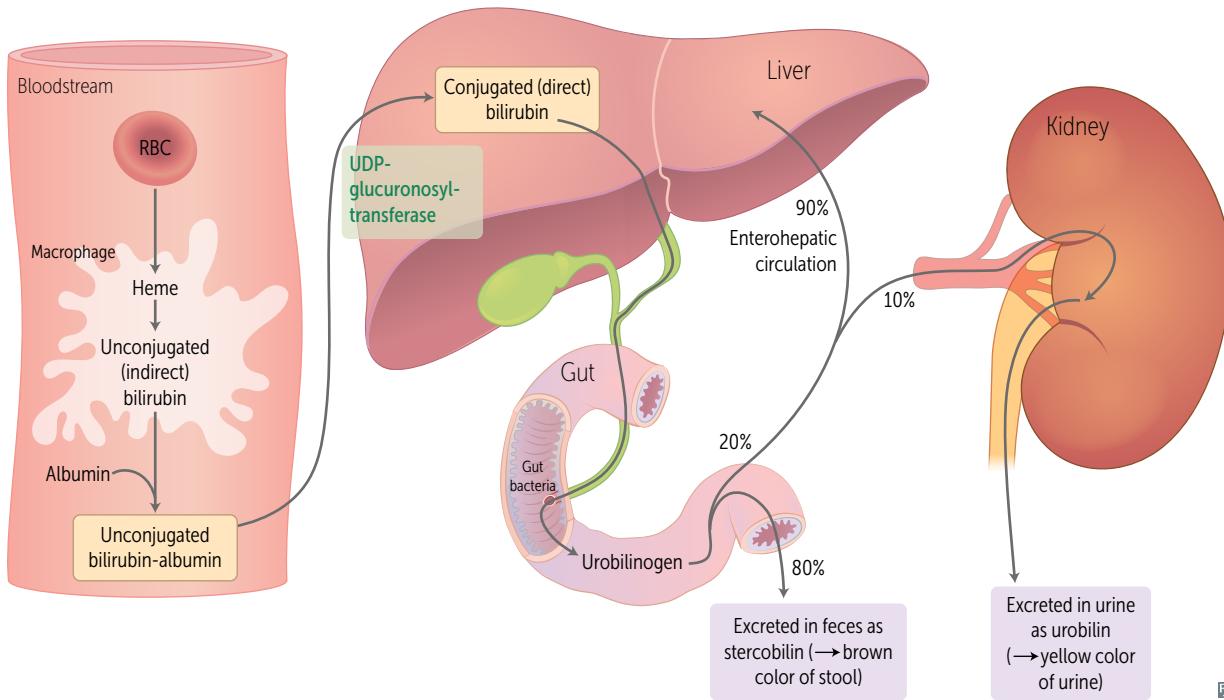
**Bilirubin**

Heme is metabolized by heme oxygenase to biliverdin, which is subsequently reduced to bilirubin.

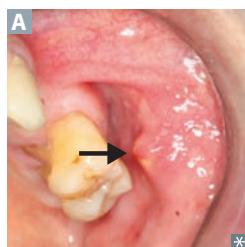
Unconjugated bilirubin is removed from blood by liver, conjugated with glucuronate, and excreted in bile.

**Direct** bilirubin: conjugated with glucuronic acid; water soluble (**dissolves in water**).

**Indirect** bilirubin: unconjugated; water **insoluble**.



## ▶ GASTROINTESTINAL—PATHOLOGY

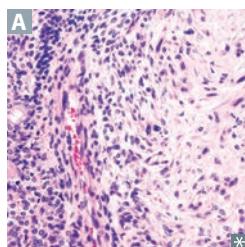
**Sialolithiasis**

Stone(s) in salivary gland duct **A**. Can occur in 3 major salivary glands (parotid, submandibular, sublingual). Single stone more common in submandibular gland (Wharton duct).

Associated with salivary stasis (eg, dehydration) and trauma.

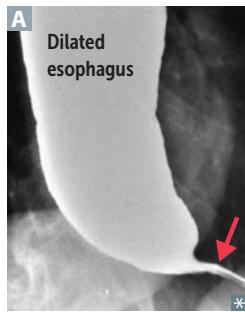
Presents as recurrent pre-/periprandial pain and swelling in affected gland.

**Sialadenitis**—inflammation of salivary gland due to obstruction, infection (eg, *S aureus*, mumps virus), or immune-mediated mechanisms (eg, Sjögren syndrome).

**Salivary gland tumors**

Most are benign and commonly affect parotid gland (80-85%). Nearly half of all submandibular gland neoplasms and most sublingual and minor salivary gland tumors are malignant. Typically present as painless mass/swelling. Facial paralysis or pain suggests malignant involvement.

- **Pleomorphic adenoma** (benign mixed tumor)—most common salivary gland tumor **A**. Composed of chondromyxoid stroma and epithelium and recurs if incompletely excised or ruptured intraoperatively. May undergo malignant transformation.
- **Mucoepidermoid carcinoma**—most common malignant tumor, has mucinous and squamous components.
- **Warthin tumor** (papillary cystadenoma lymphomatosum)—benign cystic tumor with **germinal centers**. Associated with tobacco **smoking**. Bilateral in 10%; multifocal in 10%. “**Warriors from Germany love smoking**.”

**Achalasia**

Failure of LES to relax due to degeneration of inhibitory neurons (containing NO and VIP) in the myenteric (Auerbach) plexus of esophageal wall.

1° achalasia is idiopathic. 2° achalasia may arise from Chagas disease (*T cruzi* infection) or extraesophageal malignancies (mass effect or paraneoplastic). **Chagas disease** can cause **achalasia**.

Presents with progressive dysphagia to solids and liquids (vs obstruction—primarily solids).

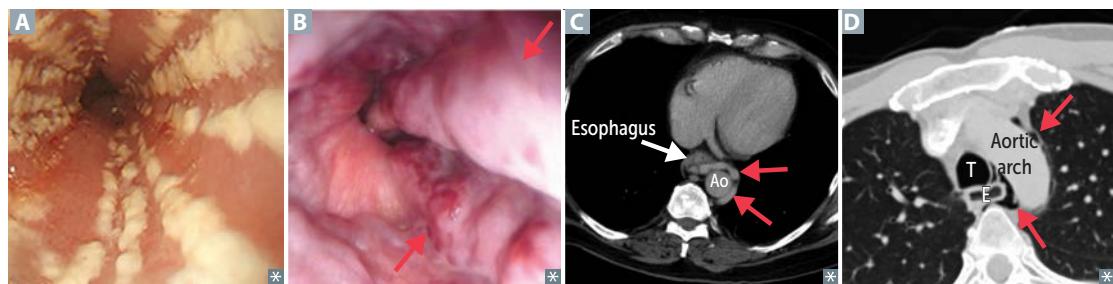
Associated with ↑ risk of esophageal cancer.

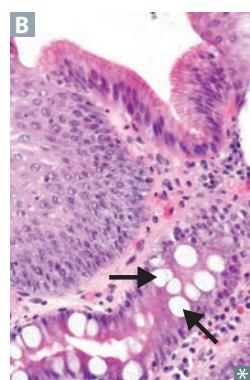
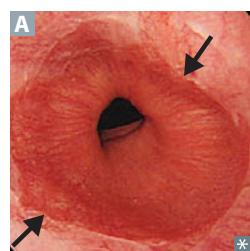
Manometry findings include uncoordinated or absent peristalsis with ↑ LES resting pressure. Barium swallow shows dilated esophagus with area of distal stenosis (“bird’s beak” **A**).

Treatment: surgery, endoscopic procedures (eg, botulinum toxin injection).

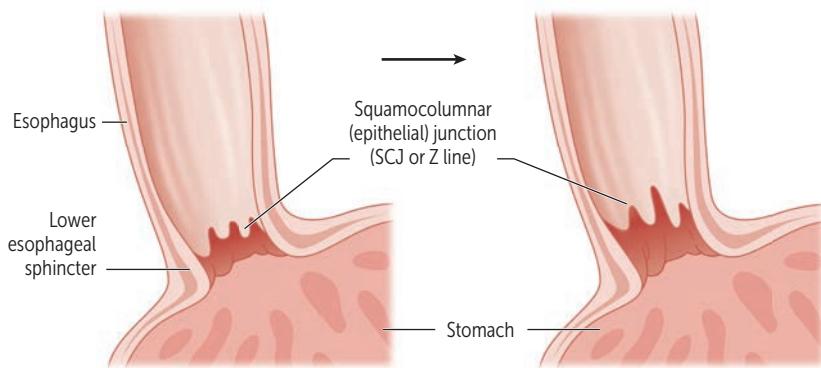
## Esophageal pathologies

<b>Gastroesophageal reflux disease</b>	Commonly presents as heartburn, regurgitation, dysphagia. May also present as chronic cough, hoarseness (laryngopharyngeal reflux). Associated with asthma. Transient decreases in LES tone.
<b>Eosinophilic esophagitis</b>	Infiltration of eosinophils in the esophagus often in atopic patients. Etiology is multifactorial. Food allergens → dysphagia, food impaction. Esophageal rings and linear furrows often seen on endoscopy.
<b>Esophagitis</b>	Associated with reflux, infection in immunocompromised ( <i>Candida</i> : white pseudomembrane <b>A</b> ; HSV-1: punched-out ulcers; CMV: linear ulcers), caustic ingestion, or pill-induced esophagitis (eg, bisphosphonates, tetracycline, NSAIDs, iron, and potassium chloride).
<b>Esophageal strictures</b>	Associated with caustic ingestion, acid reflux, and esophagitis.
<b>Plummer-Vinson syndrome</b>	Triad of dysphagia, iron deficiency anemia, esophageal webs. ↑ risk of esophageal squamous cell carcinoma ("Plumber dies"). May be associated with glossitis.
<b>Mallory-Weiss syndrome</b>	Partial thickness, longitudinal lacerations of gastroesophageal junction, confined to mucosa/submucosa, due to severe vomiting. Often presents with hematemesis +/- abdominal/back pain. Usually found in patients with alcohol use disorder, bulimia nervosa.
<b>Esophageal varices</b>	Dilated submucosal veins (red arrows in <b>B C</b> ) in lower 1/3 of esophagus 2° to portal hypertension. Common in patients with cirrhosis, may be source of life-threatening hematemesis.
<b>Distal esophageal spasm</b>	Formerly called diffuse esophageal spasm. Spontaneous, nonperistaltic (uncoordinated) contractions of the esophagus with normal LES pressure. Presents with dysphagia and angina-like chest pain. Barium swallow reveals "corkscrew" esophagus. Manometry is diagnostic. Treatment includes nitrates and CCBs.
<b>Scleroderma esophageal involvement</b>	Esophageal smooth muscle atrophy → ↓ LES pressure and distal esophageal dysmotility → acid reflux and dysphagia → stricture, Barrett esophagus, and aspiration. Part of CREST syndrome.
<b>Esophageal perforation</b>	Most commonly iatrogenic following esophageal instrumentation. Noniatrogenic causes include spontaneous rupture, foreign body ingestion, trauma, malignancy. May present with pneumomediastinum (arrows in <b>D</b> ). Subcutaneous emphysema may be due to dissecting air (signs include crepitus in the neck region or chest wall). <b>Boerhaave syndrome</b> —transmural, usually distal esophageal rupture due to violent retching.



**Barrett esophagus**

Specialized intestinal metaplasia (arrows in A)—replacement of nonkeratinized stratified squamous epithelium with intestinal epithelium (nonciliated columnar with goblet cells [arrows in B]) in distal esophagus. Due to chronic gastroesophageal reflux disease (GERD). Associated with ↑ risk of esophageal adenocarcinoma.

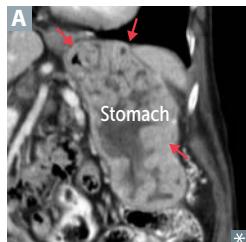
**Esophageal cancer**

Typically presents with progressive dysphagia (first solids, then liquids) and weight loss. Aggressive course due to lack of serosa in esophageal wall, allowing rapid extension. Poor prognosis due to advanced disease at presentation.

CANCER	PART OF ESOPHAGUS AFFECTED	RISK FACTORS	PREVALENCE
<b>Squamous cell carcinoma</b>	Upper 2/3	Alcohol, hot liquids, caustic strictures, smoking, achalasia	More common worldwide
<b>Adenocarcinoma</b>	Lower 1/3	Chronic GERD, Barrett esophagus, obesity, tobacco smoking	More common in America

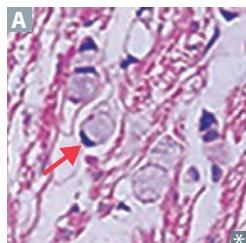
**Gastritis**

<b>Acute gastritis</b>	Erosions can be caused by: <ul style="list-style-type: none"> <li>▪ NSAIDs—<math>\downarrow</math> PGE<sub>2</sub> <math>\rightarrow</math> <math>\downarrow</math> gastric mucosa protection</li> <li>▪ <b>Burns (Curling ulcer)</b>—hypovolemia <math>\rightarrow</math> mucosal ischemia</li> <li>▪ <b>Brain</b> injury (<b>Cushing</b> ulcer)—<math>\uparrow</math> vagal stimulation <math>\rightarrow</math> <math>\uparrow</math> ACh <math>\rightarrow</math> <math>\uparrow</math> H<sup>+</sup> production</li> </ul>	Especially common among patients with alcohol use disorder and those taking daily NSAIDs (eg, for rheumatoid arthritis) <b>Burned</b> by the <b>Curling</b> iron Always <b>Cushion</b> the <b>brain</b>
<b>Chronic gastritis</b>	Mucosal inflammation, often leading to atrophy (hypochlorhydria $\rightarrow$ hypergastrinemia) and intestinal metaplasia ( $\uparrow$ risk of gastric cancers)	
<b>H pylori</b>	Most common. $\uparrow$ risk of peptic ulcer disease, MALT lymphoma	Affects antrum first and spreads to body of stomach
<b>Autoimmune</b>	Autoantibodies to the H <sup>+</sup> /K <sup>+</sup> ATPase on parietal cells and to intrinsic factor. $\uparrow$ risk of pernicious anemia	Affects body/fundus of stomach

**Ménétrier disease**

Hyperplasia of gastric mucosa  $\rightarrow$  hypertrophied rugae (“wavy” like brain gyri **A**). Causes excess mucus production with resultant protein loss and parietal cell atrophy with  $\downarrow$  acid production. Precancerous.

Presents with Weight loss, Anorexia, Vomiting, Epigastric pain, Edema (due to protein loss; pronounce “WAVEE”).

**Gastric cancer**

Most commonly gastric adenocarcinoma; lymphoma, GI stromal tumor, carcinoid (rare). Early aggressive local spread with node/liver metastases. Often presents late, with weight loss, abdominal pain, early satiety, and in some cases acanthosis nigricans or Leser-Trélat sign.

- **Intestinal**—associated with *H pylori*, dietary nitrosamines (smoked foods), tobacco smoking, achlorhydria, chronic gastritis. Commonly on lesser curvature; looks like ulcer with raised margins.
- **Diffuse**—not associated with *H pylori*; most cases due to E-cadherin mutation; signet ring cells (mucin-filled cells with peripheral nuclei) **A**; stomach wall grossly thickened and leathery (linitis plastica).

**Virchow node**—involvement of left supraclavicular node by metastasis from stomach.

**Krukenberg tumor**—metastasis to ovaries (typically bilateral). Abundant mucin-secreting, signet ring cells.

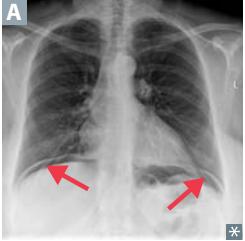
**Sister Mary Joseph nodule**—subcutaneous periumbilical metastasis.

**Blumer shelf**—palpable mass on digital rectal exam suggesting metastasis to rectouterine pouch (pouch of Douglas).

**Peptic ulcer disease**

	<b>Gastric ulcer</b>	<b>Duodenal ulcer</b>
<b>PAIN</b>	Can be <b>greater</b> with meals—weight loss	Decreases with meals—weight gain
<b>H PYLORI INFECTION</b>	~ 70%	~ 90%
<b>MECHANISM</b>	↓ mucosal protection against gastric acid	↓ mucosal protection or ↑ gastric acid secretion
<b>OTHER CAUSES</b>	NSAIDs	Zollinger-Ellison syndrome
<b>RISK OF CARCINOMA</b>	↑	Generally benign
<b>OTHER</b>	Biopsy margins to rule out malignancy	Benign-looking ulcers are not routinely biopsied

**Ulcer complications**

<b>Hemorrhage</b>	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.
<b>Obstruction</b>	Pyloric channel, duodenal.
<b>Perforation</b>	Duodenal (anterior > posterior). Anterior duodenal ulcers can perforate into the anterior abdominal cavity, potentially leading to pneumoperitoneum. May see free air under diaphragm (pneumoperitoneum) <b>A</b> with referred pain to the shoulder via irritation of phrenic nerve.
	

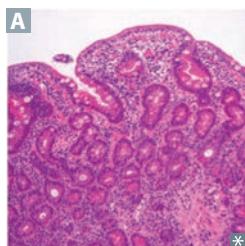
**Acute gastrointestinal bleeding**

**Upper GI bleeding**—originates **proximal** to ligament of Treitz (suspensory ligament of duodenum). Usually presents with hematemesis and/or melena. Associated with peptic ulcer disease, variceal hemorrhage.

**Lower GI bleeding**—originates **distal** to ligament of Treitz. Usually presents with hematochezia. Associated with IBD, diverticulosis, angiodysplasia, hemorrhoids, cancer.

## Malabsorption syndromes

### Celiac disease



Can cause diarrhea, steatorrhea, weight loss, weakness, vitamin and mineral deficiencies. Screen for fecal fat (eg, Sudan stain).

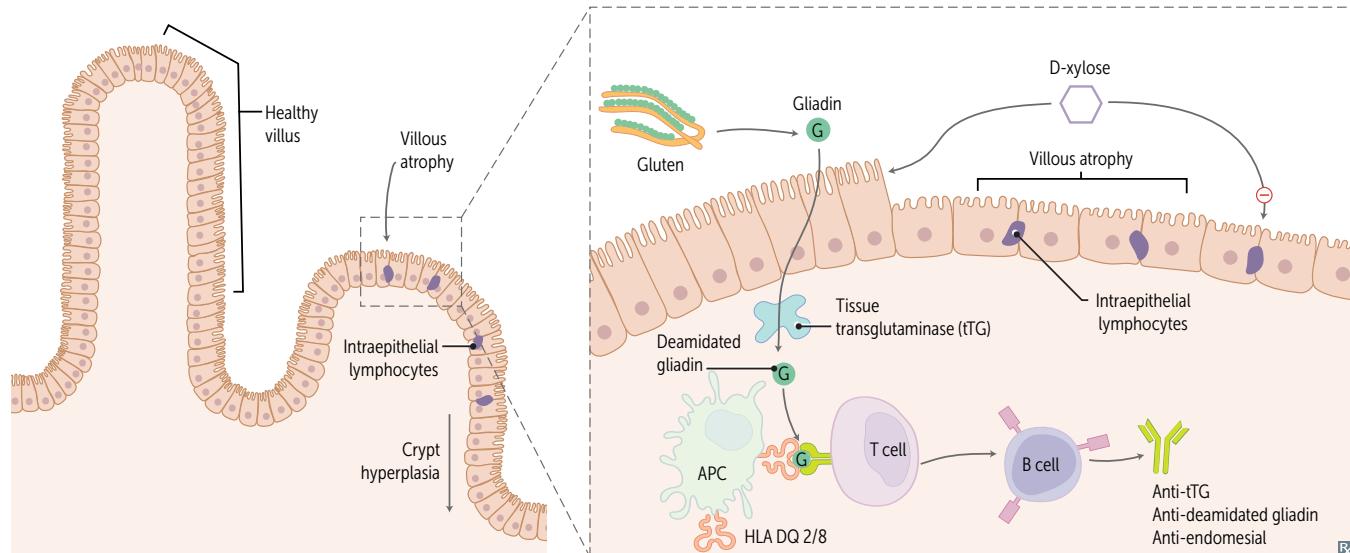
Also called gluten-sensitive enteropathy, celiac sprue. Autoimmune-mediated intolerance of gliadin (gluten protein found in wheat, barley, rye). Associated with HLA-DQ2, HLA-DQ8, northern European descent.  
Primarily affects distal duodenum and/or proximal jejunum → malabsorption and steatorrhea.  
Treatment: gluten-free diet.

Associated with dermatitis herpetiformis, ↓ bone density, moderately ↑ risk of malignancy (eg, T-cell lymphoma).

D-xylose test: abnormal.

Serology: + IgA anti-tissue transglutaminase (IgA tTG), anti-endomysial, and anti-deamidated gliadin peptide antibodies.

Histology: villous atrophy, crypt hyperplasia **A**, intraepithelial lymphocytes.



### 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 post-lactose 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 B<sub>12</sub>.

↓ duodenal bicarbonate (and pH) and fecal elastase.

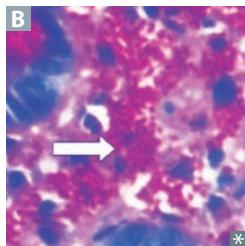
D-xylose test: normal.

### 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, B<sub>12</sub> deficiency.

### Whipple disease

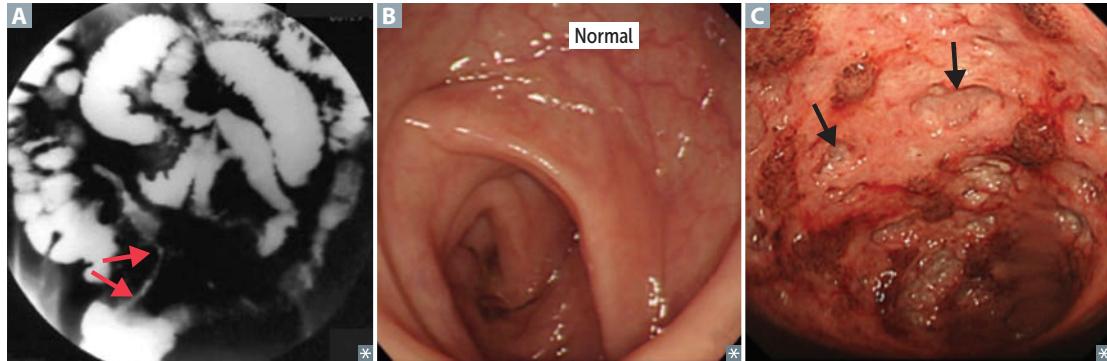


Infection with *Tropheryma whipplei* (intracellular gram +); PAS + foamy macrophages in intestinal lamina propria **B**, mesenteric nodes. Cardiac symptoms, Arthralgias, and Neurologic symptoms are common. Diarrhea/steatorrhea occur later in disease course. Most common in older males.

PASs the foamy Whipped cream in a CAN.

**Inflammatory bowel diseases**

	<b>Crohn disease</b>	<b>Ulcerative colitis</b>
<b>LOCATION</b>	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.
<b>GROSS MORPHOLOGY</b>	Transmural inflammation → fistulas. Cobblestone mucosa, creeping fat, bowel wall thickening (“string sign” on small bowel follow-through <b>A</b> ), linear ulcers, fissures.	Mucosal and submucosal inflammation only. Friable mucosa with superficial and/or deep ulcerations (compare normal <b>B</b> with diseased <b>C</b> ). Loss of haustra → “lead pipe” appearance on imaging.
<b>MICROSCOPIC MORPHOLOGY</b>	Noncaseating granulomas and lymphoid aggregates. Th1 mediated.	Crypt abscesses and ulcers, bleeding, no granulomas. Th2 mediated.
<b>COMPLICATIONS</b>	Malabsorption/malnutrition, colorectal cancer (↑ risk with pancolitis). Fistulas (eg, enterovesical fistulae, which can cause recurrent UTI and pneumaturia), phlegmon/abscess, strictures (causing obstruction), perianal disease.	Fulminant colitis, toxic megacolon, perforation.
<b>INTESTINAL MANIFESTATION</b>	Diarrhea that may or may not be bloody.	Bloody diarrhea.
<b>EXTRAINTESTINAL MANIFESTATIONS</b>	Rash (pyoderma gangrenosum, erythema nodosum), eye inflammation (episcleritis, uveitis), oral ulcerations (aphthous stomatitis), arthritis (peripheral, spondylitis).	1° sclerosing cholangitis. Associated with MPO-ANCA/p-ANCA.
<b>TREATMENT</b>	Corticosteroids, azathioprine, antibiotics (eg, ciprofloxacin, metronidazole), biologics (eg, infliximab, adalimumab).	5-aminosalicylic acid preparations (eg, mesalamine), 6-mercaptopurine, infliximab, colectomy.

**Microscopic colitis**

Inflammatory disease of colon that causes chronic watery diarrhea. Most common in older females. Colonic mucosa appears normal on endoscopy. Histology shows inflammatory infiltrate in lamina propria with thickened subepithelial collagen band or intraepithelial lymphocytes.

### Irritable bowel syndrome

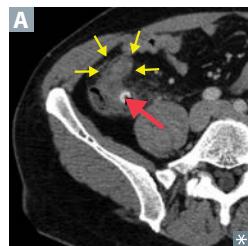
Recurrent abdominal pain associated with ≥ 2 of the following:

- Related to defecation
- Change in stool frequency
- Change in form (consistency) of stool

No structural abnormalities. Most common in middle-aged females. Chronic symptoms may be diarrhea-predominant, constipation-predominant, or mixed. Pathophysiology is multifaceted.

First-line treatment is lifestyle modification and dietary changes.

### Appendicitis



Acute inflammation of the appendix (yellow arrows in **A**), can be due to obstruction by fecolith (red arrow in **A**) (in adults) or lymphoid hyperplasia (in children).

Proximal obstruction of appendiceal lumen produces closed-loop obstruction → ↑ intraluminal pressure → stimulation of visceral afferent nerve fibers at T8-T10 → initial diffuse periumbilical pain → inflammation extends to serosa and irritates parietal peritoneum. Pain localized to RLQ/McBurney point (1/3 the distance from right anterior superior iliac spine to umbilicus). Nausea, fever; may perforate → peritonitis; may elicit psoas, obturator, and Rovsing signs, guarding and rebound tenderness on exam.

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 diverticula.”

**“True” diverticulum**—all gut wall layers outpouch (eg, Meckel).

**“False” diverticulum** or **pseudodiverticulum**—only mucosa and submucosa outpouch. Occur especially where vasa recta perforate muscularis externa.

#### Diverticulosis

Many false diverticula of the colon **B**, commonly sigmoid. Common (in ~ 50% of people > 60 years). Caused by ↑ intraluminal pressure and focal weakness in colonic wall. Associated with obesity and diets low in fiber, high in total fat/red meat.

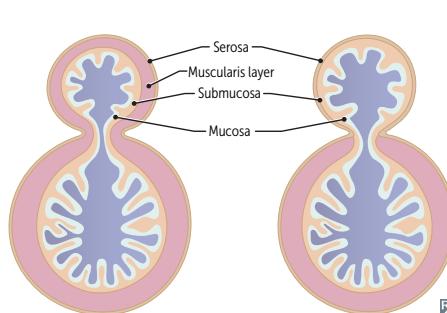
Often asymptomatic or associated with vague discomfort.

Complications include diverticular bleeding (painless hematochezia), diverticulitis.

#### Diverticulitis

Inflammation of diverticula with wall thickening (red arrows in **C**) classically causing LLQ pain, fever, leukocytosis. Treat with antibiotics.

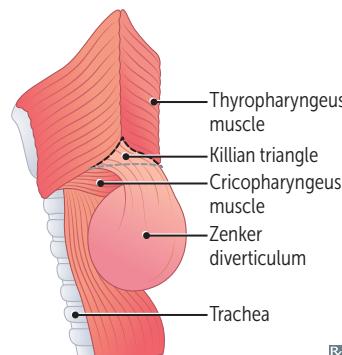
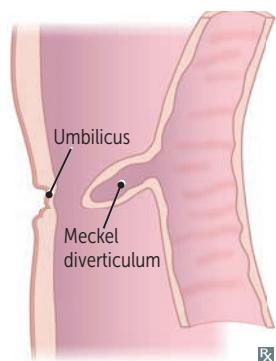
Complications: abscess, fistula (colovesical fistula → pneumaturia), obstruction (inflammatory stenosis), perforation (white arrows in **C**) (→ peritonitis). Hematochezia is rare.



**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.

**Meckel diverticulum**

**True diverticulum.** Persistence of the vitelline (omphalomesenteric) duct. May contain ectopic acid-secreting gastric mucosa and/or pancreatic tissue. Most common congenital anomaly of GI tract. Can cause hematochezia/melena (less common), RLQ pain, intussusception, volvulus, or obstruction near terminal ileum.

Diagnosis:  $^{99m}\text{Tc}$ -pertechnetate scan (aka Meckel scan) for uptake by heterotopic gastric mucosa.

The rule of **2's:**

**2** times as likely in males.

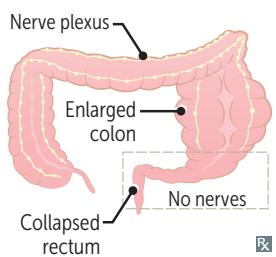
**2** inches long.

**2** feet from the ileocecal valve.

**2%** of population.

Commonly presents in first **2** years of life.

May have **2** types of epithelia (gastric/pancreatic).

**Hirschsprung disease**

Congenital megacolon characterized by lack of ganglion cells/enteric nervous plexuses (Auerbach and Meissner plexuses) in distal segment of colon. Due to failure of neural crest cell migration. Associated with loss of function mutations in *RET*.

Presents with bilious emesis, abdominal distention, and failure to pass meconium within 48 hours → chronic constipation. Normal portion of the colon proximal to the aganglionic segment is dilated, resulting in a "transition zone."

Risk ↑ with Down syndrome.

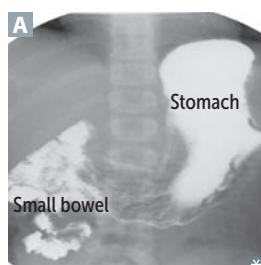
Explosive expulsion of feces (squirt sign)

→ empty rectum on digital exam.

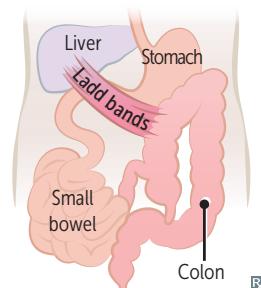
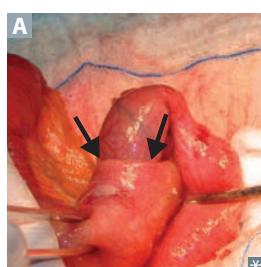
Diagnosed by absence of ganglion cells on rectal suction biopsy.

Treatment: resection.

**RET** mutation in the REcTum.

**Malrotation**

Anomaly of midgut rotation during fetal development → improper positioning of bowel (small bowel clumped on the right side) **A**, formation of fibrous bands (Ladd bands). Can lead to volvulus, duodenal obstruction.

**Intussusception**

Telescoping **A** of proximal bowel segment into a distal segment, commonly at the ileocecal junction. Most commonly idiopathic, but may be due to lead point.

Compromised blood supply → intermittent, severe, abdominal pain often with “currant jelly” dark red stools.

Majority of cases in infants, unusual in adults.

Most common pathologic lead point:

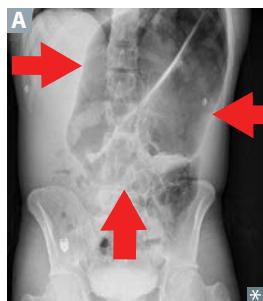
- Children—Meckel diverticulum
- Adults—intraluminal mass/tumor

Physical exam—sausage-shaped mass in right abdomen, patient may draw legs to chest to ease pain.

Imaging—Ultrasound/CT may show “target sign” **B**.

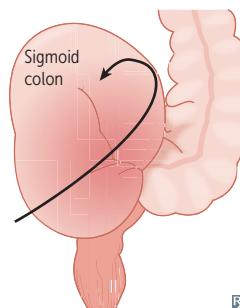


May be associated with IgA vasculitis (HSP), recent viral infection (eg, adenovirus; Peyer patch hypertrophy creates lead point).

**Volvulus**

Twisting of portion of bowel around its mesentery; can lead to obstruction and infarction. Can occur throughout the GI tract.

- Midgut volvulus more common in infants and children (**minors**)
- Sigmoid volvulus (coffee bean sign on x-ray)
- A) more common in **seniors** (elderly)

**Other intestinal disorders****Acute mesenteric ischemia**

Critical blockage of intestinal blood flow (often embolic occlusion of SMA) → small bowel necrosis A → abdominal pain out of proportion to physical findings. May see red “currant jelly” stools.

**Adhesion**

Fibrous band of scar tissue; commonly forms after surgery. Most common cause of small bowel obstruction, demonstrated by multiple dilated small bowel loops on x-ray (arrows in B).

**Angiodysplasia**

Tortuous dilation of vessels C → hematochezia. Most often found in the right-sided colon. More common in older patients. Confirmed by angiography. Associated with end-stage renal disease, von Willebrand disease, aortic stenosis.

**Chronic mesenteric ischemia**

“Intestinal angina”: atherosclerosis of celiac artery, SMA, or IMA → intestinal hypoperfusion → postprandial epigastric pain → food aversion and weight loss.

**Colonic ischemia**

Crampy abdominal pain followed by hematochezia. Commonly occurs at watershed areas (splenic flexure, rectosigmoid junction). Typically affects elderly. Thumbprint sign on imaging due to mucosal edema/hemorrhage.

**Ileus**

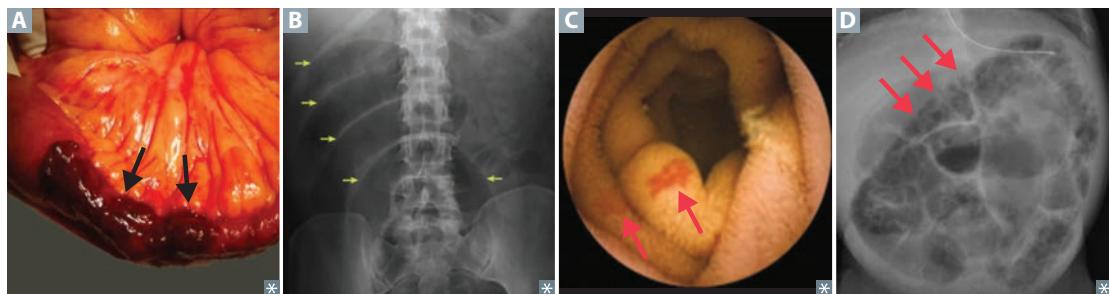
Intestinal hypomotility without obstruction → constipation and ↓ flatus; distended/tympanic abdomen with ↓ bowel sounds. Associated with abdominal surgeries, opiates, hypokalemia, sepsis. No transition zone on imaging. Treatment: bowel rest, electrolyte correction, cholinergic drugs (stimulate intestinal motility).

**Meconium ileus**

Meconium plug obstructs intestine, prevents stool passage at birth. Associated with cystic fibrosis.

**Necrotizing enterocolitis**

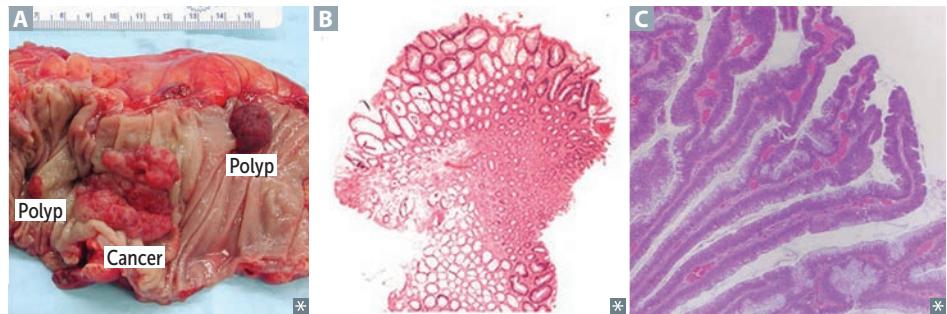
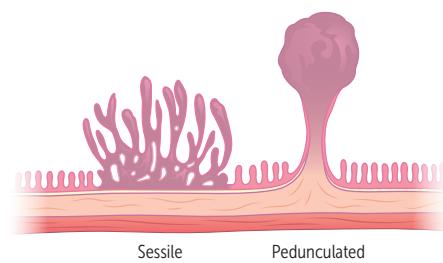
Seen in premature, formula-fed infants with immature immune system. Necrosis of intestinal mucosa (most commonly terminal ileum and proximal colon), which can lead to pneumatosis intestinalis (arrows in D), pneumoperitoneum, portal venous gas.



**Colonic polyps**

Growths of tissue within the colon **A**. Grossly characterized as flat, sessile, or pedunculated on the basis of protrusion into colonic lumen. Generally classified by histologic type.

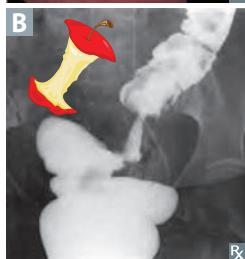
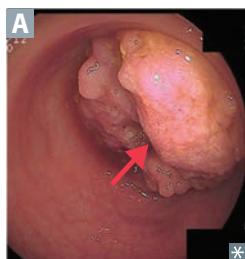
HISTOLOGIC TYPE	CHARACTERISTICS
<b>Generally nonneoplastic</b>	
<b>Hamartomatous polyps</b>	Solitary lesions do not have significant risk of transformation. Growths of normal colonic tissue with distorted architecture. Associated with Peutz-Jeghers syndrome and juvenile polyposis.
<b>Hyperplastic polyps</b>	Most common; generally smaller and predominantly located in rectosigmoid region. Occasionally evolves into serrated polyps and more advanced lesions.
<b>Inflammatory pseudopolyps</b>	Due to mucosal erosion in inflammatory bowel disease.
<b>Mucosal polyps</b>	Small, usually < 5 mm. Look similar to normal mucosa. Clinically insignificant.
<b>Submucosal polyps</b>	May include lipomas, leiomyomas, fibromas, and other lesions.
<b>Potentially malignant</b>	
<b>Adenomatous polyps</b>	Neoplastic, via chromosomal instability pathway with mutations in APC and KRAS. Tubular <b>B</b> histology has less malignant potential than villous <b>C</b> (“villous histology is villainous”); tubulovillous has intermediate malignant potential. Usually asymptomatic; may present with occult bleeding.
<b>Serrated polyps</b>	Neoplastic. Characterized by CpG island methylator phenotype (CIMP; cytosine base followed by guanine, linked by a phosphodiester bond). Defect may silence MMR gene (DNA mismatch repair) expression. Mutations lead to microsatellite instability and mutations in BRAF. “Saw-tooth” pattern of crypts on biopsy. Up to 20% of cases of sporadic CRC.

**Polyposis syndromes**

<b>Familial adenomatous polyposis</b>	Autosomal dominant mutation of APC tumor suppressor gene on chromosome 5q21-q22. 2-hit hypothesis. Thousands of polyps arise starting after puberty; pancolonic; always involves rectum. Prophylactic colectomy or else 100% progress to CRC.
<b>Gardner syndrome</b>	FAP + osseous and soft tissue tumors (eg, osteomas of skull or mandible), congenital hypertrophy of retinal pigment epithelium, impacted/supernumerary teeth.
<b>Turcot syndrome</b>	FAP or Lynch syndrome + malignant CNS tumor (eg, medulloblastoma, glioma). <b>Turcot = Turban</b> .
<b>Peutz-Jeghers syndrome</b>	Autosomal dominant syndrome featuring numerous hamartomas throughout GI tract, along with hyperpigmented macules on mouth, lips, hands, genitalia. Associated with ↑ risk of breast and GI cancers (eg, colorectal, stomach, small bowel, pancreatic).
<b>Juvenile polyposis syndrome</b>	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 called hereditary nonpolyposis colorectal cancer (HNPCC). Autosomal dominant mutation of mismatch repair genes (eg, *MLH1*, *MSH2*) with subsequent microsatellite instability. ~ 80% progress to CRC. Proximal colon is always involved. Associated with endometrial, ovarian, and skin cancers.

**Colorectal cancer****DIAGNOSIS**

Iron deficiency anemia in males (especially > 50 years old) and postmenopausal females raises suspicion.

**Screening:**

- Average risk: screen at age 50 with colonoscopy (polyp seen in A); alternatives include flexible sigmoidoscopy, fecal occult blood testing (FOBT), fecal immunochemical testing (FIT), FIT-fecal DNA, CT colonography.
- Patients with a first-degree relative who has colon cancer: screen at age 40 with colonoscopy, or 10 years prior to the relative's presentation.
- Patients with IBD are screened more regularly.

"Apple core" lesion seen on barium enema x-ray B.

CEA tumor marker: good for monitoring recurrence, should not be used for screening.

**EPIDEMIOLOGY**

Most patients are > 50 years old. ~ 25% have a family history.

**PRESENTATION**

Rectosigmoid > ascending > descending.

Most are asymptomatic. Right side (cecal, ascending) associated with occult bleeding; left side (rectosigmoid) associated with hematochezia and obstruction (narrower lumen → ↓ stool caliber).

Ascending—exophytic mass, iron deficiency anemia, weight loss.

Descending—infiltrating mass, partial obstruction, colicky pain, hematochezia.

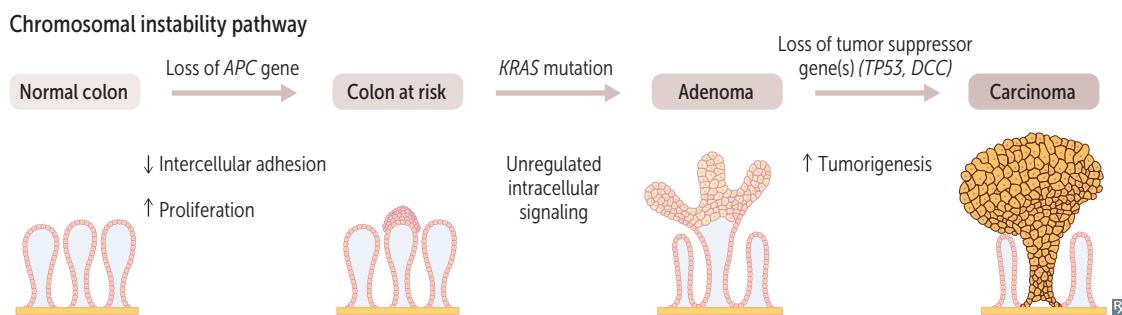
Can present with *S. bovis* (*gallopticus*) bacteremia/endocarditis or as an episode of diverticulitis.

**RISK FACTORS**

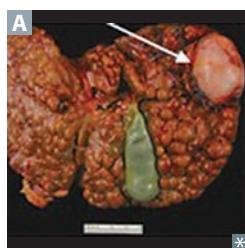
Adenomatous and serrated polyps, familial cancer syndromes, IBD, tobacco use, diet of processed meat with low fiber.

### Molecular pathogenesis of colorectal cancer

Chromosomal instability pathway: mutations in APC cause FAP and most sporadic cases of CRC via adenoma-carcinoma sequence.  
 Microsatellite instability pathway: mutations or methylation of mismatch repair genes (eg, *MLH1*) cause Lynch syndrome and some sporadic CRC via serrated polyp pathway. Usually leads to right-sided CRC.  
 Overexpression of COX-2 has been linked to colorectal cancer, NSAIDs may be chemopreventive.

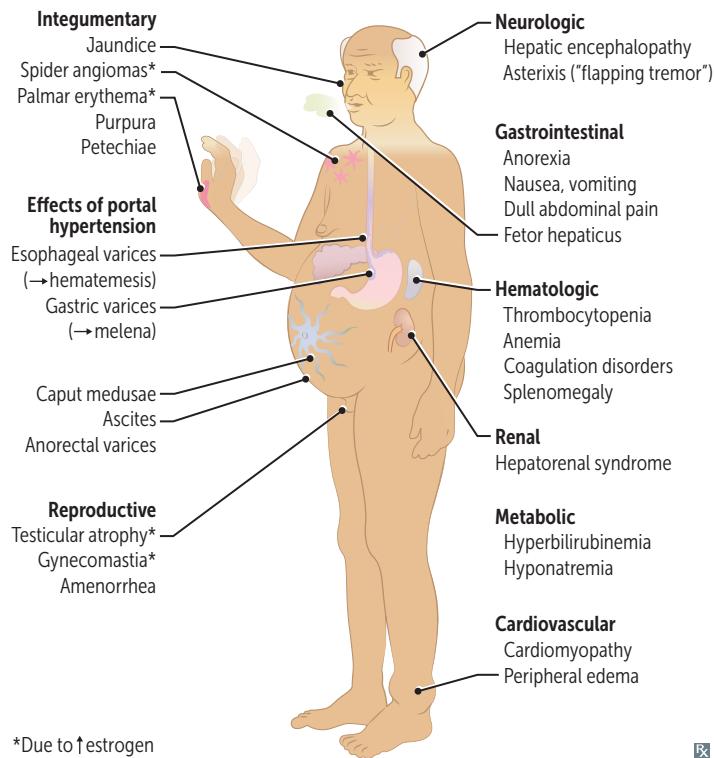


### Cirrhosis and portal hypertension



**Cirrhosis**—diffuse bridging fibrosis (via stellate cells) and regenerative nodules (arrows show splenomegaly) disrupt normal architecture of liver; ↑ risk for hepatocellular carcinoma (white arrow in A). Etiologies include alcohol, nonalcoholic steatohepatitis, chronic viral hepatitis, autoimmune hepatitis, biliary disease, genetic/metabolic disorders.

**Portal hypertension**—↑ pressure in portal venous system. Etiologies include cirrhosis (most common cause in developed countries), vascular obstruction (eg, portal vein thrombosis, Budd-Chiari syndrome), schistosomiasis.



<b>Spontaneous bacterial peritonitis</b>	Also called 1° bacterial peritonitis. Common and potentially fatal bacterial infection in patients with cirrhosis and ascites. Often asymptomatic, but can cause fevers, chills, abdominal pain, ileus, or worsening encephalopathy. Commonly caused by gram $\ominus$ organisms (eg, <i>E coli</i> , <i>Klebsiella</i> ) or less commonly gram $\oplus$ <i>Streptococcus</i> . Diagnosis: paracentesis with ascitic fluid absolute neutrophil count (ANC) $> 250$ cells/mm <sup>3</sup> . Empiric first-line treatment is 3rd generation cephalosporin (eg, cefotaxime).
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**Serum markers of liver pathology**

## ENZYMES RELEASED IN LIVER DAMAGE

<b>Aspartate aminotransferase and alanine aminotransferase</b>	↑ in most liver disease: ALT > AST ↑ in <b>alcoholic</b> liver disease: <b>AST</b> > ALT (ratio usually $> 2:1$ , AST does not typically exceed 500 U/L in alcoholic hepatitis). Make a to <b>AST</b> with <b>alcohol</b> AST > ALT in nonalcoholic liver disease suggests progression to advanced fibrosis or cirrhosis ↑↑ aminotransferases ( $> 1000$ U/L): differential includes drug-induced liver injury (eg, acetaminophen toxicity), ischemic hepatitis, acute viral hepatitis, autoimmune hepatitis
<b>Alkaline phosphatase</b>	↑ in cholestasis (eg, biliary obstruction), infiltrative disorders, bone disease
<b><math>\gamma</math>-glutamyl transpeptidase</b>	↑ in various liver and biliary diseases (just as ALP can), but not in bone disease; associated with alcohol use

## FUNCTIONAL LIVER MARKERS

<b>Bilirubin</b>	↑ in various liver diseases (eg, biliary obstruction, alcoholic or viral hepatitis, cirrhosis), hemolysis
<b>Albumin</b>	↓ in advanced liver disease (marker of liver's biosynthetic function)
<b>Prothrombin time</b>	↑ in advanced liver disease (↓ production of clotting factors, thereby measuring the liver's biosynthetic function)
<b>Platelets</b>	↓ in advanced liver disease (↓ thrombopoietin, liver sequestration) and portal hypertension (splenomegaly/splenic sequestration)

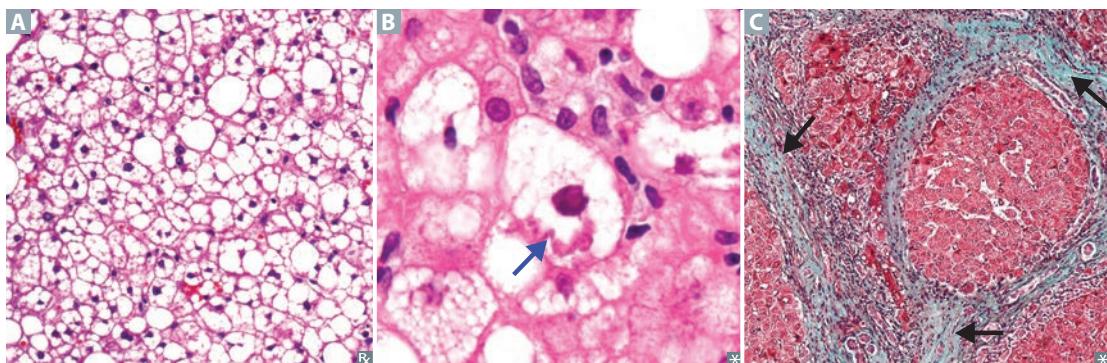
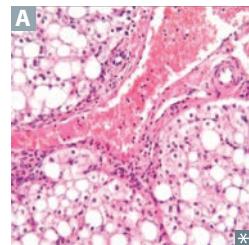
**Reye syndrome**

Rare, often fatal childhood hepatic encephalopathy.  
Associated with viral infection (especially VZV and influenza) that has been treated with aspirin. Aspirin metabolites ↓  $\beta$ -oxidation by reversible inhibition of mitochondrial enzymes.  
Findings: mitochondrial abnormalities, fatty liver (microvesicular fatty changes), hypoglycemia, vomiting, hepatomegaly, coma.

Avoid aspirin (**ASA**) in children, except in **KawASAKi** disease.  
Salicylates aren't a ray (**Reye**) of sun**SHINE** for kids:  
**S**teatosis of liver/hepatocytes  
**H**ypoglycemia/**H**epatomegaly  
**I**nfection (VZV, influenza)  
**N**ot awake (coma)  
**E**ncephalopathy

**Alcoholic liver disease**

<b>Hepatic steatosis</b>	Macrovesicular fatty change <b>A</b> that may be reversible with alcohol cessation.
<b>Alcoholic hepatitis</b>	Requires sustained, long-term consumption. Swollen and necrotic hepatocytes with neutrophilic infiltration. Mallory bodies <b>B</b> (intracytoplasmic eosinophilic inclusions of damaged keratin filaments).
<b>Alcoholic cirrhosis</b>	Final and usually irreversible form. Sclerosis around central vein (arrows in <b>C</b> ) may be seen in early disease. Regenerative nodules surrounded by fibrous bands in response to chronic liver injury → portal hypertension and end-stage liver disease.

**Nonalcoholic fatty liver disease**

Metabolic syndrome (insulin resistance); obesity → fatty infiltration of hepatocytes **A** → cellular “ballooning” and eventual necrosis. May cause cirrhosis and HCC. Independent of alcohol use.

**Autoimmune hepatitis**

Chronic inflammatory liver disease. More common in females. May be asymptomatic or present with fatigue, nausea, pruritus. May be associated with  $\oplus$  antinuclear, anti-smooth muscle and anti-liver/kidney microsomal-1 antibodies. Labs:  $\uparrow$  ALT and AST. Histology: portal and periportal lymphoplasmacytic infiltrate.

**Hepatic encephalopathy**

Cirrhosis → portosystemic shunts →  $\downarrow$   $\text{NH}_3$  metabolism → neuropsychiatric dysfunction. Reversible neuropsychiatric dysfunction ranging from disorientation/asterixis (mild) to difficult arousal or coma (severe).

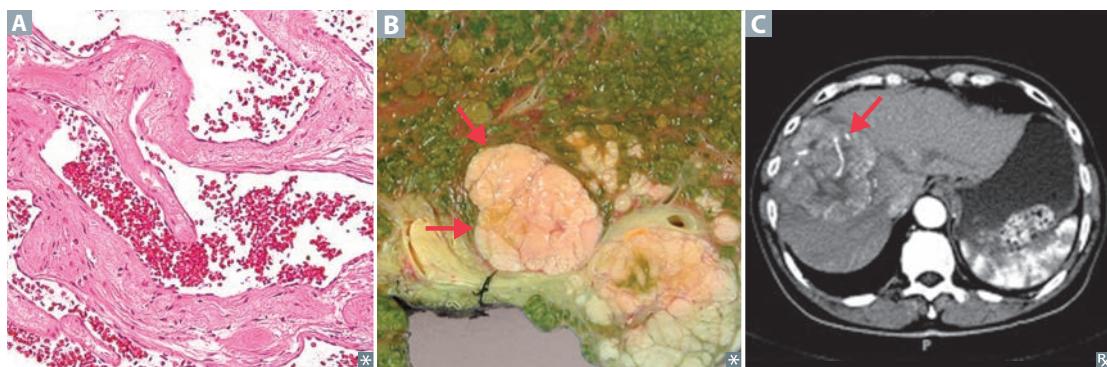
Triggers:

- $\uparrow$   $\text{NH}_3$  production and absorption (due to GI bleed, constipation, infection).
- $\downarrow$   $\text{NH}_3$  removal (due to renal failure, diuretics, bypassed hepatic blood flow post-TIPS).

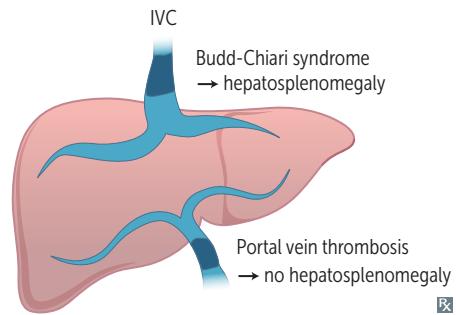
Treatment: lactulose ( $\uparrow \text{NH}_4^+$  generation) and rifaximin ( $\downarrow \text{NH}_3$ -producing gut bacteria).

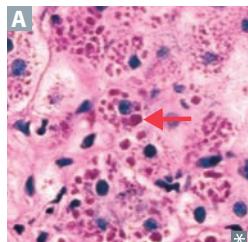
**Liver tumors**

<b>Hepatic hemangioma</b>	Also known as cavernous hemangioma. Most common benign liver tumor (venous malformation) <b>A</b> ; typically occurs at age 30–50 years. Biopsy contraindicated because of risk of hemorrhage.
<b>Focal nodular hyperplasia</b>	Second most common benign liver tumor; occurs predominantly in females aged 35–50 years. Hyperplastic reaction of hepatocytes to an aberrant dystrophic artery. Marked by central stellate scar. Usually asymptomatic and detected incidentally.
<b>Hepatic adenoma</b>	Rare, benign tumor, often related to oral contraceptive or anabolic steroid use; may regress spontaneously or rupture (abdominal pain and shock).
<b>Hepatocellular carcinoma</b>	Also known as hepatoma. Most common 1° malignant liver tumor in adults <b>B</b> . Associated with HBV (+/− cirrhosis) and all other causes of cirrhosis (including HCV, alcoholic and nonalcoholic fatty liver disease, autoimmune disease, hemochromatosis, Wilson disease, $\alpha_1$ -antitrypsin deficiency) and specific carcinogens (eg, aflatoxin from <i>Aspergillus</i> ). Findings: anorexia, jaundice, tender hepatomegaly. May lead to decompensation of previously stable cirrhosis (eg, ascites) and Budd-Chiari syndrome. Spreads hematogenously. Diagnosis: ↑ $\alpha$ -fetoprotein; ultrasound or contrast CT/MRI <b>C</b> ; biopsy if diagnosis is uncertain
<b>Hepatic angiosarcoma</b>	Rare, malignant tumor of endothelial origin; associated with exposure to arsenic, vinyl chloride.
<b>Metastases</b>	Most common malignant liver tumors overall; 1° sources include GI, breast, lung cancers. Metastases are rarely solitary.

**Budd-Chiari syndrome**

Hepatic venous outflow tract obstruction (eg, due to thrombosis, compression) with centrilobular congestion and necrosis → congestive liver disease (hepatomegaly, ascites, varices, abdominal pain, liver failure). Absence of JVD. Associated with hypercoagulable states, polycythemia vera, postpartum state, HCC. May cause nutmeg liver (mottled appearance).



**$\alpha_1$ -antitrypsin deficiency**

Misfolded gene product protein aggregates in hepatocellular ER → cirrhosis with PAS  $\oplus$  globules **A** in liver. Codominant trait. Often presents in young patients with liver damage and dyspnea without a history of tobacco smoking.

In lungs,  $\downarrow \alpha_1$ -antitrypsin  $\rightarrow$  uninhibited elastase in alveoli  $\rightarrow$   $\downarrow$  elastic tissue  $\rightarrow$  panacinar emphysema.

**Jaundice**

Abnormal yellowing of the skin and/or sclera **A** due to bilirubin deposition. Hyperbilirubinemia 2° to  $\uparrow$  production or  $\downarrow$  clearance (impaired hepatic uptake, conjugation, excretion).

**HOT Liver**—common causes of  $\uparrow$  bilirubin level:  
**H**emolysis  
**O**bstruction  
**T**umor  
**L**iver disease

**Conjugated (direct) hyperbilirubinemia**

Biliary tract obstruction: gallstones, cholangiocarcinoma, pancreatic or liver cancer, liver fluke.  
Biliary tract disease:  

- 1° sclerosing cholangitis
- 1° biliary cholangitis

Excretion defect: Dubin-Johnson syndrome, Rotor syndrome.

**Unconjugated (indirect) hyperbilirubinemia**

Hemolytic, physiologic (newborns), Crigler-Najjar, Gilbert syndrome.

**Mixed (direct and indirect) hyperbilirubinemia**

Hepatitis, cirrhosis.

**Physiologic neonatal jaundice**

At birth, lower activity of UDP-glucuronosyltransferase  $\rightarrow$  unconjugated hyperbilirubinemia  $\rightarrow$  jaundice/kernicterus (deposition of unconjugated, lipid-soluble bilirubin in the brain, particularly basal ganglia).  
Occurs after first 24 hours of life and usually resolves without treatment in 1–2 weeks.  
Treatment: phototherapy (non-UV) isomerizes unconjugated bilirubin to water-soluble form.

**Biliary atresia**

Most common reason for pediatric liver transplantation.  
Fibro-obliterative destruction of bile ducts  $\rightarrow$  cholestasis.  
Often presents as a newborn with persistent jaundice after 2 weeks of life, darkening urine, acholic stools, hepatomegaly.  
Labs:  $\uparrow$  direct bilirubin and GGT.

**Hereditary****hyperbilirubinemias****① Gilbert syndrome**

All autosomal recessive.

Mildly ↓ UDP-glucuronosyltransferase conjugation. Asymptomatic or mild jaundice usually with stress, illness, or fasting. ↑ unconjugated bilirubin without overt hemolysis. Relatively common, benign condition.

**② Crigler-Najjar syndrome, type I**

Absent UDP-glucuronosyltransferase. Presents early in life, but some patients may not have neurologic signs until later in life.

Findings: jaundice, kernicterus (bilirubin deposition in brain), ↑ unconjugated bilirubin. Treatment: plasmapheresis and phototherapy (does not conjugate UCB; but does ↑ polarity and ↑ water solubility to allow excretion). Liver transplant is curative.

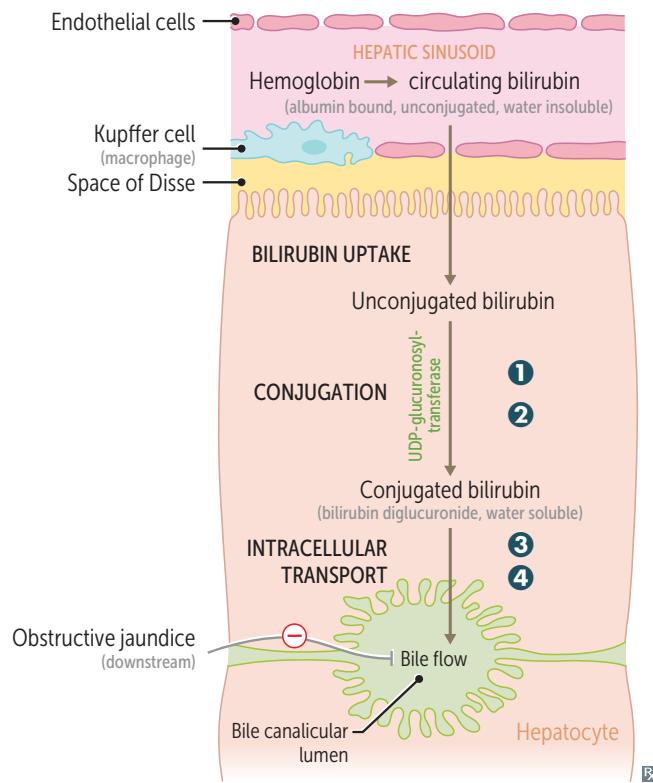
Type II is less severe and responds to phenobarbital, which ↑ liver enzyme synthesis.

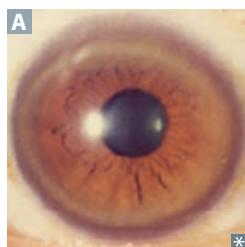
**③ Dubin-Johnson syndrome**

Conjugated hyperbilirubinemia due to defective liver excretion. Grossly black (Dark) liver due to impaired excretion of epinephrine metabolites. Benign.

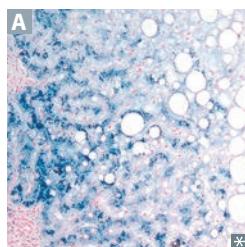
**④ Rotor syndrome**

Phenotypically similar to Dubin-Johnson, but milder in presentation without black (Regular) liver. Due to impaired hepatic storage of conjugated bilirubin.



**Wilson disease**

Also called hepatolenticular degeneration. Autosomal recessive mutations in hepatocyte copper-transporting ATPase (*ATP7B* gene; chromosome 13) → ↓ copper incorporation into apoceruloplasmin and excretion into bile → ↓ serum ceruloplasmin. Copper accumulates, especially in liver, brain (eg, basal ganglia), cornea, kidneys; ↑ urine copper. Presents before age 40 with liver disease (eg, hepatitis, acute liver failure, cirrhosis), neurologic disease (eg, dysarthria, dystonia, tremor, parkinsonism), psychiatric disease, Kayser-Fleischer rings (deposits in Descemet membrane of cornea) **A**, hemolytic anemia, renal disease (eg, Fanconi syndrome). Treatment: chelation with penicillamine or trientine, oral zinc. Liver transplant in acute liver failure related to Wilson disease.

**Hemochromatosis**

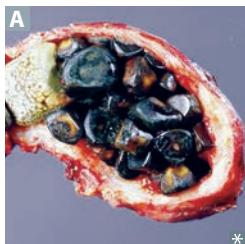
Autosomal recessive. Mutation in *HFE* gene, located on chromosome 6. Leads to abnormal **iron** sensing and ↑ intestinal absorption (↑ ferritin, ↑ iron, ↓ TIBC → ↑ transferrin saturation). Iron overload can also be 2° to chronic transfusion therapy (eg, β-thalassemia major). Iron accumulates, especially in liver, pancreas, skin, heart, pituitary, joints. Hemosiderin (iron) can be identified on liver MRI or biopsy with Prussian blue stain **A**. Presents after age 40 when total body iron > 20 g; iron loss through menstruation slows progression in females. Classic triad of cirrhosis, diabetes mellitus, skin pigmentation ("bronze diabetes"). Also causes restrictive cardiomyopathy (classic) or dilated cardiomyopathy (reversible), hypogonadism, arthropathy (calcium pyrophosphate deposition; especially metacarpophalangeal joints). HCC is common cause of death. Treatment: repeated phlebotomy, iron (**Fe**) chelation with deferasirox, deferoxamine, deferiprone.

**Biliary tract disease**

May present with pruritus, jaundice, dark urine, light-colored stool, hepatosplenomegaly. Typically with cholestatic pattern of LFTs (↑ conjugated bilirubin, ↑ cholesterol, ↑ ALP, ↑ GGT).

	PATHOLOGY	EPIDEMIOLOGY	ADDITIONAL FEATURES
<b>Primary sclerosing cholangitis</b>	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 males with ulcerative colitis.	Associated with ulcerative colitis. MPO-ANCA/ p-ANCA +. ↑ IgM. Can lead to 2° biliary cirrhosis. ↑ risk of cholangiocarcinoma and gallbladder cancer.
<b>Primary biliary cholangitis</b>	Autoimmune reaction → lymphocytic infiltrate +/- granulomas → destruction of lobular bile ducts.	Classically in middle-aged females.	Anti-mitochondrial antibody +, ↑ IgM. Associated with other autoimmune conditions (eg, Hashimoto thyroiditis, rheumatoid arthritis, celiac disease). Treatment: ursodiol.
<b>Secondary biliary cirrhosis</b>	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 acute cholangitis.

### Cholelithiasis and related pathologies



↑ cholesterol and/or bilirubin, ↓ bile salts, and gallbladder stasis all cause stones.

2 types of stones:

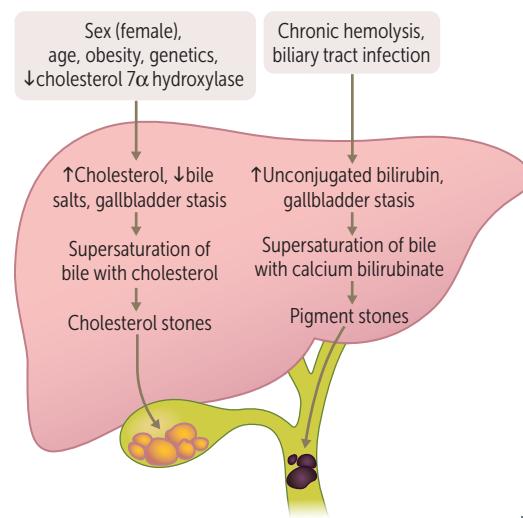
- Cholesterol stones (radiolucent with 10–20% opaque due to calcifications)—80% of stones. Associated with obesity, Crohn disease, advanced age, estrogen therapy, multiparity, rapid weight loss, medications (eg, fibrates).
- Pigment stones **A** (black = radiopaque,  $\text{Ca}^{2+}$  bilirubinate, hemolysis; brown = radiolucent, infection). Associated with Crohn disease, chronic hemolysis, alcoholic cirrhosis, advanced age, biliary infections, total parenteral nutrition (TPN).

Risk factors (**4 F's**):

1. **Female**
2. **Fat** (obesity)
3. **Fertile** (multiparity)
4. **Forty**

Most common complication is cholecystitis; can also cause acute pancreatitis, acute cholangitis.

Diagnose with ultrasound. Treat with elective cholecystectomy if symptomatic.



Rx

#### RELATED PATHOLOGIES

##### Biliary colic

#### CHARACTERISTICS

Associated with nausea/vomiting and dull RUQ pain. Neurohormonal activation (eg, by CCK after a fatty meal) triggers contraction of gallbladder, forcing stone into cystic duct. Labs are normal, ultrasound shows cholelithiasis.

##### Choledocholithiasis

Presence of gallstone(s) in common bile duct, often leading to elevated ALP, GGT, direct bilirubin, and/or AST/ALT.

##### Cholecystitis



Acute or chronic inflammation of gallbladder.

**Calculus cholecystitis**—most common type; due to gallstone impaction in the cystic duct resulting in inflammation and gallbladder wall thickening (arrows in **B**); can produce 2° infection.

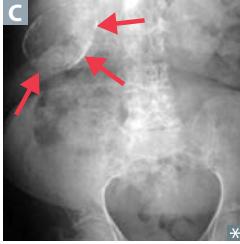
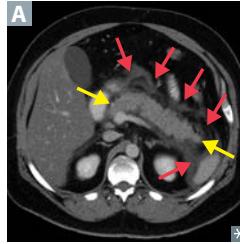
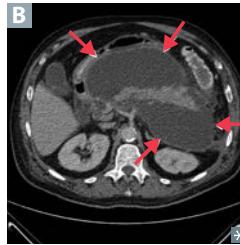
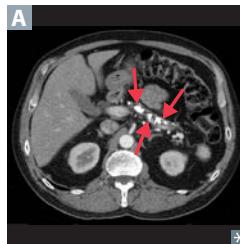
**Acalculous cholecystitis**—due to gallbladder stasis, hypoperfusion, or infection (CMV); seen in critically ill patients.

Murphy sign: inspiratory arrest on RUQ palpation due to pain. Pain may radiate to right shoulder (due to irritation of phrenic nerve). ↑ ALP if bile duct becomes involved (eg, acute cholangitis).

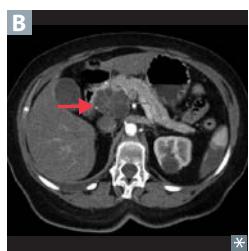
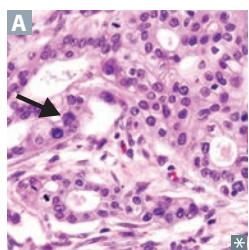
Diagnose with ultrasound or cholescintigraphy (HIDA scan). Failure to visualize gallbladder on HIDA scan suggests obstruction.

**Gallstone ileus**—fistula between gallbladder and GI tract → stone enters GI lumen → obstructs at ileocecal valve (narrowest point); can see air in biliary tree (pneumobilia). Rigler triad: radiographic findings of pneumobilia, small bowel obstruction, gallstone (usually in iliac fossa).

**Cholelithiasis and related pathologies (continued)**

RELATED PATHOLOGIES	CHARACTERISTICS
<b>Porcelain gallbladder</b>	Calcified gallbladder due to chronic cholecystitis; usually found incidentally on imaging <b>C</b> . Treatment: prophylactic cholecystectomy generally recommended due to ↑ risk of gallbladder cancer (mostly adenocarcinoma).
	
<b>Acute cholangitis</b>	Also called ascending cholangitis. Infection of biliary tree usually due to obstruction that leads to stasis/bacterial overgrowth. Charcot triad of cholangitis includes jaundice, fever, RUQ pain. Reynolds pentad is Charcot triad plus altered mental status and shock (hypotension).
<b>Cholangiocarcinoma</b>	Malignant tumor of bile duct epithelium. Risk factors include 1° sclerosing cholangitis, liver fluke infections. Usually presents late with fatigue, weight loss, abdominal pain, jaundice. Imaging may show biliary tract obstruction. Histology: infiltrating neoplastic glands associated with desmoplastic stroma.
 	Autodigestion of pancreas by pancreatic enzymes ( <b>A</b> ) shows pancreas [yellow arrows] surrounded by edema [red arrows]. Causes: <b>Idiopathic, Gallstones, Ethanol, Trauma, Steroids, Mumps, Autoimmune disease, Scorpion sting, Hypercalcemia/Hypertriglyceridemia (&gt; 1000 mg/dL), ERCP, Drugs</b> (eg, sulfa drugs, NRTIs, protease inhibitors). <b>I GET SMASHED.</b> 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>B</b> (lined by granulation tissue, not epithelium), abscess, necrosis, hemorrhage, infection, organ failure (ALI/ARDS, shock, renal failure), hypocalcemia (precipitation of Ca <sup>2+</sup> soaps).
<b>Chronic pancreatitis</b>	Chronic inflammation, atrophy, calcification of the pancreas <b>A</b> . Major risk factors include alcohol use disorder and genetic predisposition (eg, cystic fibrosis); can be idiopathic. Complications include pancreatic insufficiency and pseudocysts. Pancreatic insufficiency (typically when <10% pancreatic function) may manifest with steatorrhea, fat-soluble vitamin deficiency, diabetes mellitus. Amylase and lipase may or may not be elevated (almost always elevated in acute pancreatitis).
	

### Pancreatic adenocarcinoma



Very aggressive tumor arising from pancreatic ducts (disorganized glandular structure with cellular infiltration **A**); often metastatic at presentation, with average survival ~ 1 year after diagnosis. Tumors more common in pancreatic head **B** (lead to obstructive jaundice). Associated with CA 19-9 tumor marker (also CEA, less specific).

Risk factors:

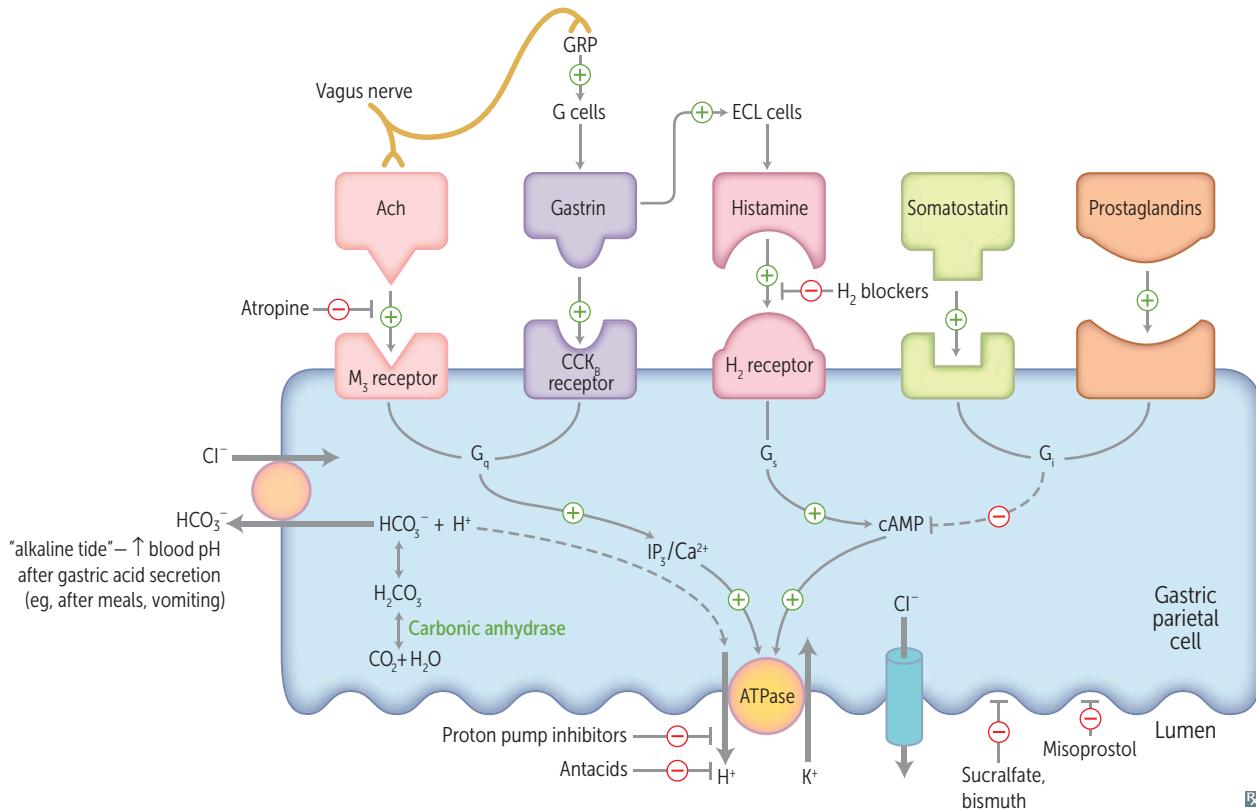
- Tobacco smoking
- Chronic pancreatitis (especially > 20 years)
- Diabetes
- Age > 50 years

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)

### ▶ GASTROINTESTINAL—PHARMACOLOGY

#### Acid suppression therapy



<b>H<sub>2</sub>-blockers</b>	Cimetidine, famotidine, nizatidine.	Take H <sub>2</sub> blockers before you <b>dine</b> . Think “ <b>table for 2</b> ” to remember H <sub>2</sub> .
MECHANISM	Reversible block of histamine H <sub>2</sub> -receptors → ↓ H <sup>+</sup> 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. Cimetidine ↓ renal excretion of creatinine. Other H <sub>2</sub> blockers are relatively free of these effects.	

<b>Proton pump inhibitors</b>	Omeprazole, lansoprazole, esomeprazole, pantoprazole, dexlansoprazole.	
MECHANISM	Irreversibly inhibit H <sup>+</sup> /K <sup>+</sup> ATPase in stomach parietal cells.	
CLINICAL USE	Peptic ulcer, gastritis, esophageal reflux, Zollinger-Ellison syndrome, component of therapy for <i>H pylori</i> , stress ulcer prophylaxis.	
ADVERSE EFFECTS	↑ risk of <i>C difficile</i> infection, pneumonia, acute interstitial nephritis. Vitamin B <sub>12</sub> malabsorption; ↓ serum Mg <sup>2+</sup> and ↓ Ca <sup>2+</sup> absorption (potentially leading to increased fracture risk in elderly).	

<b>Antacids</b>	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:	
<b>Aluminum hydroxide</b>	Constipation, Hypophosphatemia, Osteodystrophy, Proximal muscle weakness, Seizures	Aluminum amount of feces <b>CHOPS</b>
<b>Calcium carbonate</b>	Hypercalcemia (milk-alkali syndrome), rebound acid ↑	Can chelate and ↓ effectiveness of other drugs (eg, tetracycline)
<b>Magnesium hydroxide</b>	Diarrhea, hyporeflexia, hypotension, cardiac arrest	Mg <sup>2+</sup> = Must go 2 the bathroom

<b>Bismuth, sucralfate</b>		
MECHANISM	Bind to ulcer base, providing physical protection and allowing HCO <sub>3</sub> <sup>-</sup> secretion to reestablish pH gradient in the mucous layer. Sucralfate requires acidic environment, not given with PPIs/H <sub>2</sub> blockers.	
CLINICAL USE	↑ ulcer healing, travelers' diarrhea (bismuth). Bismuth also used in quadruple therapy for <i>H pylori</i> gastritis.	

<b>Misoprostol</b>		
MECHANISM	PGE <sub>1</sub> analog. ↑ production and secretion of gastric mucous barrier, ↓ acid production.	
CLINICAL USE	Prevention of NSAID-induced peptic ulcers (NSAIDs block PGE <sub>1</sub> production). Also used off-label for induction of labor (ripen cervix).	
ADVERSE EFFECTS	Diarrhea. Contraindicated in patients 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.

**Sulfasalazine**

MECHANISM	A combination of sulfapyridine (antibacterial) and 5-aminosalicylic acid (anti-inflammatory). Activated by colonic bacteria.
CLINICAL USE	Ulcerative colitis, Crohn disease (colitis component).
ADVERSE EFFECTS	Malaise, nausea, sulfonamide toxicity, reversible oligospermia.

**Loperamide**

MECHANISM	Agonist at $\mu$ -opioid receptors; slows gut motility. Poor CNS penetration (low addictive potential).
CLINICAL USE	Diarrhea.
ADVERSE EFFECTS	Constipation, nausea.

**Ondansetron**

MECHANISM	5-HT <sub>3</sub> antagonist. Acts peripherally (↓ vagal stimulation) and centrally. Potent antiemetic.
CLINICAL USE	Control vomiting postoperatively and in patients undergoing cancer chemotherapy.
ADVERSE EFFECTS	Headache, constipation, QT interval prolongation, serotonin syndrome.

**Aprepitant**

MECHANISM	Substance P antagonist. Blocks NK <sub>1</sub> (neurokinin-1) receptors in brain.
CLINICAL USE	Antiemetic for chemotherapy-induced nausea and vomiting.

**Metoclopramide**

MECHANISM	D <sub>2</sub> receptor antagonist. ↑ resting tone, contractility, LES tone, motility, promotes gastric emptying. Does not influence colon transport time.
CLINICAL USE	Diabetic and postoperative gastroparesis, antiemetic, persistent GERD.
ADVERSE EFFECTS	↑ parkinsonian effects, tardive dyskinesia. Restlessness, drowsiness, fatigue, depression, diarrhea. Drug interaction with digoxin and diabetic agents. Contraindicated in patients with small bowel obstruction, Parkinson disease (due to D <sub>2</sub> -receptor blockade), ↓ seizure threshold.

**Orlistat**

MECHANISM	Inhibits gastric and pancreatic lipase → ↓ breakdown and absorption of dietary fats. Taken with fat-containing meals.
CLINICAL USE	Weight loss.
ADVERSE EFFECTS	Abdominal pain, flatulence, bowel urgency/frequent bowel movements, steatorrhea; ↓ absorption of fat-soluble vitamins.

**Laxatives**

Indicated for constipation or patients on opiates requiring a bowel regimen.

	EXAMPLES	MECHANISM	ADVERSE EFFECTS
<b>Bulk-forming laxatives</b>	Psyllium, methylcellulose	Soluble fibers draw water into gut lumen, forming a viscous liquid that promotes peristalsis	Bloating
<b>Osmotic laxatives</b>	Magnesium hydroxide, magnesium citrate, polyethylene glycol, lactulose	Provides osmotic load to draw water into GI lumen Lactulose also treats hepatic encephalopathy: gut flora degrade lactulose into metabolites (lactic acid, acetic acid) that promote nitrogen excretion as $\text{NH}_4^+$	Diarrhea, dehydration; may be misused by patients with bulimia nervosa; overuse may cause metabolic alkalosis
<b>Stimulants</b>	Senna, bisacodyl	Enteric nerve stimulation → colonic contraction	Diarrhea, melena; overuse may cause metabolic alkalosis
<b>Emollients</b>	Docusate	Promotes incorporation of water and fat into stool	Diarrhea; overuse may cause metabolic alkalosis

## ► NOTES

# Hematology and Oncology

*“You’re always somebody’s type! (blood type, that is)”*

—BloodLink

*“The best blood will at some time get into a fool or a mosquito.”*

—Austin O’Malley

*“A life touched by cancer is not a life destroyed by cancer.”*

—Drew Boswell, *Climbing the Cancer Mountain*

*“Without hair, a queen is still a queen.”*

—Prajakta Mhadnak

*“Blood can circulate forever if you keep donating it.”*

—Anonymous

When studying hematology, pay close attention to the many cross connections to immunology. Make sure you master the different types of anemias. Be comfortable interpreting blood smears. When reviewing oncologic drugs, focus on mechanisms and adverse effects rather than details of clinical uses, which may be lower yield.

Please note that solid tumors are covered in their respective organ system chapters.

► Embryology	414
► Anatomy	416
► Physiology	420
► Pathology	424
► Pharmacology	445

## ► HEMATOLOGY AND ONCOLOGY—EMBRYOLOGY

**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:  $\zeta$  and  $\epsilon$ .

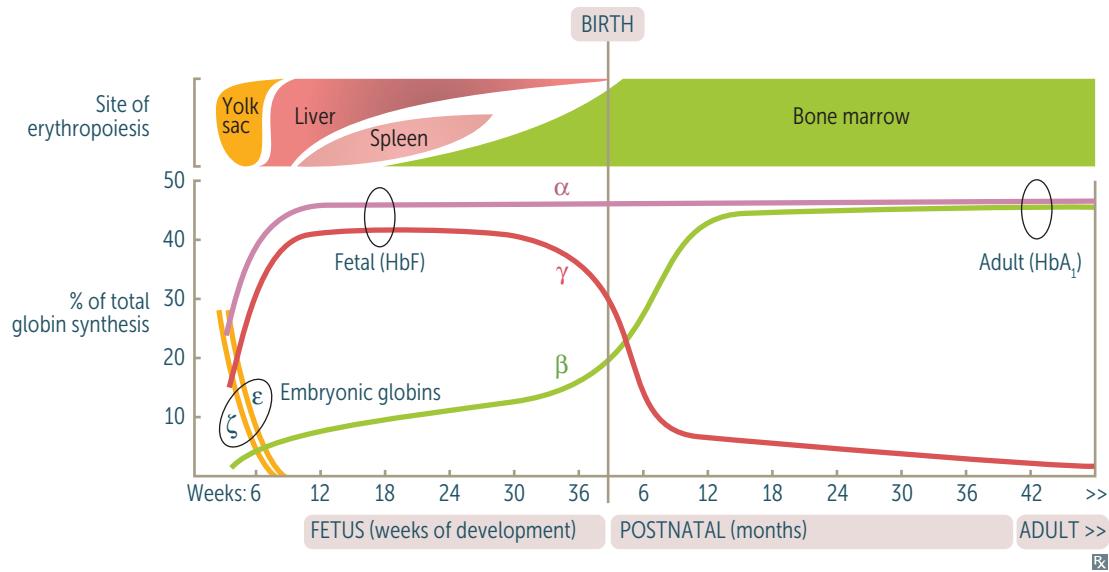
Fetal hemoglobin ( $\text{HbF}$ ) =  $\alpha_2\gamma_2$ .

Adult hemoglobin ( $\text{HbA}_1$ ) =  $\alpha_2\beta_2$ .

$\text{HbF}$  has higher affinity for  $\text{O}_2$  due to less avid binding of 2,3-BPG, allowing  $\text{HbF}$  to extract  $\text{O}_2$  from maternal hemoglobin ( $\text{HbA}_1$  and  $\text{HbA}_2$ ) across the placenta.  $\text{HbA}_2$  ( $\alpha_2\delta_2$ ) is a form of adult hemoglobin present in small amounts.

From fetal to adult hemoglobin:

Alpha always; gamma goes, becomes beta.



**Blood groups**

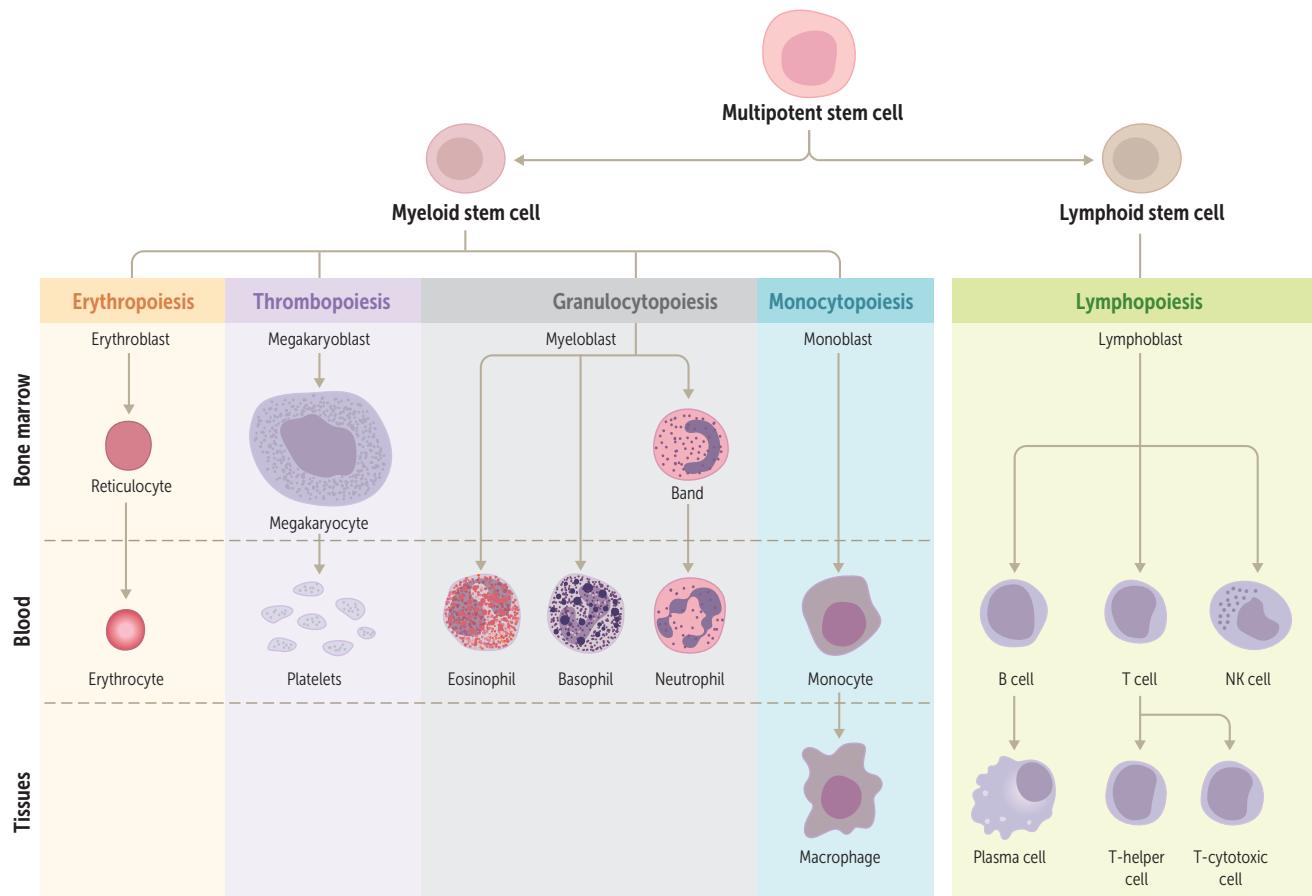
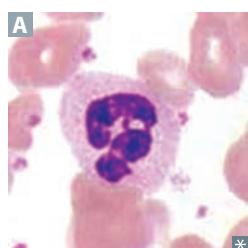
	ABO classification				Rh classification	
	A	B	AB	O	Rh+	Rh-
RBC type						
Group antigens on RBC surface	A 	B 	A & B 	NONE	Rh (D) 	NONE
Antibodies in plasma	Anti-B 	Anti-A 	NONE	Anti-A  Anti-B  IgG (predominantly), IgM	NONE	Anti-D  IgG
Clinical relevance						
Compatible RBC types to receive	A, O	B, O	AB, A, B, O	O	Rh+, Rh-	Rh-
Compatible RBC types to donate to	A, AB	B, AB	AB	A, B, AB, O	Rh+	Rh+, Rh-

Rx

**Hemolytic disease of the fetus and newborn** Also known as erythroblastosis fetalis.

	Rh hemolytic disease	ABO hemolytic disease
INTERACTION	Rh- pregnant patient; Rh+ fetus.	Type O pregnant patient; type A or B fetus.
MECHANISM	First pregnancy: patient exposed to fetal blood (often during delivery) → formation of maternal anti-D IgG. Subsequent pregnancies: anti-D IgG crosses placenta → attacks fetal and newborn RBCs → hemolysis.	Preexisting pregnant patient anti-A and/or anti-B IgG antibodies cross the placenta → attack fetal and newborn RBCs → hemolysis.
PRESENTATION	Hydrops fetalis, jaundice shortly after birth, kernicterus.	Mild jaundice in the neonate within 24 hours of birth. Unlike Rh hemolytic disease, can occur in firstborn babies and is usually less severe.
TREATMENT/PREVENTION	Prevent by administration of anti-D IgG to Rh- pregnant patients during third trimester and early postpartum period (if fetus Rh+). Prevents maternal anti-D IgG production.	Treatment: phototherapy or exchange transfusion.

## ► HEMATOLOGY AND ONCOLOGY—ANATOMY

**Hematopoiesis****Neutrophils**

Acute inflammatory response cells. Phagocytic.

Multilobed nucleus **A**. Specific granules contain leukocyte alkaline phosphatase (LAP), collagenase, lysozyme, and lactoferrin. Azurophilic granules (lysosomes) contain proteinases, acid phosphatase, myeloperoxidase, and  $\beta$ -glucuronidase.

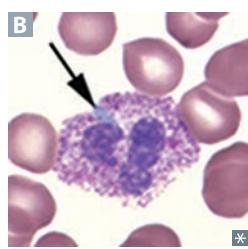
Inflammatory states (eg, bacterial infection) cause neutrophilia and changes in neutrophil morphology, such as left shift, toxic granulation (dark blue, coarse granules), Döhle bodies (light blue, peripheral inclusions, arrow in **B**), and cytoplasmic vacuoles.

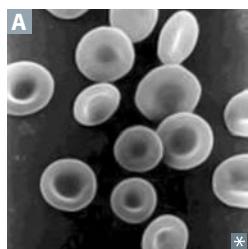
Neutrophil chemotactic agents: C5a, IL-8,

$LTB_4$ , 5-HETE (leukotriene precursor), kallikrein, platelet-activating factor, N-formylmethionine (bacterial proteins). Hypersegmented neutrophils (nucleus has 6+ lobes) are seen in vitamin  $B_{12}$ /folate deficiency.

**Left shift**—↑ neutrophil precursors (eg, band cells, metamyelocytes) in peripheral blood. Reflects states of ↑ myeloid proliferation (eg, inflammation, CML).

**Leukoerythroblastic reaction**—left shift accompanied by immature RBCs. Suggests bone marrow infiltration (eg, myelofibrosis, metastasis).



**Erythrocytes**

Carry O<sub>2</sub> to tissues and CO<sub>2</sub> to lungs. Anucleate and lack organelles; biconcave **A**, with large surface area-to-volume ratio for rapid gas exchange. Life span of ~120 days in healthy adults; 60-90 days in neonates. Source of energy is glucose (90% used in glycolysis, 10% used in HMP shunt). Membranes contain Cl<sup>-</sup>/HCO<sub>3</sub><sup>-</sup> antiporter, which allow RBCs to export HCO<sub>3</sub><sup>-</sup> and transport CO<sub>2</sub> from the periphery to the lungs for elimination.

*Erythro* = red; *cyte* = cell.

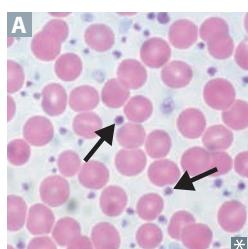
Erythrocytosis = polycythemia = ↑ Hct.

Anisocytosis = varying sizes.

Poikilocytosis = varying shapes.

Reticulocyte = immature RBC; reflects erythroid proliferation.

Bluish color (polychromasia) on Wright-Giemsa stain of reticulocytes represents residual ribosomal RNA.

**Thrombocytes (platelets)**

Involved in 1° hemostasis. Anucleate, small cytoplasmic fragments **A** derived from megakaryocytes. Life span of 8–10 days (platelets). When activated by endothelial injury, aggregate with other platelets and interact with fibrinogen to form platelet plug. Contain dense granules (Ca<sup>2+</sup>, ADP, Serotonin, Histamine; CASH) and α granules (vWF, fibrinogen, fibronectin, platelet factor 4). Approximately 1/3 of platelet pool is stored in the spleen.

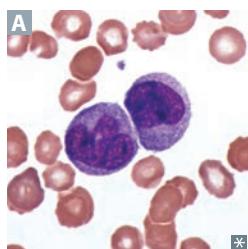
Thrombocytopenia or ↓ platelet function results in petechiae.

vWF receptor: GpIb.

Fibrinogen receptor: GpIIb/IIIa.

Thrombopoietin stimulates megakaryocyte proliferation.

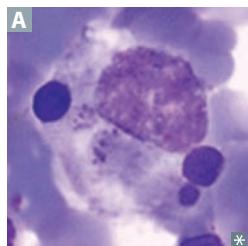
Alpha granules contain vWF, fibrinogen, fibronectin, platelet factor four.

**Monocytes**

Found in blood, differentiate into macrophages in tissues.

Large, kidney-shaped nucleus **A**. Extensive “frosted glass” cytoplasm.

*Mono* = one (nucleus); *cyte* = cell.

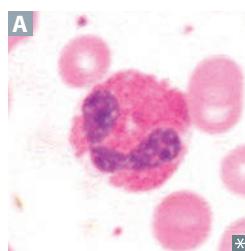
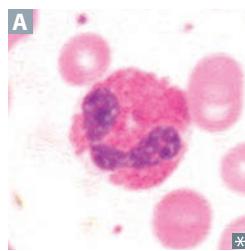
**Macrophages**

Phagocytose bacteria, cellular debris, and senescent RBCs. Long life in tissues. Differentiate from circulating blood monocytes **A**. Activated by γ-interferon. Can function as antigen-presenting cell via MHC II. Important cellular component of granulomas (eg, TB, sarcoidosis), where they may fuse to form giant cells.

*Macro* = large; *phage* = eater.

Macrophage naming varies by specific tissue type (eg, Kupffer cells in liver, histiocytes in connective tissue, Langerhans cells in skin, osteoclasts in bone, microglial cells in brain).

Lipid A from bacterial LPS binds CD14 on macrophages to initiate septic shock.

**Eosinophils**

Defend against helminthic infections (major basic protein). Bilobate nucleus. Packed with large eosinophilic granules of uniform size **A**. Highly phagocytic for antigen-antibody complexes.

Produce histaminase, major basic protein (MBP), a helminthotoxin, eosinophil peroxidase, eosinophil cationic protein, and eosinophil-derived neurotoxin.

*Eosin* = pink dye; *philic* = loving.

Causes of eosinophilia (**PACMAN Eats**):

Parasites

Asthma

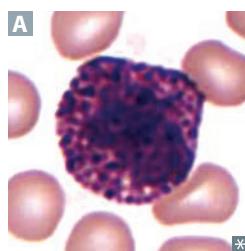
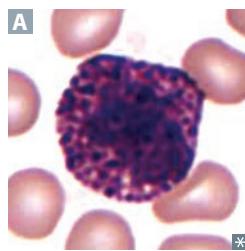
Chronic adrenal insufficiency

Myeloproliferative disorders

Allergic processes

Neoplasia (eg, Hodgkin lymphoma)

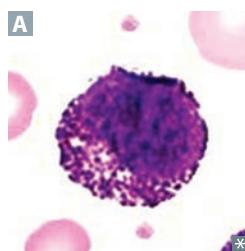
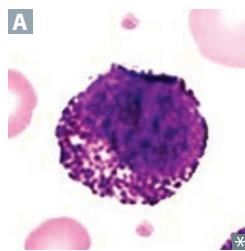
Eosinophilic granulomatosis with polyangiitis

**Basophils**

Mediate allergic reaction. Densely basophilic granules **A** contain heparin (anticoagulant) and histamine (vasodilator). Leukotrienes synthesized and released on demand.

**Basophilic**—stains readily with **basic** stains.

Basophilia is uncommon, but can be a sign of myeloproliferative disorders, particularly CML.

**Mast cells**

Mediate local tissue allergic reactions. Contain basophilic granules **A**. Originate from same precursor as basophils but are not the same cell type. Can bind the Fc portion of IgE to membrane. Activated by tissue trauma, C3a and C5a, surface IgE cross-linking by antigen (IgE receptor aggregation) → degranulation → release of histamine, heparin, tryptase, and eosinophil chemotactic factors.

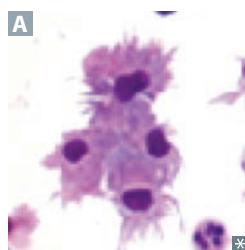
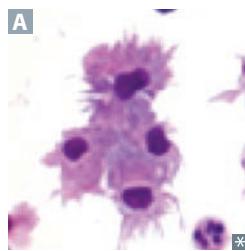
Involved in type I hypersensitivity reactions.

Cromolyn sodium prevents mast cell degranulation (used for asthma prophylaxis).

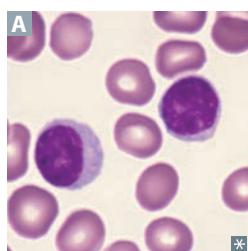
Vancomycin, opioids, and radiocontrast dye can elicit IgE-independent mast cell degranulation.

**Mastocytosis**—rare; proliferation of mast cells in skin and/or extracutaneous organs. Associated with c-KIT mutations and ↑ serum tryptase.

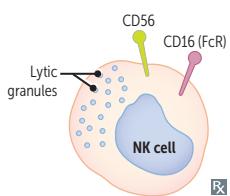
↑ histamine → flushing, pruritus, hypotension, abdominal pain, diarrhea, peptic ulcer disease.

**Dendritic cells**

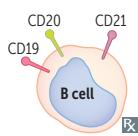
Highly phagocytic antigen-presenting cells (APCs) **A**. Function as link between innate and adaptive immune systems. Express MHC class II and Fc receptors on surface. Can present exogenous antigens on MHC class I (cross-presentation).

**Lymphocytes**

Refer to B cells, T cells, and NK cells. B cells and T cells mediate adaptive immunity. NK cells are part of the innate immune response. Round, densely staining nucleus with small amount of pale cytoplasm **A**.

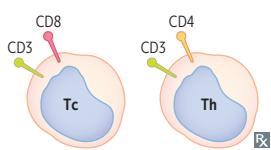
**Natural killer cells**

Important in innate immunity, especially against intracellular pathogens. Larger than B and T cells, with distinctive cytoplasmic lytic granules (containing perforin and granzymes) that, when released, act on target cells to induce apoptosis. Distinguish between healthy and infected cells by identifying cell surface proteins (induced by stress, malignant transformation, or microbial infections).

**B cells**

Mediate humoral immune response. Originate from stem cells in bone marrow and matures in marrow. Migrate to peripheral lymphoid tissue (follicles of lymph nodes, white pulp of spleen, unencapsulated lymphoid tissue). When antigen is encountered, B cells differentiate into plasma cells (which produce antibodies) and memory cells. Can function as an APC.

**B** = bone marrow.

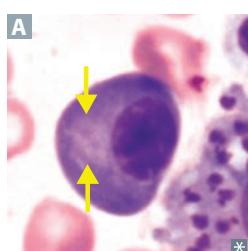
**T cells**

Mediate cellular immune response. Originate from stem cells in the bone marrow, but mature in the thymus. Differentiate into cytotoxic T cells (express CD8, recognize MHC I), helper T cells (express CD4, recognize MHC II), and regulatory T cells. CD28 (costimulatory signal) necessary for T-cell activation. Most circulating lymphocytes are T cells (80%).

**T** = thymus.

CD4+ helper T cells are the primary target of HIV.

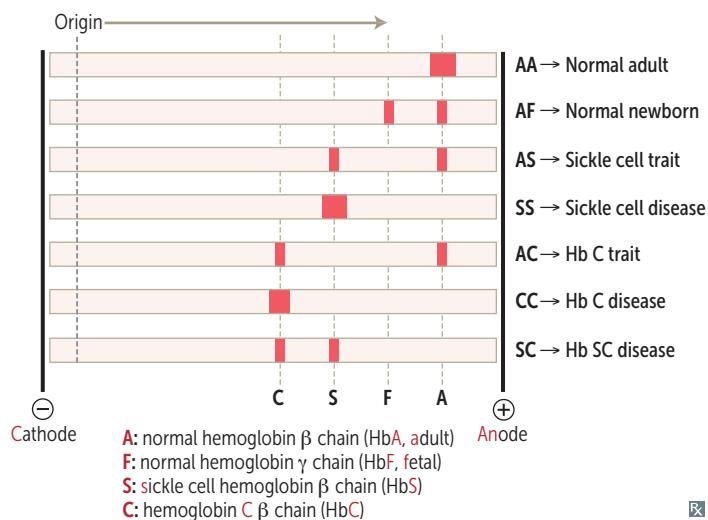
**Rule of 8:** MHC II × CD4 = 8;  
MHC I × CD8 = 8.

**Plasma cells**

Produce large amounts of antibody specific to a particular antigen. “Clock-face” chromatin distribution and eccentric nucleus, abundant RER, and well-developed Golgi apparatus (arrows in **A**). Found in bone marrow and normally do not circulate in peripheral blood.

Multiple myeloma is a plasma cell dyscrasia.

## ► HEMATOLOGY AND ONCOLOGY—PHYSIOLOGY

**Hemoglobin electrophoresis**

On a gel, hemoglobin migrates from the negatively charged cathode to the positively charged anode. HbA migrates the farthest, followed by HbF, HbS, and HbC. This is because the missense mutations in HbS and HbC replace glutamic acid  $\ominus$  with valine (neutral) and lysine  $\oplus$ , respectively, making HbC and HbS more positively charged than HbA.

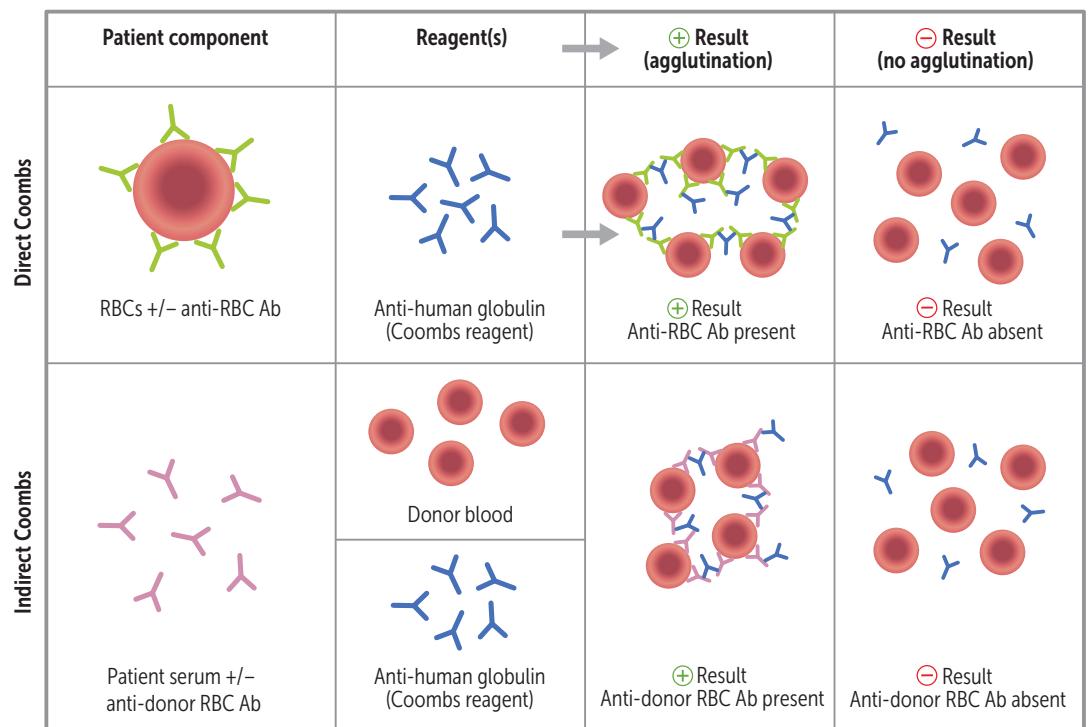
**A Fat Santa Claus can't (cathode → anode) go far.**

**Coombs test**

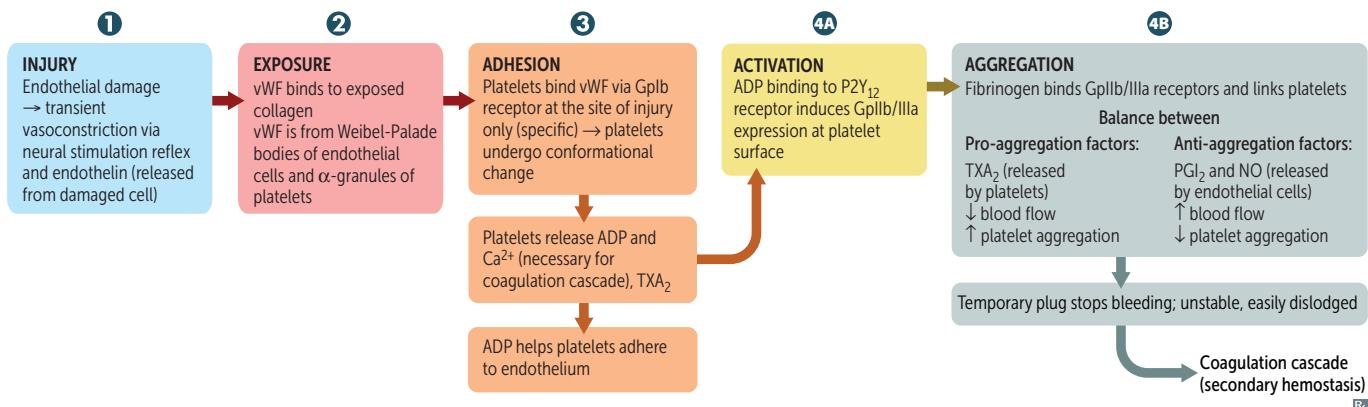
Also called antiglobulin test. Detects the presence of antibodies against circulating RBCs.

**Direct Coombs test**—anti-Ig antibody (Coombs reagent) added to patient's RBCs. RBCs agglutinate if RBCs are coated with Ig. Used for AIHA diagnosis.

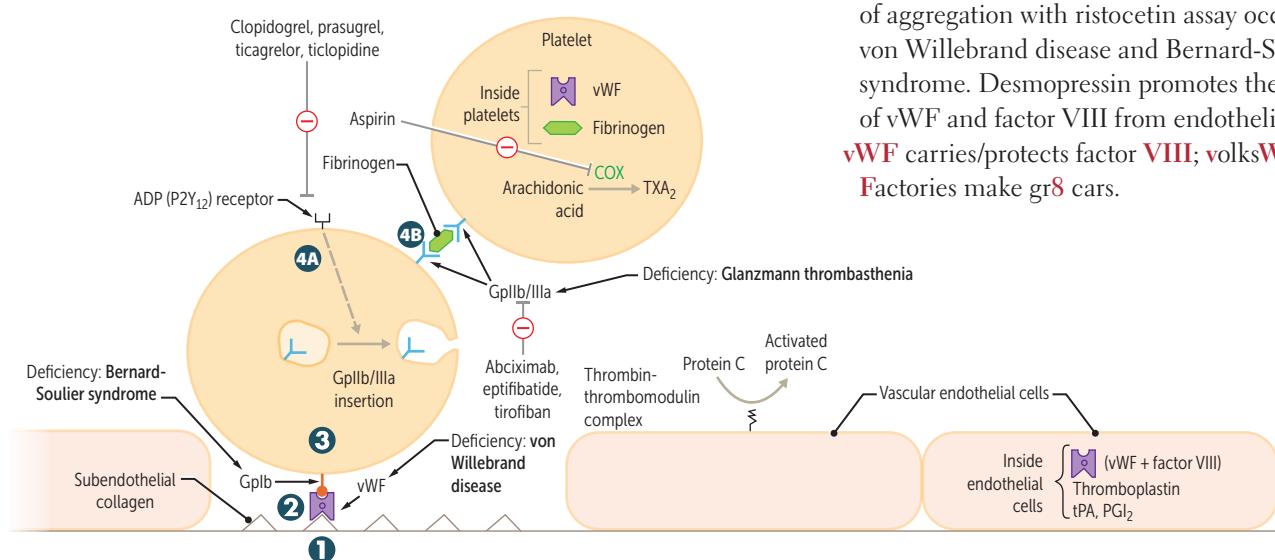
**Indirect Coombs test**—normal RBCs added to patient's serum. If serum has anti-RBC surface Ig, RBCs agglutinate when Coombs reagent is added. Used for pretransfusion testing.



### Platelet plug formation (primary hemostasis)

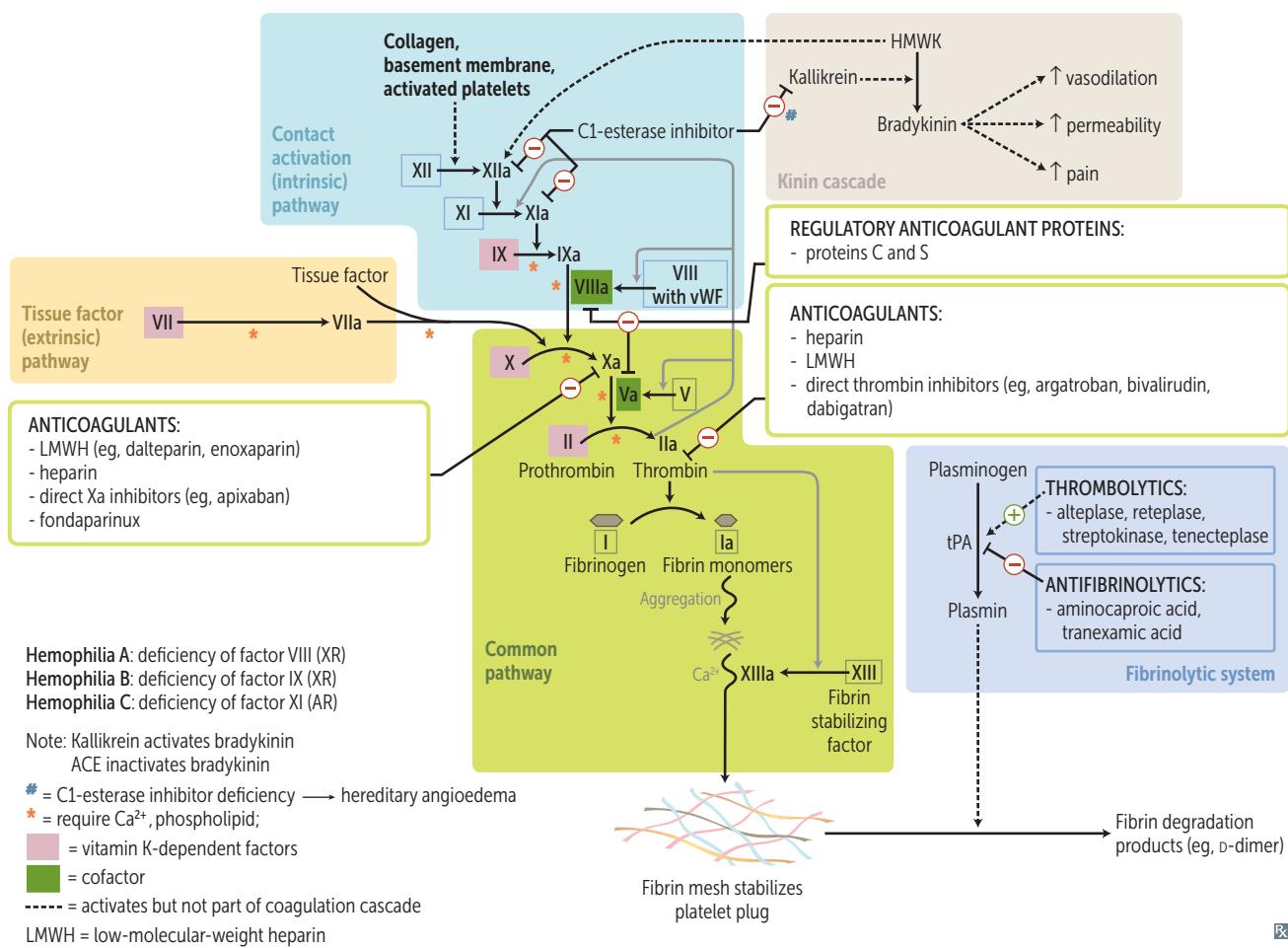


### Thrombogenesis



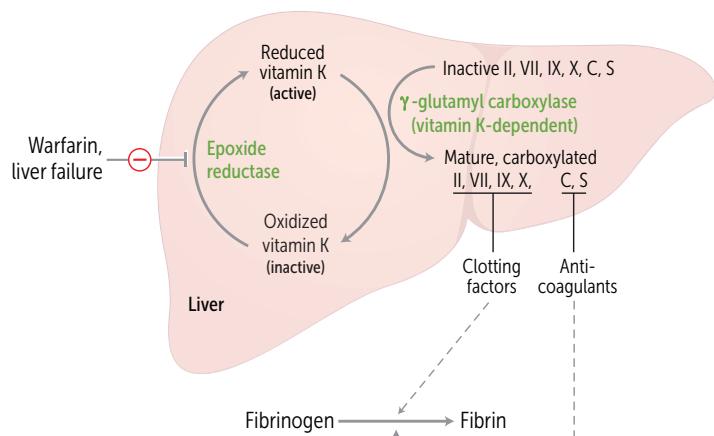
Formation of insoluble fibrin mesh.  
Aspirin irreversibly inhibits cyclooxygenase, thereby inhibiting TXA<sub>2</sub> synthesis.  
Clopidogrel, prasugrel, ticagrelor, and ticlopidine inhibit ADP-induced expression of GpIIb/IIIa by blocking P2Y<sub>12</sub> receptor.  
Abciximab, eptifibatide, and tirofiban inhibit GpIIb/IIIa directly.  
Ristocetin activates vWF to bind GpIb. Failure of aggregation with ristocetin assay occurs in von Willebrand disease and Bernard-Soulier syndrome. Desmopressin promotes the release of vWF and factor VIII from endothelial cells.  
**vWF carries/protects factor VIII; volksWagen**  
Factories make gr8 cars.

### Coagulation and kinin pathways

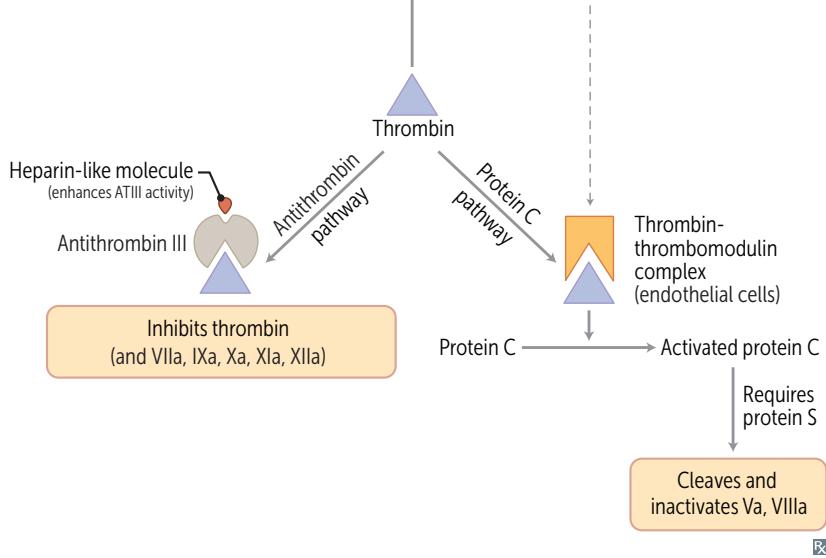


## Vitamin K-dependent coagulation

### Procoagulation



### Anticoagulation



**Vitamin K deficiency** → ↓ synthesis of factors II, VII, IX, X, protein C, protein S.

Warfarin inhibits vitamin K epoxide reductase.

Vitamin K administration can potentially reverse inhibitory effect of warfarin on clotting factor synthesis (delayed). FFP or PCC administration reverses action of warfarin immediately and can be given with vitamin K in cases of severe bleeding.

Neonates lack enteric bacteria, which produce vitamin K. Early administration of vitamin K overcomes neonatal deficiency/coagulopathy.

Factor VII (seven)—shortest half-life.

Factor II (two)—longest (too long) half-life.

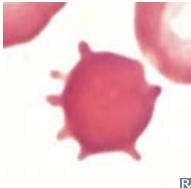
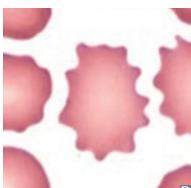
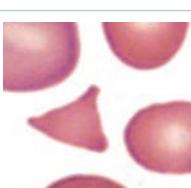
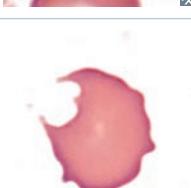
Antithrombin inhibits thrombin (factor IIa) and factors VIIa, IXa, Xa, XIa, XIIa.

Heparin enhances the activity of antithrombin. Principal targets of antithrombin: thrombin and factor Xa.

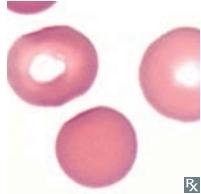
Factor V Leiden mutation produces a factor V resistant to inhibition by activated protein C. tPA is used clinically as a thrombolytic.

## ► HEMATOLOGY AND ONCOLOGY—PATHOLOGY

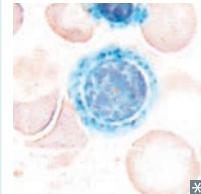
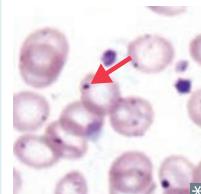
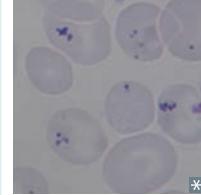
**RBC morphology**

TYPE	EXAMPLE	ASSOCIATED PATHOLOGY	NOTES
<b>Acanthocytes ("spur cells")</b>		Liver disease, abetalipoproteinemia, vitamin E deficiency	Projections of varying size at irregular intervals (acanthocytes are asymmetric).
<b>Echinocytes ("burr cells")</b>		Liver disease, ESRD, pyruvate kinase deficiency	Smaller and more uniform projections than acanthocytes (echinocytes are even).
<b>Dacrocytes ("teardrop cells")</b>		Bone marrow infiltration (eg, myelofibrosis)	RBC "sheds a tear" because it's mechanically squeezed out of its home in the bone marrow
<b>Schistocytes (eg, "helmet" cells)</b>		MAHAs (eg, DIC, TTP/HUS, HELLP syndrome), mechanical hemolysis (eg, heart valve prosthesis)	Fragmented RBCs
<b>Degmacytes ("bite cells")</b>		G6PD deficiency	Due to removal of Heinz bodies by splenic macrophages (they "deg" them out of/bite them off of RBCs)
<b>Elliptocytes</b>		Hereditary elliptocytosis	Caused by mutation in genes encoding RBC membrane proteins (eg, spectrin)

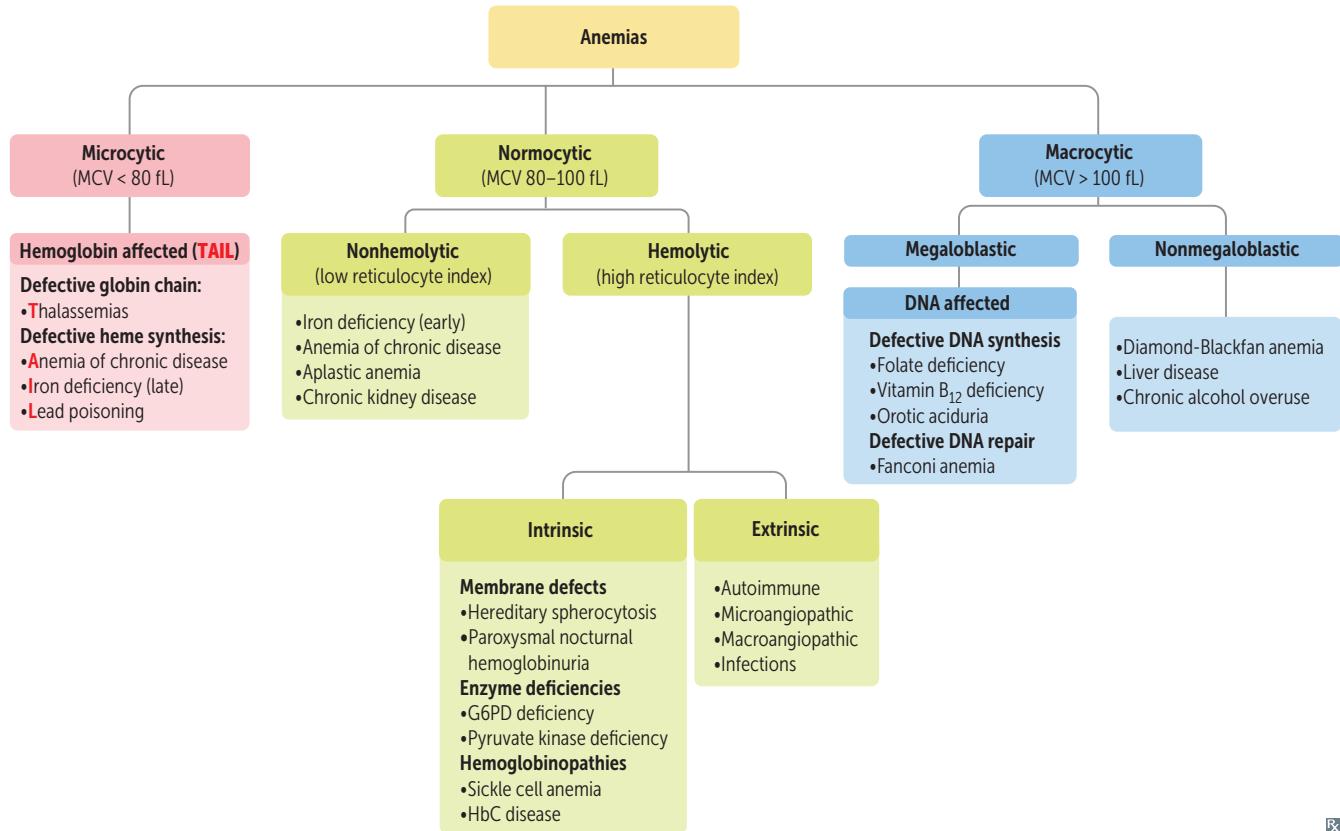
**RBC morphology (continued)**

TYPE	EXAMPLE	ASSOCIATED PATHOLOGY	NOTES
Spherocytes	 Rx	Hereditary spherocytosis, autoimmune hemolytic anemia	Small, spherical cells without central pallor ↓ surface area-to-volume ratio
Macro-ovalocytes	 Rx	Megaloblastic anemia (also hypersegmented PMNs)	
Target cells	 Rx	HbC disease, Asplenia, Liver disease, Thalassemia	“HALT,” said the hunter to his target ↑ surface area-to-volume ratio
Sickle cells	 *	Sickle cell anemia	Sickling occurs with low O <sub>2</sub> conditions (eg, high altitude, acidosis)

**RBC inclusions****Bone marrow**

TYPE	EXAMPLE	ASSOCIATED PATHOLOGY	NOTES
<b>Iron granules</b>		Sideroblastic anemias (eg, lead poisoning, myelodysplastic syndromes, chronic alcohol overuse)	Perinuclear mitochondria with excess iron (forming ring in ringed sideroblasts) Require Prussian blue stain to be visualized
<b>Peripheral smear</b>			
<b>Howell-Jolly bodies</b>		Functional hyposplenia (eg, sickle cell disease), asplenia	Basophilic nuclear remnants (do not contain iron) Usually removed by splenic macrophages
<b>Basophilic stippling</b>		Sideroblastic anemias, thalassemias	Basophilic ribosomal precipitates (do not contain iron)
<b>Pappenheimer bodies</b>		Sideroblastic anemia	Basophilic granules (contain iron)
<b>Heinz bodies</b>		G6PD deficiency	Denatured and precipitated hemoglobin (contain iron) Phagocytic removal of Heinz bodies → bite cells Requires supravital stain (eg, crystal violet) to be visualized

## Anemias



## Reticulocyte production index

Also called corrected reticulocyte count. Used to correct falsely elevated reticulocyte count in anemia. Measures appropriate bone marrow response to anemic conditions (effective erythropoiesis). High RPI (>3) indicates compensatory RBC production; low RPI (<2) indicates inadequate response to correct anemia. Calculated as:

$$\text{RPI} = \frac{\text{reticulocyte \%} \times \text{actual Hct}}{\text{normal Hct} (\approx 45\%)}$$

**Microcytic,****hypochromic anemias**

MCV &lt; 80 fL.

**Iron deficiency**

↓ iron due to chronic bleeding (eg, GI loss, menorrhagia), malnutrition, absorption disorders, GI surgery (eg, gastrectomy), or ↑ demand (eg, pregnancy) → ↓ final step in heme synthesis. Labs: ↓ iron, ↑ TIBC, ↓ ferritin, ↑ free erythrocyte protoporphyrin, ↑ RDW, ↓ RI. Microcytosis and hypochromasia (↑ central pallor) **A**. Symptoms: fatigue, conjunctival pallor **B**, pica (persistent craving and compulsive eating of nonfood substances), spoon nails (koilonychia). May manifest as glossitis, cheilosis, **Plummer-Vinson syndrome** (triad of iron deficiency anemia, esophageal webs, and dysphagia).

 **$\alpha$ -thalassemia**

$\alpha$ -globin gene deletions on chromosome 16 → ↓  $\alpha$ -globin synthesis. May have *cis* deletion (deletions occur on same chromosome) or *trans* deletion (deletions occur on separate chromosomes). Normal is  $\alpha\alpha/\alpha\alpha$ . Often ↑ RBC count, in contrast to iron deficiency anemia.

NUMBER OF $\alpha$ -GLOBIN GENES DELETED	DISEASE	CLINICAL OUTCOME
1 ( $\alpha\alpha/\alpha-$ )	$\alpha$ -thalassemia minima	No anemia (silent carrier)
2 ( $\alpha-/alpha-$ ; <i>trans</i> ) or ( $\alpha\alpha/-$ ; <i>cis</i> )	$\alpha$ -thalassemia minor	Mild microcytic, hypochromic anemia; <i>cis</i> deletion may worsen outcome for the carrier's offspring
3 ( $--/-\alpha$ )	Hemoglobin H disease (HbH); excess $\beta$ -globin forms $\beta_4$	Moderate to severe microcytic hypochromic anemia
4 ( $--/-$ )	Hemoglobin Barts disease; no $\alpha$ -globin, excess $\gamma$ -globin forms $\gamma_4$	Hydrops fetalis; incompatible with life

 **$\beta$ -thalassemia**

Point mutations in splice sites and promoter sequences on chromosome 11 → ↓  $\beta$ -globin synthesis. ↑ prevalence in people of Mediterranean descent.

**$\beta$ -thalassemia minor** (heterozygote):  $\beta$  chain is underproduced. Usually asymptomatic. Diagnosis confirmed by ↑ HbA<sub>2</sub> (> 3.5%) on electrophoresis.

**$\beta$ -thalassemia major** (homozygote):  $\beta$  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 (eg, “chipmunk” facies). Extramedullary hematopoiesis → hepatosplenomegaly. ↑ risk of parvovirus B19-induced aplastic crisis. ↑ HbF ( $\alpha_2\gamma_2$ ), HbA<sub>2</sub> ( $\alpha_2\delta_2$ ). HbF is protective in the infant and disease becomes symptomatic only after 6 months, when fetal hemoglobin declines.

**HbS/ $\beta$ -thalassemia heterozygote**: mild to moderate sickle cell disease depending on amount of  $\beta$ -globin production.

**Microcytic, hypochromic anemias (continued)****Lead poisoning**

Lead inhibits ferrochelatase and ALA dehydratase → ↓ heme synthesis and ↑ RBC protoporphyrin.

Also inhibits rRNA degradation → RBCs retain aggregates of rRNA (basophilic stippling).

Symptoms of **LEAD** poisoning:

- **Lead Lines** on gingivae (Burton lines) and on metaphyses of long bones **D** on x-ray.
- **Encephalopathy** and **Erythrocyte basophilic stippling**.
- **Abdominal colic** and sideroblastic **Anemia**.
- **Drops**—wrist and foot drop.

Treatment: chelation with succimer, EDTA, dimercaprol.

Exposure risk ↑ in old houses with chipped paint (children) and workplace (adults).

**Sideroblastic anemia**

Causes: genetic (eg, X-linked defect in ALA synthase gene), acquired (myelodysplastic syndromes), and reversible (alcohol is most common; also lead poisoning, vitamin B<sub>6</sub> deficiency, copper deficiency, drugs [eg, isoniazid, linezolid]).

Lab findings: ↑ iron, normal/↓ TIBC, ↑ ferritin. Ringed sideroblasts (with iron-laden, Prussian blue-stained mitochondria) seen in bone marrow **E**. Peripheral blood smear: basophilic stippling of RBCs. Some acquired variants may be normocytic or macrocytic.

Treatment: pyridoxine (B<sub>6</sub>, cofactor for ALA synthase).

**Interpretation of iron studies**

	<b>Iron deficiency</b>	<b>Chronic disease</b>	<b>Hemochromatos</b>	<b>Pregnancy/OCP use</b>
Serum iron	↓	↓	↑	—
Transferrin or TIBC	↑	↓ <sup>a</sup>	↓	↑
Ferritin	↓	↑	↑	—
% transferrin saturation (serum iron/TIBC)	↓↓	—/↓	↑↑	↓

↑↓ = 1° disturbance.

**Transferrin**—transports iron in blood.

TIBC—indirectly measures transferrin.

Ferritin—1° iron storage protein of body.

<sup>a</sup>Evolutionary reasoning—pathogens use circulating iron to thrive. The body has adapted a system in which iron is stored within the cells of the body and prevents pathogens from acquiring circulating iron.

**Macrocytic anemias**

MCV &gt; 100 fL.

	DESCRIPTION	FINDINGS
<b>Megaloblastic anemia</b>	<p>Impaired DNA synthesis → maturation of nucleus of precursor cells in bone marrow delayed relative to maturation of cytoplasm.</p> <p>Causes: vitamin B<sub>12</sub> deficiency, folate deficiency, medications (eg, hydroxyurea, phenytoin, methotrexate, sulfa drugs).</p>	RBC macrocytosis, hypersegmented neutrophils (arrow in <b>A</b> ), glossitis.
<b>Folate deficiency</b>	<p>Causes: malnutrition (eg, chronic alcohol overuse), malabsorption, drugs (eg, methotrexate, trimethoprim, phenytoin), ↑ requirement (eg, hemolytic anemia, pregnancy).</p>	↑ homocysteine, normal methylmalonic acid. <b>No neurologic symptoms</b> (vs B <sub>12</sub> deficiency).
<b>Vitamin B<sub>12</sub> (cobalamin) deficiency</b>	<p>Causes: pernicious anemia, malabsorption (eg, Crohn disease), pancreatic insufficiency, gastrectomy, insufficient intake (eg, veganism), <i>Diphyllobothrium latum</i> (fish tapeworm).</p>	↑ homocysteine, ↑ methylmalonic acid. <b>Neurologic symptoms:</b> reversible dementia, subacute combined degeneration (due to involvement of B <sub>12</sub> in fatty acid pathways and myelin synthesis): spinocerebellar tract, lateral corticospinal tract, dorsal column dysfunction. Folate supplementation in vitamin B <sub>12</sub> deficiency can correct the anemia, but worsens neurologic symptoms. Historically diagnosed with the Schilling test, a test that determines if the cause is dietary insufficiency vs malabsorption. Anemia 2° to insufficient intake may take several years to develop due to liver's ability to store B <sub>12</sub> (vs folate deficiency, which takes weeks to months).
<b>Orotic aciduria</b>	<p>Inability to convert orotic acid to UMP (de novo pyrimidine synthesis pathway) because of defect in UMP synthase.</p> <p>Autosomal recessive. Presents in children as failure to thrive, developmental delay, and megaloblastic anemia refractory to folate and B<sub>12</sub>. No hyperammonemia (vs ornithine transcarbamylase deficiency—↑ orotic acid with hyperammonemia).</p>	Orotic acid in urine. Treatment: uridine monophosphate or uridine triacetate to bypass mutated enzyme.
<b>Nonmegaloblastic anemia</b>	Macrocytic anemia in which DNA synthesis is normal. Causes: chronic alcohol overuse, liver disease.	RBC macrocytosis without hypersegmented neutrophils.
<b>Diamond-Blackfan anemia</b>	A congenital form of pure red cell aplasia (vs Fanconi anemia, which causes pancytopenia). 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.

**Normocytic,  
normochromic  
anemias**

Normocytic, normochromic anemias are classified as nonhemolytic or hemolytic. The hemolytic anemias are further classified according to the cause of the hemolysis (intrinsic vs extrinsic to the RBC) and by the location of the hemolysis (intravascular vs extravascular). Hemolysis can lead to increases in LDH, reticulocytes, unconjugated bilirubin, pigmented gallstones, and urobilinogen in urine.

**Intravascular  
hemolysis**

Findings: ↓ haptoglobin, ↑ schistocytes on blood smear. Characteristic hemoglobinuria, hemosiderinuria, and urobilinogen in urine. Notable causes are mechanical hemolysis (eg, prosthetic valve), paroxysmal nocturnal hemoglobinuria, microangiopathic hemolytic anemias.

**Extravascular  
hemolysis**

Mechanism: macrophages in spleen clear RBCs. Findings: spherocytes in peripheral smear (most commonly due to hereditary spherocytosis and autoimmune hemolytic anemia), no hemoglobinuria/hemosiderinuria. Can present with urobilinogen in urine.

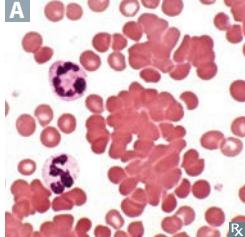
**Nonhemolytic, normocytic anemias**

	DESCRIPTION	FINDINGS
<b>Anemia of chronic disease</b>	Inflammation (eg, ↑ IL-6) → ↑ hepcidin (released by liver, binds ferroportin on intestinal mucosal cells and macrophages, thus inhibiting iron transport) → ↓ release of iron from macrophages and ↓ iron absorption from gut. Associated with conditions such as chronic infections, neoplastic disorders, chronic kidney disease, and autoimmune diseases (eg, SLE, rheumatoid arthritis).	↓ iron, ↓ TIBC, ↑ ferritin. Normocytic, but can become microcytic. Treatment: address underlying cause of inflammation, judicious use of blood transfusion, consider erythropoiesis-stimulating agents such as EPO (eg, in chronic kidney disease).
<b>Aplastic anemia</b>	Failure or destruction of hematopoietic stem cells. Causes (reducing volume from inside diaphysis): <ul style="list-style-type: none"> <li>▪ Radiation</li> <li>▪ Viral agents (eg, EBV, HIV, hepatitis viruses)</li> <li>▪ Fanconi anemia (autosomal recessive DNA repair defect → bone marrow failure); normocytosis or macrocytosis on CBC</li> <li>▪ Idiopathic (immune mediated, 1° stem cell defect); may follow acute hepatitis</li> <li>▪ Drugs (eg, benzene, chloramphenicol, alkylating agents, antimetabolites)</li> </ul>	↓ reticulocyte count, ↑ EPO. Pancytopenia characterized by anemia, leukopenia, and thrombocytopenia (not to be confused with aplastic crisis, which causes anemia only). Normal cell morphology, but hypocellular bone marrow with fatty infiltration <b>A</b> (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 anemias**

	DESCRIPTION	FINDINGS
<b>Hereditary spherocytosis</b>	<p>Primarily autosomal dominant. Due to defect in proteins interacting with RBC membrane skeleton and plasma membrane (eg, ankyrin, band 3, protein 4.2, spectrin).</p> <p>Small, round RBCs with less surface area and no central pallor (<math>\uparrow</math> MCHC) <math>\rightarrow</math> premature removal by spleen (extravascular hemolysis).</p>	<p>Splenomegaly, pigmented gallstones, aplastic crisis (parvovirus B19 infection).</p> <p>Labs: <math>\downarrow</math> mean fluorescence of RBCs in eosin 5-maleimide (EMA) binding test, <math>\uparrow</math> fragility in osmotic fragility test. Normal to <math>\downarrow</math> MCV with abundance of RBCs.</p> <p>Treatment: splenectomy.</p>
<b>G6PD deficiency</b>	<p>X-linked recessive. G6PD defect</p> <ul style="list-style-type: none"> <li><math>\rightarrow \downarrow</math> NADPH <math>\rightarrow \downarrow</math> reduced glutathione</li> <li><math>\rightarrow \uparrow</math> RBC susceptibility to oxidative stress (eg, sulfa drugs, antimalarials, <b>fava beans</b>)</li> <li><math>\rightarrow</math> hemolysis.</li> </ul> <p>Causes extravascular and intravascular hemolysis.</p>	<p>Back pain, hemoglobinuria a few days after oxidant <b>stress</b>.</p> <p>Labs: blood smear shows RBCs with <b>Heinz bodies</b> and <b>bite cells</b>.</p> <p><b>“Stress makes me eat bites of fava beans with Heinz ketchup.”</b></p>
<b>Pyruvate kinase deficiency</b>	<p>Autosomal recessive. Pyruvate kinase defect</p> <ul style="list-style-type: none"> <li><math>\rightarrow \downarrow</math> ATP <math>\rightarrow</math> rigid RBCs <math>\rightarrow</math> extravascular hemolysis. Increases levels of 2,3-BPG</li> <li><math>\rightarrow \downarrow</math> hemoglobin affinity for <math>O_2</math>.</li> </ul>	<p>Hemolytic anemia in a newborn.</p> <p>Labs: blood smear shows burr cells.</p>
<b>Paroxysmal nocturnal hemoglobinuria</b>	<p>Hematopoietic stem cell mutation</p> <ul style="list-style-type: none"> <li><math>\rightarrow \uparrow</math> complement-mediated intravascular hemolysis, especially at night. Acquired PIGA mutation <math>\rightarrow</math> impaired GPI anchor synthesis for decay-accelerating factor (DAF/CD55) and membrane inhibitor of reactive lysis (MIRL/CD59), which protect RBC membrane from complement.</li> </ul>	<p>Triad: Coombs <math>\ominus</math> hemolytic anemia, pancytopenia, venous thrombosis (eg, Budd-Chiari syndrome).</p> <p>Pink/red urine in morning. Associated with aplastic anemia, acute leukemias.</p> <p>Labs: CD55/59 <math>\ominus</math> RBCs on flow cytometry.</p> <p>Treatment: eculizumab (targets terminal complement protein C5).</p>
<b>Sickle cell anemia</b>	<p>Point mutation in <math>\beta</math>-globin gene <math>\rightarrow</math> single amino acid substitution (glutamic acid <math>\rightarrow</math> valine). Mutant HbA is termed HbS. Causes extravascular and intravascular hemolysis.</p> <p>Pathogenesis: low <math>O_2</math>, high altitude, or acidosis precipitates sickling (deoxygenated HbS polymerizes) <math>\rightarrow</math> anemia, vaso-occlusive disease. Newborns are initially asymptomatic because of <math>\uparrow</math> HbF and <math>\downarrow</math> HbS.</p> <p>Heterozygotes (sickle cell trait) have resistance to malaria.</p> <p>Most common autosomal recessive disease in Black population.</p> <p>Sickle cells are crescent-shaped RBCs <b>A</b>. “Crew cut” on skull x-ray due to marrow expansion from <math>\uparrow</math> erythropoiesis (also seen in thalassemias).</p>	<p>Complications in sickle cell disease:</p> <ul style="list-style-type: none"> <li>▪ Aplastic crisis (transient arrest of erythropoiesis due to parvovirus B19).</li> <li>▪ Autosplenectomy (Howell-Jolly bodies) <math>\rightarrow \uparrow</math> risk of infection by encapsulated organisms (eg, <i>S pneumoniae</i>).</li> <li>▪ Splenic infarct/sequestration crisis.</li> <li>▪ <i>Salmonella</i> osteomyelitis.</li> <li>▪ Painful vaso-occlusive crises: dactylitis (painful swelling of hands/feet), priapism, acute chest syndrome (respiratory distress, new pulmonary infiltrates on CXR, common cause of death), avascular necrosis, stroke.</li> <li>▪ Sickling in renal medulla (<math>\downarrow</math> <math>Po_2</math>) <math>\rightarrow</math> renal papillary necrosis <math>\rightarrow</math> hematuria.</li> </ul> <p>Hb electrophoresis: <math>\downarrow\downarrow</math> HbA, <math>\uparrow</math> HbF, <math>\uparrow\uparrow</math> HbS.</p> <p>Treatment: hydroxyurea (<math>\uparrow</math> HbF), hydration.</p>
<b>HbC disease</b>	Glutamic acid-to-lysine (lysine) mutation in $\beta$ -globin. Causes extravascular hemolysis.	<p>Patients with HbSC (1 of each mutant gene) have milder disease than HbSS patients.</p> <p>Blood smear in homozygotes: hemoglobin crystals inside RBCs, target cells.</p>

**Extrinsic hemolytic anemias**

	DESCRIPTION	FINDINGS
<b>Autoimmune hemolytic anemia</b>	A normocytic anemia that is usually idiopathic and Coombs $\oplus$ . Two types:	Spherocytes and agglutinated RBCs <b>A</b> on peripheral blood smear.
<b>A</b> 	<ul style="list-style-type: none"> <li>▪ <b>Warm AIHA</b>—chronic anemia in which primarily IgG causes extravascular hemolysis. Seen in SLE and CLL and with certain drugs (eg, <math>\beta</math>-lactams, <math>\alpha</math>-methyldopa). “<b>Warm weather is Good.</b>”</li> <li>▪ <b>Cold AIHA</b>—acute anemia in which primarily IgM + complement cause RBC agglutination and extravascular hemolysis upon exposure to cold <math>\rightarrow</math> painful, blue fingers and toes. Seen in CLL, <i>Mycoplasma pneumoniae</i> infections, infectious mononucleosis.</li> </ul>	Warm AIHA treatment: steroids, rituximab, splenectomy (if refractory). Cold AIHA treatment: cold avoidance, rituximab.
<b>Microangiopathic hemolytic anemia</b>	RBCs are damaged when passing through obstructed or narrowed vessels. Causes intravascular hemolysis. Seen in DIC, TTP/HUS, SLE, HELLP syndrome, hypertensive emergency.	<b>Schisto</b> cytes (eg, “helmet cells”) are seen on peripheral blood smear due to mechanical destruction ( <i>schisto</i> = to split) of RBCs.
<b>Macroangiopathic hemolytic anemia</b>	Prosthetic heart valves and aortic stenosis may also cause hemolytic anemia 2° to mechanical destruction of RBCs.	Schistocytes on peripheral blood smear.
<b>Hemolytic anemia due to infection</b>	$\uparrow$ destruction of RBCs (eg, malaria, <i>Babesia</i> ).	

**Leukopenias**

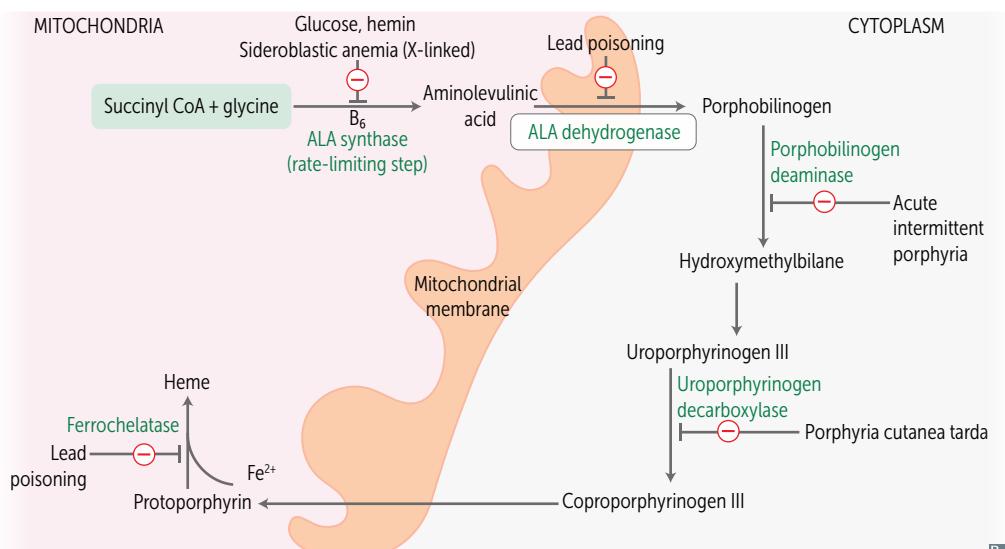
CELL TYPE	CELL COUNT	CAUSES
<b>Neutropenia</b>	Absolute neutrophil count $< 1500 \text{ cells/mm}^3$ Severe infections typical when $< 500 \text{ cells/mm}^3$	Sepsis/postinfection, drugs (including chemotherapy), aplastic anemia, SLE, radiation
<b>Lymphopenia</b>	Absolute lymphocyte count $< 1500 \text{ cells/mm}^3$ ( $< 3000 \text{ cells/mm}^3$ in children)	HIV, DiGeorge syndrome, SCID, SLE, corticosteroids <sup>a</sup> , radiation, sepsis, postoperative
<b>Eosinopenia</b>	Absolute eosinophil count $< 30 \text{ cells/mm}^3$	Cushing syndrome, corticosteroids <sup>a</sup>

<sup>a</sup>Corticosteroids cause neutrophilia, despite causing eosinopenia and lymphopenia. Corticosteroids  $\downarrow$  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.

### 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
<b>Lead poisoning</b>	Ferrochelatase and ALA dehydratase	Protoporphyrin, ALA (blood)	Microcytic anemia (basophilic stippling in peripheral smear <b>A</b> , ringed sideroblasts in bone marrow), GI and kidney disease. Children—exposure to lead paint → mental deterioration. Adults—environmental exposure (eg, batteries, ammunition) → headache, memory loss, demyelination (peripheral neuropathy).
<b>Acute intermittent porphyria</b>	Porphobilinogen deaminase, previously called uroporphyrinogen I synthase (autosomal dominant mutation)	Porphobilinogen, ALA	Symptoms ( <b>5 P's</b> ): <ul style="list-style-type: none"> <li>▪ Painful abdomen</li> <li>▪ Port wine–colored Pee</li> <li>▪ Polyneuropathy</li> <li>▪ Psychological disturbances</li> <li>▪ Precipitated by factors that ↑ ALA synthase (eg, drugs [CYP450 inducers], alcohol, starvation)</li> </ul> Treatment: hemin and glucose.
<b>Porphyria cutanea tarda</b>	Uroporphyrinogen decarboxylase	Uroporphyrin (tea-colored urine)	Blistering cutaneous photosensitivity and hyperpigmentation <b>B</b> . Most common porphyria. Exacerbated with alcohol consumption. Causes: familial, hepatitis <b>C</b> . Treatment: phlebotomy, sun avoidance, antimalarials (eg, hydroxychloroquine).



**Iron poisoning**

	<b>Acute</b>	<b>Chronic</b>
<b>FINDINGS</b>	High mortality rate associated with accidental ingestion by children (adult iron tablets may look like candy).	Seen in patients with 1° (hereditary) or 2° (eg, chronic blood transfusions for thalassemia or sickle cell disease) hemochromatosis.
<b>MECHANISM</b>	Cell death due to formation of free radicals and peroxidation of membrane lipids.	
<b>SYMPOTMS/SIGNS</b>	Abdominal pain, vomiting, GI bleeding. Radiopaque pill seen on x-ray. May progress to anion gap metabolic acidosis and multiorgan failure. Leads to scarring with GI obstruction.	Arthropathy, cirrhosis, cardiomyopathy, diabetes mellitus and skin pigmentation (“bronze diabetes”), hypogonadism.
<b>TREATMENT</b>	Chelation (eg, deferoxamine, deferasirox), gastric lavage.	Phlebotomy (patients without anemia) or chelation.

**Coagulation disorders**

PT—tests function of common and extrinsic pathway (factors I, II, V, VII, and X). Defect → ↑ PT (Play Tennis outside [extrinsic pathway]).

INR (international normalized ratio) = patient PT/control PT. 1 = normal, > 1 = prolonged. Most common test used to follow patients on warfarin, which prolongs INR.

PTT—tests function of common and intrinsic pathway (all factors except VII and XIII). Defect → ↑ PTT (Play Table Tennis inside).

Coagulation disorders can be due to clotting factor deficiencies or acquired factor inhibitors (most commonly against factor VIII). Diagnosed with a mixing study, in which normal plasma is added to patient's plasma. Clotting factor deficiencies should correct (the PT or PTT returns to within the appropriate normal range), whereas factor inhibitors will not correct.

DISORDER	PT	PTT	MECHANISM AND COMMENTS
<b>Hemophilia A, B, or C</b>	—	↑	Intrinsic pathway coagulation defect (↑ PTT). <ul style="list-style-type: none"> <li>▪ A: deficiency of factor <b>VIII</b>; X-linked recessive. Pronounce “hemophilia <b>eight</b>.”</li> <li>▪ B: deficiency of factor IX; X-linked recessive.</li> <li>▪ C: deficiency of factor XI; autosomal recessive.</li> </ul> Hemorrhage in hemophilia—hemarthroses (bleeding into joints, eg, knee <b>A</b> ), easy bruising, bleeding after trauma or surgery (eg, dental procedures). Treatment: desmopressin, factor VIII concentrate, emicizumab (A); factor IX concentrate (B); factor XI concentrate (C).
<b>Vitamin K deficiency</b>	↑	↑	General coagulation defect. Bleeding time normal. ↓ activity of factors II, VII, IX, X, protein C, protein S.

**Platelet disorders**

All platelet disorders have ↑ bleeding time (BT), mucous membrane bleeding, and microhemorrhages (eg, petechiae, epistaxis). Platelet count (PC) is usually low, but may be normal in qualitative disorders.

DISORDER	PC	BT	NOTES
<b>Bernard-Soulier syndrome</b>	-/↓	↑	Autosomal recessive defect in adhesion. ↓ GpIb → ↓ platelet-to-vWF adhesion. Labs: abnormal ristocetin test, large platelets.
<b>Glanzmann thrombasthenia</b>	-	↑	Autosomal recessive defect in aggregation. ↓ GpIIb/IIIa (↓ integrin $\alpha_{IIb}\beta_3$ ) → ↓ platelet-to-platelet aggregation and defective platelet plug formation. Labs: blood smear shows no platelet clumping.
<b>Immune thrombocytopenia</b>	↓	↑	Destruction of platelets in spleen. Anti-GpIIb/IIIa antibodies → splenic macrophages phagocytose platelets. May be idiopathic or 2° to autoimmune disorders (eg, SLE), viral illness (eg, HIV, HCV), malignancy (eg, CLL), or drug reactions. Labs: ↑ megakaryocytes on bone marrow biopsy, ↓ platelet count. Treatment: steroids, IVIG, rituximab, TPO receptor agonists (eg, eltrombopag, romiplostim), or splenectomy for refractory ITP.

**Thrombotic microangiopathies**

Disorders overlap significantly in symptomatology.

	<b>Thrombotic thrombocytopenic purpura</b>	<b>Hemolytic-uremic syndrome</b>
<b>EPIDEMIOLOGY</b>	Typically females	Typically children
<b>PATHOPHYSIOLOGY</b>	Inhibition or deficiency of ADAMTS13 (a vWF metalloprotease) → ↓ degradation of vWF multimers → ↑ large vWF multimers → ↑ platelet adhesion and aggregation (microthrombi formation)	Commonly caused by Shiga toxin-producing <i>Escherichia coli</i> (STEC) infection (serotype O157:H7)
<b>PRESENTATION</b>	Triad of thrombocytopenia (↓ platelets), microangiopathic hemolytic anemia (↓ Hb, schistocytes, ↑ LDH), acute kidney injury (↑ Cr)	
<b>DIFFERENTIATING SYMPTOMS</b>	Triad + fever + neurologic symptoms	Triad + bloody diarrhea
<b>LABS</b>	Normal PT and PTT helps distinguish TTP and HUS (coagulation pathway is not activated) from DIC (coagulation pathway is activated)	
<b>TREATMENT</b>	Plasma exchange, steroids, rituximab	Supportive care

**Mixed platelet and coagulation disorders**

DISORDER	PC	BT	PT	PTT	NOTES
<b>von Willebrand disease</b>	—	↑	—	—/↑	Intrinsic pathway coagulation defect: ↓ vWF → ↑ PTT (vWF carries/protects factor VIII). Defect in platelet plug formation: ↓ vWF → defect in platelet-to-vWF adhesion. Most are autosomal dominant. Mild but most common inherited bleeding disorder. No platelet aggregation with ristocetin cofactor assay. Treatment: desmopressin, which releases vWF stored in endothelium.
<b>Disseminated intravascular coagulation</b>	↓	↑	↑	↑	Widespread clotting factor activation → deficiency in clotting factors → bleeding state (eg, blood oozing from puncture sites). Causes: Snake bites, Sepsis (gram ⊖), Trauma, Obstetric complications, acute Pancreatitis, malignancy, nephrotic syndrome, transfusion ( <b>SSTOP making new thrombi</b> ). Labs: schistocytes, ↑ fibrin degradation products (D-dimers), ↓ fibrinogen, ↓ factors V and VIII.

**Hereditary thrombophilias**

DISEASE	DESCRIPTION
<b>Antithrombin deficiency</b>	Has no direct effect on the PT, PTT, or thrombin time but diminishes the increase in PTT following standard heparin dosing. Can also be acquired: renal failure/nephrotic syndrome → antithrombin loss in urine → ↓ inhibition of factors IIa and Xa.
<b>Factor V Leiden</b>	Production of mutant factor V (guanine → adenine DNA point mutation → Arg506Gln mutation near the cleavage site) that is resistant to degradation by activated protein C. Complications include DVT, cerebral vein thrombosis, recurrent pregnancy loss.
<b>Protein C or S deficiency</b>	↓ ability to inactivate factors Va and VIIa. ↑ risk of warfarin-induced skin necrosis. Together, protein <b>C Cancels</b> , and protein <b>S Stops</b> , coagulation.
<b>Prothrombin G20210A mutation</b>	Point mutation in 3' untranslated region → ↑ production of prothrombin → ↑ plasma levels and venous clots.

**Blood transfusion therapy**

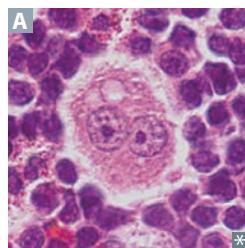
COMPONENT	DOSAGE EFFECT	CLINICAL USE
Packed RBCs	↑ Hb and O <sub>2</sub> carrying capacity	Acute blood loss, severe anemia
Platelets	↑ platelet count ( $\uparrow \sim 5000/\text{mm}^3/\text{unit}$ )	Stop significant bleeding (thrombocytopenia, qualitative platelet defects)
Fresh frozen plasma/ prothrombin complex concentrate	↑ coagulation factor levels; FFP contains all coagulation factors and plasma proteins; PCC generally contains factors II, VII, IX, and X, as well as protein C and S	Cirrhosis, immediate anticoagulation 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 Ca<sup>2+</sup> chelator), and hyperkalemia (RBCs may lyse in old blood units).

**Leukemia vs lymphoma**

Leukemia	Lymphoid or myeloid neoplasm with widespread involvement of bone marrow. Tumor cells are usually found in peripheral blood.
Lymphoma	Discrete tumor mass arising from lymph nodes. Variable clinical presentation (eg, arising in atypical sites, leukemic presentation).

Hodgkin vs non-Hodgkin lymphoma	Hodgkin	Non-Hodgkin
	Both may present with constitutional ("B") signs/symptoms: low-grade fever, night sweats, weight loss.	
	Localized, single group of nodes with contiguous spread (stage is strongest predictor of prognosis). Better prognosis.	Multiple lymph nodes involved; extranodal involvement common; noncontiguous spread. Worse prognosis.
	Characterized by Reed-Sternberg cells.	Majority involve B cells; a few are of T-cell lineage.
	Bimodal distribution: young adulthood and > 55 years; more common in males except for nodular sclerosing type.	Can occur in children and adults.
	Associated with EBV.	May be associated with autoimmune diseases and viral infections (eg, HIV, EBV, HTLV).

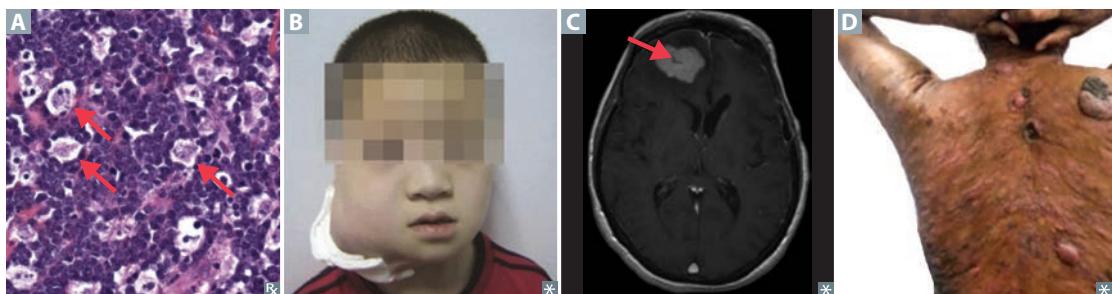
**Hodgkin lymphoma**

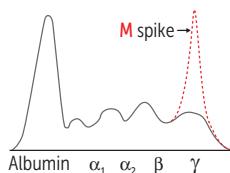
Contains Reed-Sternberg cells: distinctive tumor giant cells; binucleate or bilobed with the 2 halves as mirror images ("owl eyes" **A**). RS cells are CD15+ and CD30+ B-cell origin.  $2 \text{ owl eyes} \times 15 = 30$ .

SUBTYPE	NOTES
Nodular sclerosis	Most common
Lymphocyte rich	<b>Best</b> prognosis (the <b>rich</b> have <b>better</b> bank accounts)
Mixed cellularity	Eosinophilia; seen in immunocompromised patients
Lymphocyte depleted	<b>Worst</b> prognosis (the <b>poor</b> have <b>worse</b> bank accounts); seen in immunocompromised patients

**Non-Hodgkin lymphoma**

TYPE	OCURS IN	GENETICS	COMMENTS
<b>Neoplasms of mature B cells</b>			
<b>Burkitt lymphoma</b>	Adolescents or young adults	t(8;14)—translocation of c-myc (8) and heavy-chain Ig (14)	“Starry sky” appearance, sheets of lymphocytes with interspersed “tingible body” macrophages (arrows in <b>A</b> ). Associated with EBV. Jaw lesion <b>B</b> in endemic form in Africa; pelvis or abdomen in sporadic form.
<b>Diffuse large B-cell lymphoma</b>	Usually older adults, but 20% in children	Mutations in <i>BCL-2</i> , <i>BCL-6</i>	Most common type of non-Hodgkin lymphoma in adults.
<b>Follicular lymphoma</b>	Adults	t(14;18)—translocation of heavy-chain Ig (14) and <i>BCL-2</i> (18)	Indolent course with painless “waxing and waning” lymphadenopathy. Bcl-2 normally inhibits apoptosis.
<b>Mantle cell lymphoma</b>	Adult <b>males</b> >> adult females	t(11;14)—translocation of cyclin D1 (11) and heavy-chain Ig (14), CD5+	Very aggressive, patients typically present with late-stage disease.
<b>Marginal zone lymphoma</b>	Adults	t(11;18)	Associated with chronic inflammation (eg, Sjögren syndrome, chronic gastritis [MALT lymphoma; may regress with <i>H pylori</i> eradication]).
<b>Primary central nervous system lymphoma</b>	Adults	EBV related; associated with HIV/AIDS	Considered an AIDS-defining illness. Variable presentation: confusion, memory loss, seizures. CNS mass (often single, ring-enhancing lesion on MRI) in immunocompromised patients <b>C</b> , needs to be distinguished from toxoplasmosis via CSF analysis or other lab tests.
<b>Neoplasms of mature T cells</b>			
<b>Adult T-cell lymphoma</b>	Adults	Caused by HTLV (associated with IV drug use)	Adults present with cutaneous lesions; common in Japan ( <b>T-cell in Tokyo</b> ), West Africa, and the Caribbean. Lytic bone lesions, hypercalcemia.
<b>Mycosis fungoides/ Sézary syndrome</b>	Adults		Mycosis fungoides: skin patches and plaques <b>D</b> (cutaneous T-cell lymphoma), characterized by atypical CD4+ cells with “cerebriform” nuclei and intraepidermal neoplastic cell aggregates (Pautrier microabscess). May progress to Sézary syndrome (T-cell leukemia).



**Plasma cell dyscrasias**

Characterized by monoclonal immunoglobulin (paraprotein) overproduction due to plasma cell disorder.

Labs: serum protein electrophoresis (SPEP) or free light chain (FLC) assay for initial tests (M spike on SPEP represents overproduction of a monoclonal Ig fragment). For urinalysis, use 24-hr urine protein electrophoresis (UPEP) to detect light chain, as routine urine dipstick detects only albumin.

Confirm with bone marrow biopsy.

**Multiple myeloma**

Overproduction of IgG (55% of cases) > IgA.

Clinical features: **CRAB**

- Hyper**C**alcemia
- **R**enal involvement
- **A**nemia
- **B**one lytic lesions (“punched out” on X-ray **A**) → back pain.

Peripheral blood smear shows rouleaux formation **B** (RBCs stacked like poker chips).

Urinalysis shows Ig light chains (Bence Jones proteinuria) with  $\ominus$  urine dipstick.

Bone marrow analysis shows > 10% monoclonal plasma cells with clock-face chromatin **C** and intracytoplasmic inclusions containing IgG.

Complications: ↑ infection risk, 1° amyloidosis (AL).

**Waldenstrom macroglobulinemia**

Overproduction of IgM (**macro**globulinemia because IgM is the **largest** Ig).

Clinical features:

- Peripheral neuropathy
- No CRAB findings
- Hyperviscosity syndrome:
  - Headache
  - Blurry vision
  - Raynaud phenomenon
  - Retinal hemorrhages

Bone marrow analysis shows >10% small lymphocytes with intranuclear pseudoinclusions containing IgM (lymphoplasmacytic lymphoma).

Complication: thrombosis.

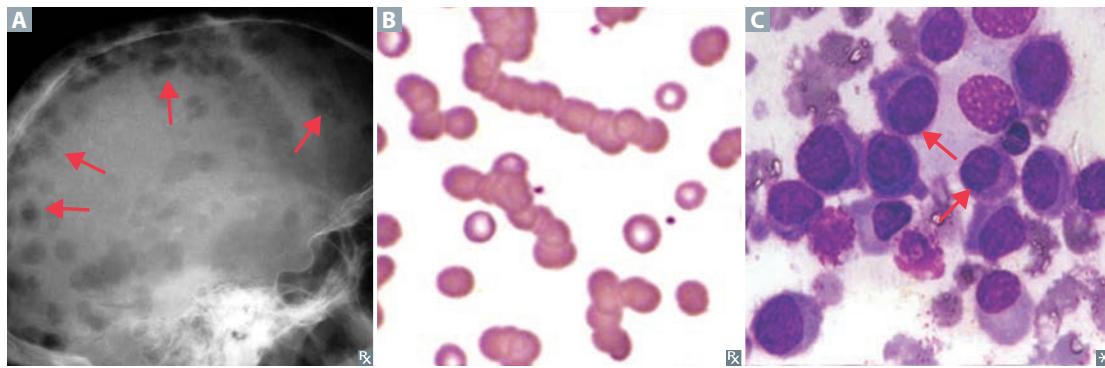
**Monoclonal gammopathy of undetermined significance**

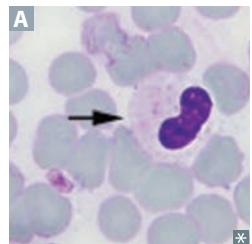
Overproduction of any Ig type.

Usually asymptomatic. No CRAB findings.

Bone marrow analysis shows < 10% monoclonal plasma cells.

Complication: 1-2% risk per year of transitioning to multiple myeloma.



**Myelodysplastic syndromes**

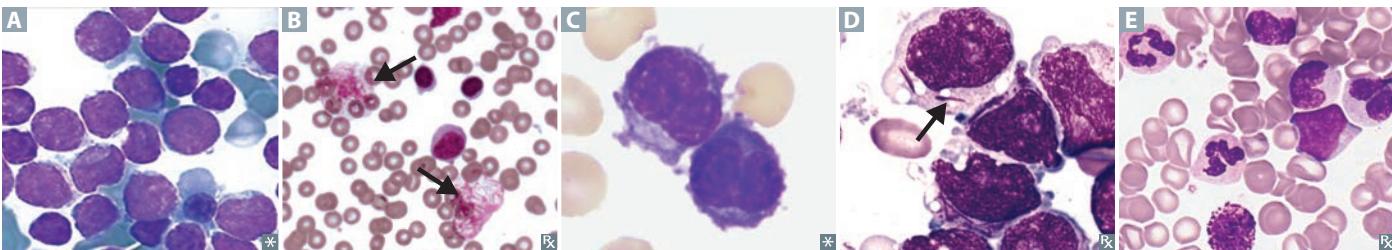
Stem cell disorders involving ineffective hematopoiesis → defects in cell maturation of nonlymphoid lineages. Bone marrow blasts <20% (vs >20% in AML). Caused by de novo mutations or environmental exposure (eg, radiation, benzene, chemotherapy). Risk of transformation to AML.

**Pseudo-Pelger-Huët anomaly**—neutrophils with bilobed (“duet”) nuclei **A**. Associated with myelodysplastic syndromes or drugs (eg, immunosuppressants).

**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), although some cases present with normal/↓ WBCs.

Leukemic cell infiltration of liver, spleen, lymph nodes, and skin (leukemia cutis) possible.

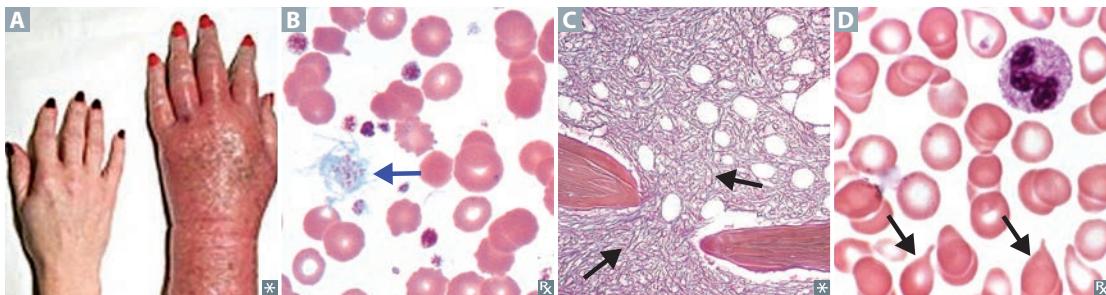
TYPE	NOTES
<b>Lymphoid neoplasms</b>	
<b>Acute lymphoblastic leukemia/lymphoma</b>	<p>Most frequently occurs in children; less common in adults (worse prognosis). T-cell ALL can present as mediastinal mass (presenting as SVC-like syndrome). Associated with Down syndrome. Peripheral blood and bone marrow have ↑↑↑ lymphoblasts <b>A</b>. TdT+ (marker of pre-T and pre-B cells), CD10+ (marker of pre-B cells).</p> <p>Most responsive to therapy.</p> <p>May spread to CNS and testes.</p> <p>t(12;21) → better prognosis; t(9;22) (Philadelphia chromosome) → worse prognosis.</p>
<b>Chronic lymphocytic leukemia/small lymphocytic lymphoma</b>	<p>Age &gt; 60 years. Most common adult leukemia. CD20+, CD23+, CD5+ B-cell neoplasm. Often asymptomatic, progresses slowly; smudge cells <b>B</b> in peripheral blood smear; autoimmune hemolytic anemia. <b>CLL</b> = Crushed Little Lymphocytes (smudge cells).</p> <p>Richter transformation—CLL/SLL transformation into an aggressive lymphoma, most commonly diffuse large B-cell lymphoma (DLBCL).</p>
<b>Hairy cell leukemia</b>	<p>Adult males. Mature B-cell tumor. Cells have filamentous, hair-like projections (fuzzy appearing on LM <b>C</b>). Peripheral lymphadenopathy is uncommon.</p> <p>Causes marrow fibrosis → dry tap on aspiration. Patients usually present with massive splenomegaly and pancytopenia.</p> <p>Stains <b>TRAP</b> (Tartrate-Resistant Acid Phosphatase) + (TRAPped in a hairy situation). TRAP stain largely replaced with flow cytometry. Associated with <i>BRAF</i> mutations.</p> <p>Treatment: purine analogs (cladribine, pentostatin).</p>
<b>Myeloid neoplasms</b>	
<b>Acute myelogenous leukemia</b>	<p>Median onset 65 years. Auer rods <b>D</b>; myeloperoxidase + cytoplasmic inclusions seen mostly in APL (formerly M3 AML); ↑↑↑ circulating myeloblasts on peripheral smear.</p> <p>Risk factors: prior exposure to alkylating chemotherapy, radiation, myeloproliferative disorders, Down syndrome (typically acute megakaryoblastic leukemia [formerly M7 AML]). APL: t(15;17), responds to all-trans retinoic acid (vitamin A) and arsenic trioxide, which induce differentiation of promyelocytes; DIC is a common presentation.</p>
<b>Chronic myelogenous leukemia</b>	<p>Peak incidence: 45–85 years; median age: 64 years. Defined by the Philadelphia chromosome (t[9;22], <i>BCR-ABL</i>) and myeloid stem cell proliferation. Presents with dysregulated production of mature and maturing granulocytes (eg, neutrophils, metamyelocytes, myelocytes, basophils <b>E</b>) and splenomegaly. May accelerate and transform to AML or ALL (“blast crisis”).</p> <p>Responds to BCR-ABL tyrosine kinase inhibitors (eg, imatinib).</p>
 <p><b>A:</b> Peripheral blood smear showing numerous large, dark-staining myeloblasts with prominent azurophilic granules (Auer rods).</p> <p><b>B:</b> Peripheral blood smear showing small, dark-staining smudge cells.</p> <p><b>C:</b> Low-magnification light micrograph showing a hairy cell with its characteristic fuzzy surface.</p> <p><b>D:</b> High-magnification light micrograph showing a myeloblast with an Auer rod.</p> <p><b>E:</b> Peripheral blood smear showing mature neutrophils, metamyelocytes, and myelocytes.</p>	

**Myeloproliferative neoplasms**

Malignant hematopoietic neoplasms with varying impacts on WBCs and myeloid cell lines.

<b>Polycythemia vera</b>	Primary polycythemia. Disorder of ↑ RBCs, usually due to acquired <i>JAK2</i> mutation. May present as intense itching after shower (aquagenic pruritus). Rare but classic symptom is erythromelalgia (severe, burning pain and red-blue coloration) due to episodic blood clots in vessels of the extremities <b>A</b> . ↓ EPO (vs 2° polycythemia, which presents with endogenous or artificially ↑ EPO). Treatment: phlebotomy, hydroxyurea, ruxolitinib ( <i>JAK1/2</i> inhibitor).
<b>Essential thrombocythemia</b>	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>B</b> . Erythromelalgia may occur.
<b>Myelofibrosis</b>	Atypical megakaryocyte hyperplasia → ↑ TGF-β secretion → ↑ fibroblast activity → obliteration of bone marrow with fibrosis <b>C</b> . Associated with massive splenomegaly and “teardrop” RBCs <b>D</b> . “Bone marrow <b>cries</b> because it’s fibrosed and is a dry tap.”

	RBCs	WBCs	PLATELETS	PHILADELPHIA CHROMOSOME	JAK2 MUTATIONS
<b>Polycythemia vera</b>	↑	↑	↑	⊖	⊕
<b>Essential thrombocythemia</b>	–	–	↑	⊖	⊕ (30–50%)
<b>Myelofibrosis</b>	↓	Variable	Variable	⊖	⊕ (30–50%)
<b>CML</b>	↓	↑	↑	⊕	⊖

**Leukemoid reaction vs chronic myelogenous leukemia**

	Leukemoid reaction	Chronic myelogenous leukemia
<b>DEFINITION</b>	Reactive neutrophilia >50,000 cells/mm <sup>3</sup>	Myeloproliferative neoplasm ⊕ for BCR-ABL
<b>NEUTROPHIL MORPHOLOGY</b>	Toxic granulation, Döhle bodies, cytoplasmic vacuoles	Pseudo-Pelger-Huët anomaly
<b>LAP SCORE</b>	↑	↓ (LAP enzyme ↓ in malignant neutrophils)
<b>EOSINOPHILS AND BASOPHILS</b>	Normal	↑

**Polycythemia**

	PLASMA VOLUME	RBC MASS	O <sub>2</sub> SATURATION	EPO LEVELS	ASSOCIATIONS
Relative	↓	—	—	—	Dehydration, burns.
Appropriate absolute	—	↑	↓	↑	Lung disease, congenital heart disease, high altitude.
Inappropriate absolute	—	↑	—	↑	Exogenous EPO: athlete abuse (“blood doping”). Inappropriate EPO secretion: malignancy (eg, RCC, HCC).
Polycythemia vera	↑	↑↑	—	↓	EPO ↓ in PCV due to negative feedback suppressing renal EPO production.

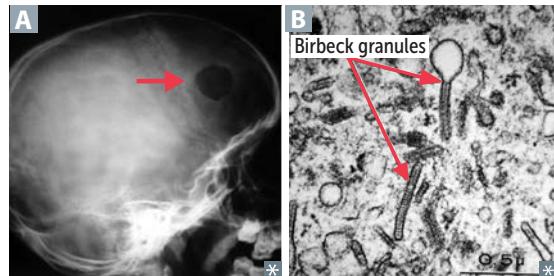
↑↓ = 1° disturbance

**Chromosomal translocations**

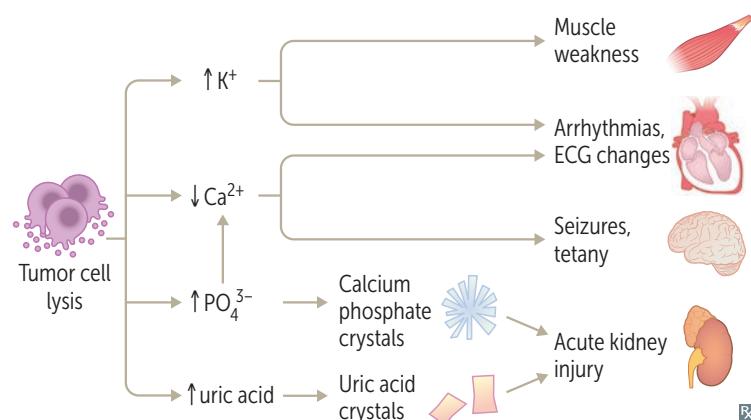
TRANSLOCATION	ASSOCIATED DISORDER	NOTES
t(8;14)	Burkitt (Burk-8) lymphoma (c-myc activation)	
t(11;14)	Mantle cell lymphoma (cyclin D1 activation)	
t(11;18)	Marginal zone lymphoma	
t(14;18)	Follicular lymphoma (BCL-2 activation)	
t(15;17)	APL (formerly M3 type of AML)	
t(9;22) (Philadelphia chromosome)	CML (BCR-ABL hybrid), ALL (less common); 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.

**Langerhans cell histiocytosis**

Collective group of proliferative disorders of 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**.

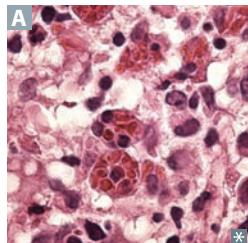


### Tumor lysis syndrome



Oncologic emergency triggered by massive tumor cell lysis, seen most often with lymphomas/leukemias. Usually caused by treatment initiation, but can occur spontaneously with fast-growing cancers. Release of  $K^+$  → hyperkalemia, release of  $PO_4^{3-}$  → hyperphosphatemia, hypocalcemia due to  $Ca^{2+}$  sequestration by  $PO_4^{3-}$ .  $\uparrow$  nucleic acid breakdown → hyperuricemia → acute kidney injury. Prevention and treatment include aggressive hydration, allopurinol, rasburicase.

### Hemophagocytic lymphohistiocytosis



Systemic overactivation of macrophages and cytotoxic T cells → fever, pancytopenia, hepatosplenomegaly,  $\uparrow\uparrow$  serum ferritin levels. Can be inherited or 2° to strong immunologic activation (eg, after EBV infection, malignancy). Bone marrow biopsy shows macrophages phagocytosing marrow elements A.

### ► HEMATOLOGY AND ONCOLOGY—PHARMACOLOGY

#### Heparin

MECHANISM	Activates antithrombin, which $\downarrow$ action primarily of factors IIa (thrombin) and 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). Monitor PTT.
ADVERSE EFFECTS	Bleeding (reverse with protamine sulfate), heparin-induced thrombocytopenia (HIT), osteoporosis (with long-term use), drug-drug interactions. <ul style="list-style-type: none"> <li>■ <b>HIT type 1</b>—mild (platelets <math>&gt;100,000/mm^3</math>), transient, nonimmunologic drop in platelet count that typically occurs within the first 2 days of heparin administration. Not clinically significant.</li> <li>■ <b>HIT type 2</b>—development of IgG antibodies against heparin-bound platelet factor 4 (PF4) that typically occurs 5–10 days after heparin administration. Antibody-heparin-PF4 complex binds and activates platelets → removal by splenic macrophages and thrombosis → <math>\downarrow\downarrow</math> platelet count. Highest risk with unfractionated heparin.</li> </ul>
NOTES	Low-molecular-weight heparins (eg, enoxaparin, dalteparin) act mainly on factor Xa. Fondaparinux acts only on factor Xa. Have better bioavailability and 2–4x longer half life than unfractionated heparin; can be administered subcutaneously and without lab monitoring. LMWHs undergo renal clearance (vs hepatic clearance of unfractionated heparin) and must be used with caution in patients with renal insufficiency. Not easily reversible.

**Warfarin****MECHANISM**

Inhibits vitamin K epoxide reductase by competing with vitamin K → inhibition of vitamin K-dependent  $\gamma$ -carboxylation of 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 extrinsic pathway and ↑ PT. Long half-life.  
“The ex-President went to war(farin).”

**CLINICAL USE**

Chronic anticoagulation (eg, venous thromboembolism prophylaxis and prevention of stroke in atrial fibrillation). Not used in pregnant patients (because warfarin, unlike heparin, crosses placenta). Monitor PT/INR.

**ADVERSE EFFECTS**

Bleeding, teratogenic effects, skin/tissue necrosis A, drug-drug interactions (metabolized by cytochrome P-450 [CYP2C9]).

Initial risk of hypercoagulation: protein C has shorter half-life than factors II and X. Existing protein C depletes before existing factors II and X deplete, and before warfarin can reduce factors II and X production → hypercoagulation. Skin/tissue necrosis within first few days of large doses believed to be due to small vessel microthrombosis.

Heparin “bridging”: heparin frequently used when starting warfarin. Heparin’s activation of antithrombin enables anticoagulation during initial, transient hypercoagulable state caused by warfarin. Initial heparin therapy reduces risk of recurrent venous thromboembolism and skin/tissue necrosis.

For reversal of warfarin, give vitamin K. For rapid reversal, give FFP or PCC.

**Heparin vs warfarin**

	<b>Heparin</b>	<b>Warfarin</b>
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
DURATION OF ACTION	Hours	Days
MONITORING	PTT (intrinsic pathway)	PT/INR (extrinsic pathway)
CROSSES PLACENTA	No	Yes (teratogenic)

**Direct coagulation factor inhibitors**

DRUG	MECHANISM	CLINICAL USE	ADVERSE EFFECTS
<b>Bivalirudin, argatroban, dabigatran</b>	Directly inhibit thrombin (factor IIa)	Venous thromboembolism, atrial fibrillation. Can be used in HIT, when heparin is BAD for the patient	Bleeding (reverse dabigatran with idarucizumab) Dabigatran is the only oral agent in class Do not require lab monitoring
<b>Apixaban, edoxaban, rivaroxaban</b>	Directly inhibit factor Xa	Treatment and prophylaxis for DVT and PE; stroke prophylaxis in patients with atrial fibrillation	Bleeding (reverse with andexanet alfa) Oral agents that do not usually require lab monitoring

**Anticoagulation reversal**

ANTICOAGULANT	REVERSAL AGENT	NOTES
<b>Heparin</b>	Protamine sulfate	⊕ charged peptide that binds ⊖ charged heparin
<b>Warfarin</b>	Vitamin K (slow) +/- FFP or PCC (rapid)	
<b>Dabigatran</b>	Idarucizumab	Monoclonal antibody Fab fragments
<b>Direct factor Xa inhibitors</b>	Andexanet alfa	Recombinant modified factor Xa (inactive)

**Antiplatelets**

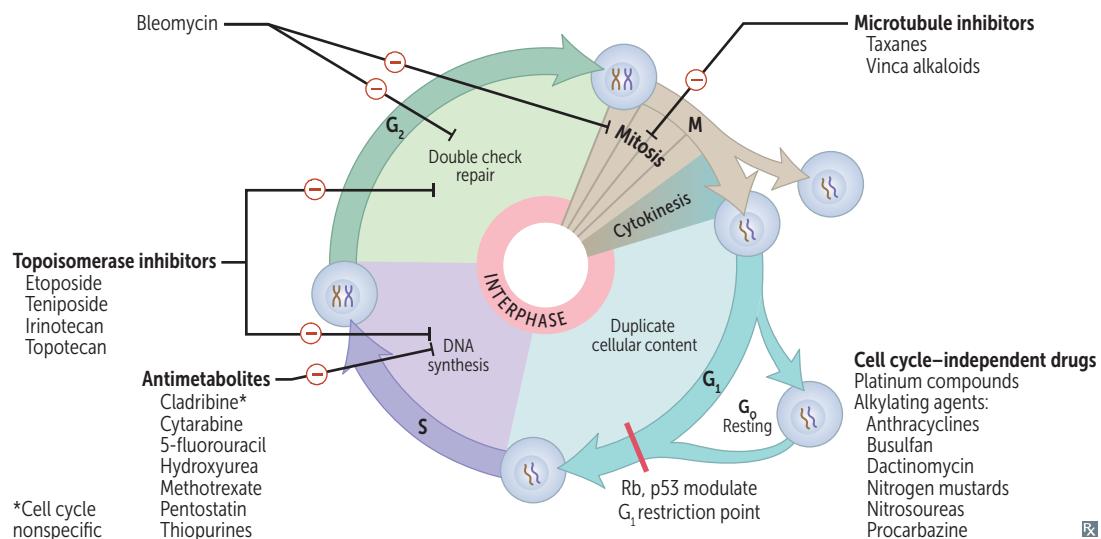
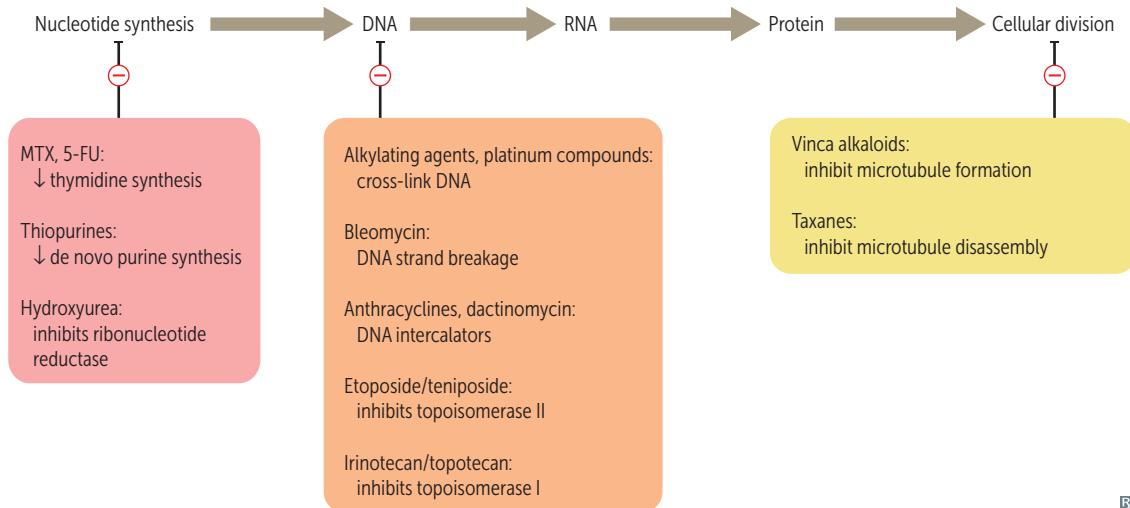
All work by ↓ platelet aggregation.

DRUG	MECHANISM	CLINICAL USE	ADVERSE EFFECTS
<b>Aspirin</b>	Irreversibly blocks COX → ↓ TXA <sub>2</sub> release	Acute coronary syndrome; coronary stenting. ↓ incidence or recurrence of thrombotic stroke	Gastric ulcers, tinnitus, allergic reactions, renal injury
<b>Clopidogrel, prasugrel, ticagrelor, ticlopidine</b>	Block ADP (P2Y <sub>12</sub> ) receptor → ↓ ADP-induced expression of GpIIb/IIIa	Same as aspirin; dual antiplatelet therapy	Neutropenia (ticlopidine); TTP may be seen
<b>Abciximab, eptifibatide, tirofiban</b>	Block GpIIb/IIIa (fibrinogen receptor) on activated platelets. Abciximab is made from monoclonal antibody Fab fragments	Unstable angina, percutaneous coronary intervention	Bleeding, thrombocytopenia
<b>Cilostazol, dipyridamole</b>	Block phosphodiesterase → ↓ cAMP in platelets	Intermittent claudication, stroke prevention, cardiac stress testing, prevention of coronary stent restenosis	Nausea, headache, facial flushing, hypotension, abdominal pain

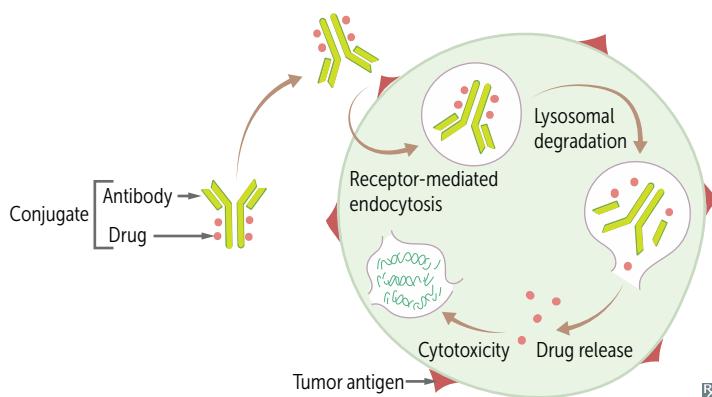
**Thrombolytics**

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. Nonspecific reversal with antifibrinolytics (eg, aminocaproic acid, tranexamic acid), platelet transfusions, and factor corrections (eg, cryoprecipitate, FFP, PCC).

**Cancer therapy—cell cycle****Cancer therapy—targets**

### Antibody-drug conjugates



Formed by linking monoclonal antibodies with cytotoxic chemotherapeutic drugs.

Antibody selectivity against tumor antigens allows targeted drug delivery to tumor cells while sparing healthy cells → ↑ efficacy and ↓ toxicity.

Example: ado-trastuzumab emtansine (T-DM1) for HER2 + breast cancer.

### Antitumor antibiotics

All are cell cycle nonspecific, except bleomycin which is G<sub>2</sub>/M phase specific.

DRUG	MECHANISM	CLINICAL USE	ADVERSE EFFECTS
<b>Bleomycin</b>	Induces free radical formation → breaks in DNA strands	Testicular cancer, Hodgkin lymphoma	Pulmonary fibrosis, skin hyperpigmentation
<b>Dactinomycin (actinomycin D)</b>	Intercalates into DNA, preventing RNA synthesis	Wilms tumor, Ewing sarcoma, rhabdomyosarcoma	Myelosuppression
<b>Anthracyclines</b> <i>Doxorubicin, daunorubicin</i>	Generate free radicals Intercalate in DNA → breaks in DNA → ↓ replication Inhibit topoisomerase II	Solid tumors, leukemias, lymphomas	Dilated cardiomyopathy (often irreversible; prevent with dexrazoxane), myelosuppression, alopecia

**Antimetabolites**

All are S-phase specific except cladribine, which is cell cycle nonspecific.

DRUG	MECHANISM	CLINICAL USE	ADVERSE EFFECTS
<b>Thiopurines</b> <b>Azathioprine, 6-mercaptopurine</b>	Purine (thiol) analogs → ↓ de novo purine synthesis AZA is converted to 6-MP, which is then activated by HGPRT	Rheumatoid arthritis, IBD, SLE, ALL; steroid-refractory disease Prevention of organ rejection Weaning from steroids	Myelosuppression; GI, liver toxicity 6-MP is inactivated by xanthine oxidase (↑ toxicity with allopurinol or febuxostat)
<b>Cladribine, pentostatin</b>	Purine analogs → multiple mechanisms (eg, inhibition of ADA, DNA strand breaks)	Hairy cell leukemia	Myelosuppression
<b>Cytarabine (arabinofuranosyl cytidine)</b>	Pyrimidine analog → DNA chain termination Inhibits DNA polymerase	Leukemias (AML), lymphomas	Myelosuppression
<b>5-Fluorouracil</b>	Pyrimidine analog bioactivated to 5-FdUMP → thymidylate synthase inhibition → ↓ dTMP → ↓ DNA synthesis Capecitabine is a prodrug	Colon cancer, pancreatic cancer, actinic keratosis, basal cell carcinoma (topical) Effects enhanced with the addition of leucovorin	Myelosuppression, palmar-plantar erythrodysesthesia (hand-foot syndrome)
<b>Hydroxyurea</b>	Inhibits ribonucleotide reductase → ↓ DNA synthesis	Myeloproliferative disorders (eg, CML, polycythemia vera), sickle cell disease (↑ HbF)	Severe myelosuppression, megaloblastic anemia
<b>Methotrexate</b>	Folic acid analog that competitively inhibits dihydrofolate reductase → ↓ dTMP → ↓ DNA synthesis	Cancers: leukemias (ALL), lymphomas, choriocarcinoma, sarcomas Nonneoplastic: ectopic pregnancy, medical abortion (with misoprostol), rheumatoid arthritis, psoriasis, IBD, vasculitis	Myelosuppression (reversible with leucovorin “rescue”), hepatotoxicity, mucositis (eg, mouth ulcers), pulmonary fibrosis, folate deficiency (teratogenic), nephrotoxicity

**Alkylating agents**

All are cell cycle nonspecific.

DRUG	MECHANISM	CLINICAL USE	ADVERSE EFFECTS
<b>Busulfan</b>	Cross-links DNA	Used to ablate patient's bone marrow before bone marrow transplantation	Severe myelosuppression (in almost all cases), pulmonary fibrosis, hyperpigmentation
<b>Nitrogen mustards</b> <i>Cyclophosphamide, ifosfamide</i>	Cross-link DNA Require bioactivation by liver	Solid tumors, leukemia, lymphomas, rheumatic disease (eg, SLE, granulomatosis with polyangiitis)	Myelosuppression, SIADH, Fanconi syndrome (ifosfamide), hemorrhagic cystitis and bladder cancer (prevent with mesna)
<b>Nitrosoureas</b> <i>Carmustine, lomustine</i>	Cross-link DNA Require bioactivation Cross blood-brain barrier → CNS entry	Brain tumors (including glioblastoma multiforme) Put <b>nitro</b> in your <b>Mustang</b> and travel the <b>globe</b>	CNS toxicity (convulsions, dizziness, ataxia)
<b>Procarbazine</b>	Mechanism unknown Weak MAO inhibitor	Hodgkin lymphoma, brain tumors	Bone marrow suppression, pulmonary toxicity, leukemia, disulfiram-like reaction

**Platinum compounds**

Cisplatin, carboplatin, oxaliplatin.

MECHANISM	Cross-link DNA. Cell cycle nonspecific.
CLINICAL USE	Solid tumors (eg, testicular, bladder, ovarian, GI, lung), lymphomas.
ADVERSE EFFECTS	Nephrotoxicity (eg, Fanconi syndrome; prevent with amifostine), peripheral neuropathy, ototoxicity.

**Microtubule inhibitors**

All are M-phase specific.

DRUG	MECHANISM	CLINICAL USE	ADVERSE EFFECTS
<b>Taxanes</b> <i>Docetaxel, paclitaxel</i>	Hyper <b>stabilize</b> polymerized microtubules → prevent mitotic spindle breakdown	Various tumors (eg, ovarian and breast carcinomas)	Myelosuppression, neuropathy, hypersensitivity <b>Taxes stabilize society</b>
<b>Vinca alkaloids</b> <i>Vincristine, vinblastine</i>	Bind β-tubulin and inhibit its polymerization into microtubules → prevent mitotic spindle formation	Solid tumors, leukemias, Hodgkin and non-Hodgkin lymphomas	Vincristine ( <b>crisps</b> the nerves): neurotoxicity (axonal neuropathy), constipation (including ileus) Vinblastine ( <b>blasts</b> the marrow): myelosuppression

**Topoisomerase inhibitors**

All cause ↑ DNA degradation resulting in cell cycle arrest in S and G<sub>2</sub> phases.

DRUG	MECHANISM	CLINICAL USE	ADVERSE EFFECTS
<b>Irinotecan, topotecan</b>	Inhibit topoisomerase I “-tecone”	Colon, ovarian, small cell lung cancer	Severe myelosuppression, diarrhea
<b>Etoposide, teniposide</b>	Inhibit topoisomerase II “-bothside”	Testicular, small cell lung cancer, leukemia, lymphoma	Myelosuppression, alopecia

**Tamoxifen**

MECHANISM	Selective estrogen receptor modulator with complex mode of action: antagonist in breast tissue, partial agonist in endometrium and bone. Blocks the binding of estrogen to ER in ER + cells.
CLINICAL USE	Prevention and treatment of breast cancer, prevention of gynecomastia in patients undergoing prostate cancer therapy.
ADVERSE EFFECTS	Hot flashes, ↑ risk of thromboembolic events (eg, DVT, PE) and endometrial cancer.

**Anticancer monoclonal antibodies**

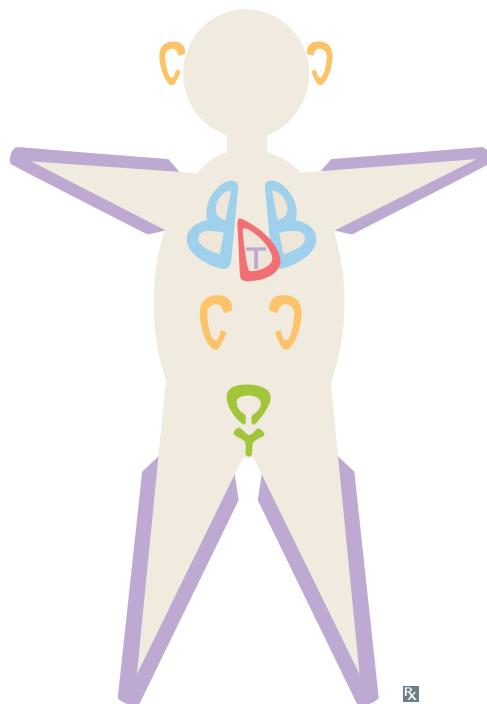
AGENT	TARGET	CLINICAL USE	ADVERSE EFFECTS
<b>Alemtuzumab</b>	CD52	Chronic lymphocytic leukemia (CLL), multiple sclerosis.	↑ risk of infections and autoimmunity (eg, ITP)
<b>Bevacizumab</b>	VEGF (inhibits blood vessel formation)	Colorectal cancer (CRC), renal cell carcinoma (RCC), non–small cell lung cancer (NSCLC), angioproliferative retinopathy	Hemorrhage, blood clots, impaired wound healing
<b>Cetuximab, panitumumab</b>	EGFR	Metastatic CRC (wild-type RAS), head and neck cancer	Rash, elevated LFTs, diarrhea
<b>Rituximab</b>	CD20	Non-Hodgkin lymphoma, CLL, rheumatoid arthritis, ITP, TTP, AIHA, multiple sclerosis	↑ risk of PML in patients with JC virus
<b>Trastuzumab</b>	HER2 (“trust HER”)	Breast cancer, gastric cancer	Dilated <b>cardiomyopathy</b> (often reversible). “Heartcepitin”
<b>Pembrolizumab, nivolumab, cemiplimab</b>	PD-1	Various tumors (eg, NSCLC, RCC, melanoma, urothelial carcinoma)	↑ risk of autoimmunity (eg, dermatitis, enterocolitis, hepatitis, pneumonitis, endocrinopathies)
<b>Atezolizumab, durvalumab, avelumab</b>	PD-L1		
<b>Ipilimumab</b>	CTLA-4		

**Anticancer small molecule inhibitors**

AGENT	TARGET	CLINICAL USE	ADVERSE EFFECTS
<b>Alectinib</b>	<b>ALK</b>	Non–small cell lung cancer	Edema, rash, diarrhea
<b>Erlotinib, gefitinib, afatinib</b>	<b>EGFR</b>	Non–small cell lung cancer	Rash, diarrhea
<b>Imatinib, dasatinib, nilotinib</b>	BCR-ABL (also other tyrosine kinases [eg, c-KIT])	CML, ALL, GISTs	Myelosuppression, ↑ LFTs, edema, myalgias
<b>Ruxolitinib</b>	JAK1/2	Polycythemia vera	Bruises, ↑ LFTs
<b>Bortezomib, ixazomib, carfilzomib</b>	Proteasome (induce arrest at G2-M phase → apoptosis)	Multiple myeloma, mantle cell lymphoma	Peripheral neuropathy, herpes zoster reactivation
<b>Vemurafenib, encorafenib, dabrafenib</b>	<b>BRAF</b>	Melanoma Often co-administered with MEK inhibitors (eg, trametinib)	Rash, fatigue, nausea, diarrhea
<b>Palbociclib</b>	Cyclin-dependent kinase 4/6 (induces arrest at G1-S phase → apoptosis)	Breast cancer	Myelosuppression, pneumonitis
<b>Olaparib</b>	Poly(ADP-ribose) polymerase (↓ DNA repair)	Breast, ovarian, pancreatic, and prostate cancers	Myelosuppression, edema, diarrhea

**Amelioration of adverse effects of chemotherapy**

DRUG	MECHANISM	CLINICAL USE
<b>Amifostine</b>	Free radical scavenger	Nephrotoxicity from platinum compounds
<b>Dexrazoxane</b>	Iron chelator	Cardiotoxicity from anthracyclines
<b>Leucovorin (folinic acid)</b>	Tetrahydrofolate precursor	Myelosuppression from methotrexate (leucovorin “rescue”); also enhances the effects of 5-FU
<b>Mesna</b>	Sulfhydryl compound that binds acrolein (toxic metabolite of cyclophosphamide/ifosfamide)	Hemorrhagic cystitis from cyclophosphamide/ifosfamide
<b>Rasburicase</b>	Recombinant uricase that catalyzes metabolism of uric acid to allantoin	Tumor lysis syndrome
<b>Ondansetron, granisetron</b>	5-HT <sub>3</sub> receptor antagonists	Acute nausea and vomiting (usually within 1-2 hr after chemotherapy)
<b>Prochlorperazine, metoclopramide</b>	D <sub>2</sub> receptor antagonists	
<b>Aprepitant, fosaprepitant</b>	NK <sub>1</sub> receptor antagonists	Delayed nausea and vomiting (>24 hr after chemotherapy)
<b>Filgrastim, sargramostim</b>	Recombinant G(M)-CSF	Neutropenia
<b>Epoetin alfa</b>	Recombinant erythropoietin	Anemia

**Key chemotoxicities**

Cisplatin, Carboplatin → ototoxicity

Vincristine → peripheral neuropathy  
Bleomycin, Busulfan → pulmonary fibrosis  
Doxorubicin, Daunorubicin → cardiotoxicity  
Trastuzumab → cardiotoxicity  
Cisplatin, Carboplatin → nephrotoxicity

Cyclophosphamide → hemorrhagic cystitis

Nonspecific common toxicities of nearly all cytotoxic chemotherapies include myelosuppression (neutropenia, anemia, thrombocytopenia), GI toxicity (nausea, vomiting, mucositis), alopecia.

# Musculoskeletal, Skin, and Connective Tissue

*“Rigid, the skeleton of habit alone upholds the human frame.”*

—Virginia Woolf, *Mrs. Dalloway*

*“Beauty may be skin deep, but ugly goes clear to the bone.”*

—Redd Foxx

*“The finest clothing made is a person’s own skin, but, of course, society demands something more than this.”*

—Mark Twain

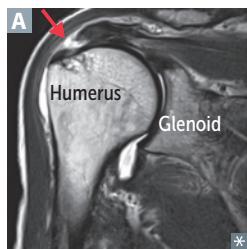
*“To thrive in life you need three bones. A wishbone. A backbone. And a funny bone.”*

—Reba McEntire

This chapter provides information you will need to understand certain anatomical dysfunctions, rheumatic diseases, and dermatologic conditions. Be able to interpret 3D anatomy in the context of radiologic imaging. For the rheumatic diseases, create instructional cases or personas that include the most likely presentation and symptoms: risk factors, gender, important markers (eg, autoantibodies), and other epidemiologic factors. Doing so will allow you to answer the higher order questions that are likely to be asked on the exam.

► Anatomy and Physiology	456
► Pathology	469
► Dermatology	487
► Pharmacology	499

## ► MUSCULOSKELETAL, SKIN, AND CONNECTIVE TISSUE—ANATOMY AND PHYSIOLOGY

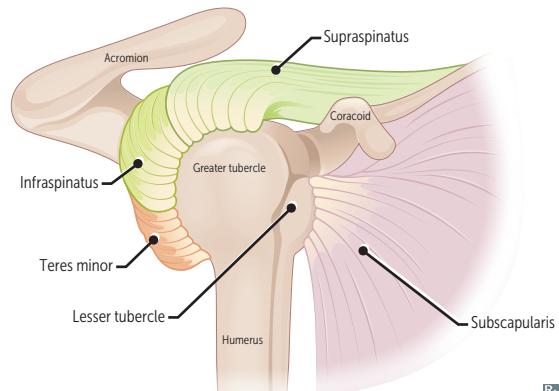
**Rotator cuff muscles**

Shoulder muscles that form the rotator cuff:

- **Supraspinatus** (suprascapular nerve)—abducts arm initially (before the action of the deltoid); most common rotator cuff injury (trauma or degeneration and impingement → tendinopathy or tear [arrow in A]), assessed by “empty/full can” test
- **Infraspinatus** (suprascapular nerve)—externally rotates arm; pitching injury
- **teres minor** (axillary nerve)—adducts and externally rotates arm
- **Subscapularis** (upper and lower subscapular nerves)—internally rotates and adducts arm

Innervated primarily by C5-C6.

**SItS** (small t is for teres **minor**).

**Arm abduction**

DEGREE	MUSCLE	NERVE
0°–15°	Supraspinatus	Suprascapular
15°–90°	Deltoid	Axillary
> 90°	Trapezius	Accessory
> 90°	Serratus Anterior	Long Thoracic ( <b>SALT</b> )

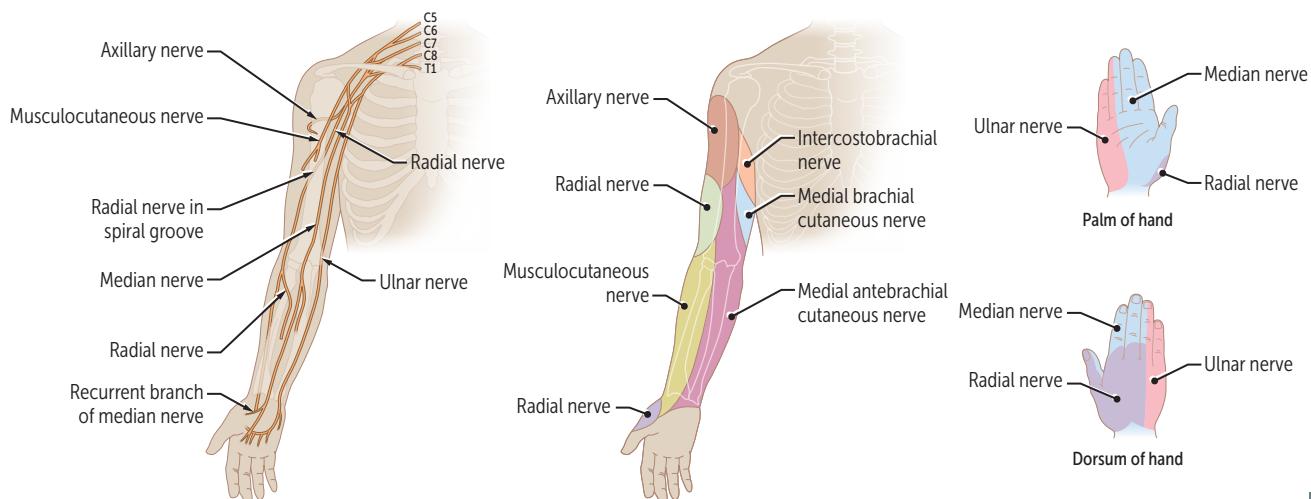
**Upper extremity nerves**

NERVE	CAUSES OF INJURY	PRESENTATION
<b>Axillary (C5-C6)</b>	Fractured surgical neck of humerus Anterior dislocation of humerus	Flattened deltoid Loss of arm abduction at shoulder (> 15°) Loss of sensation over deltoid and lateral arm
<b>Musculocutaneous (C5-C7)</b>	Upper trunk compression	↓ biceps (C5-6) reflex Loss of forearm flexion and supination Loss of sensation over radial and dorsal forearm
<b>Radial (C5-T1)</b>	Compression of axilla, eg, due to crutches or sleeping with arm over chair (“Saturday night palsy”) Midshaft fracture of humerus Repetitive pronation/supination of forearm, eg, due to screwdriver use (“finger drop”)	Injuries above the elbow cause loss of sensation over posterior arm/forearm and dorsal hand, wrist drop (loss of elbow, wrist, and finger extension) with ↓ grip strength (wrist extension necessary for maximal action of flexors) Injuries below the elbow cause distal paresthesias without wrist drop Tricep function and posterior arm sensation spared in midshaft fracture

**Upper extremity nerves (continued)**

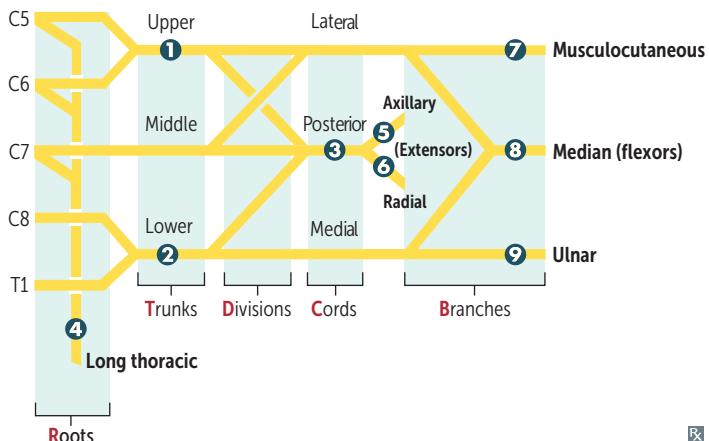
NERVE	CAUSES OF INJURY	PRESENTATION
<b>Median (C5-T1)</b>	Supracondylar fracture of humerus → proximal lesion of the nerve Carpal tunnel syndrome and wrist laceration → distal lesion of the nerve	“Ape hand” and “Hand of benediction” Loss of wrist flexion and function of the lateral two <b>Lumbricals</b> , <b>Opponens pollicis</b> , <b>Abductor pollicis brevis</b> , <b>Flexor pollicis brevis (LOAF)</b> Loss of sensation over thenar eminence and dorsal and palmar aspects of lateral $3\frac{1}{2}$ fingers with proximal lesion
<b>Ulnar (C8-T1)</b>	Fracture of medial epicondyle of humerus “funny bone” (proximal lesion) Fractured hook of hamate (distal lesion) from fall on outstretched hand	“Ulnar claw” on digit extension Radial deviation of wrist upon flexion (proximal lesion) ↓ flexion of ulnar fingers, abduction and adduction of fingers (interossei), thumb adduction, actions of ulnar 2 lumbrical muscles Loss of sensation over ulnar $1\frac{1}{2}$ fingers including hypothenar eminence
<b>Recurrent branch of median nerve (C5-T1)</b>	Superficial laceration of palm	“Ape hand” Loss of thenar muscle group: opposition, abduction, and flexion of thumb No loss of sensation

Humerus fractures, proximally to distally, follow the **ARM** (**Axillary** → **Radial** → **Median**)



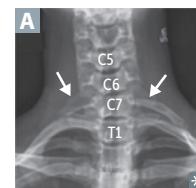
**Brachial plexus lesions**

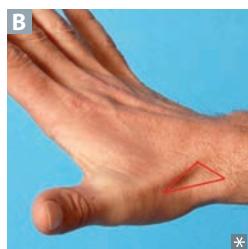
- ➊ Erb palsy ("waiter's tip")
- ➋ Klumpke palsy (claw hand)
- ➌ Wrist drop
- ➍ Winged scapula
- ➎ Deltoid paralysis
- ➏ "Saturday night palsy" (wrist drop)
- ➐ Difficulty flexing elbow, variable sensory loss
- ➑ Decreased thumb function, "hand of benediction"
- ➒ Intrinsic muscles of hand, claw hand



Divisions of brachial plexus:

Randy  
Travis  
Drinks  
Cold  
Beer

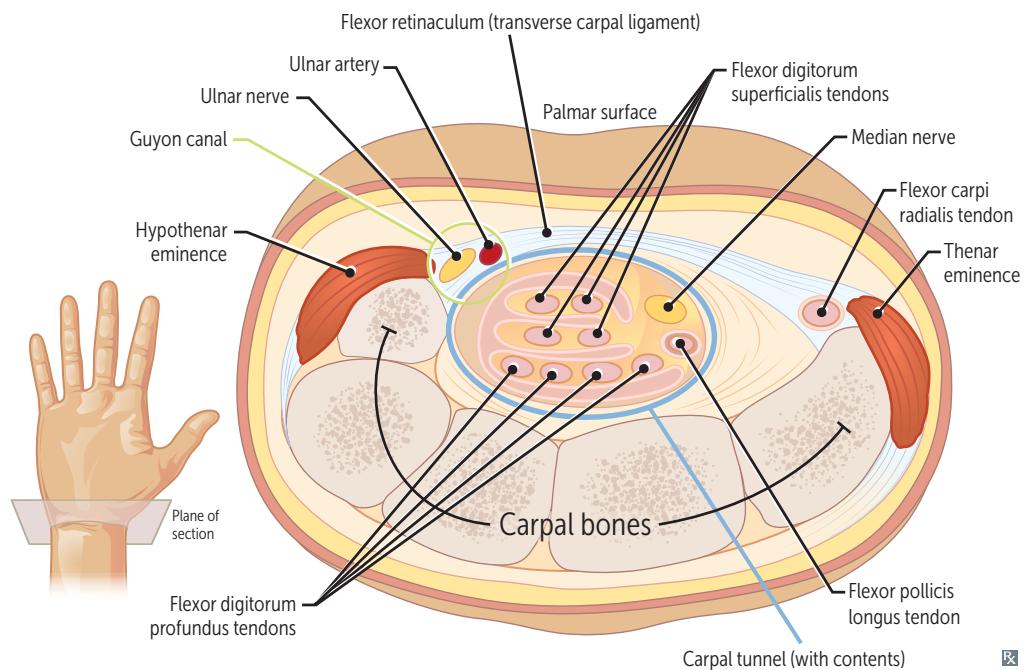
CONDITION	INJURY	CAUSES	MUSCLE DEFICIT	FUNCTIONAL DEFICIT	PRESENTATION
<b>Erb palsy ("waiter's tip")</b>	Traction or tear of <b>upper trunk</b> : C5-C6 roots	Infants—lateral traction on neck during delivery Adults—trauma	Deltoid, supraspinatus  Infraspinatus, supraspinatus  Biceps brachii Herb gets DIBs on tips	Abduction (arm hangs by side)  Lateral rotation (arm medially rotated)  Flexion, supination (arm extended and pronated)	
<b>Klumpke palsy</b>	Traction or tear of <b>lower trunk</b> : C8-T1 roots	Infants—upward force on arm during delivery Adults—trauma (eg, grabbing a tree branch to break a fall)	Intrinsic hand muscles: lumbricals, interossei, thenar, hypothenar	Claw hand: lumbricals normally flex MCP joints and extend DIP and PIP joints	
<b>Thoracic outlet syndrome</b>	Compression of <b>lower trunk</b> and subclavian vessels, most commonly within the scalene triangle	Cervical rib (arrows in A), Pancoast tumor	Same as Klumpke palsy	Atrophy of intrinsic hand muscles; ischemia, pain, and edema due to vascular compression	 A
<b>Winged scapula</b>	Lesion of long thoracic nerve, roots C5-C7 ("wings of heaven")	Axillary node dissection after mastectomy, stab wounds	Serratus anterior	Inability to anchor scapula to thoracic cage → cannot abduct arm above horizontal position B	 B

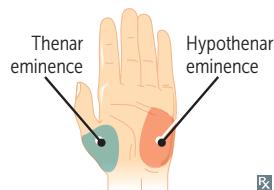
**Wrist region**

**Scaphoid, lunate, triquetrum, pisiform, hamate, capitate, trapezoid, trapezium A.** (So long to pinky, here comes the thumb)

Scaphoid (palpable in anatomic snuff box **B**) is the most commonly fractured carpal bone, typically due to a fall on an outstretched hand. Complications of proximal scaphoid fractures include avascular necrosis and nonunion due to retrograde blood supply from a branch of the radial artery. Occult fracture not always seen on initial x-ray.

Dislocation of lunate may impinge median nerve and cause carpal tunnel syndrome.



**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 (ulnar)—abduct the fingers.  
Palmar interossei (ulnar)—adduct the fingers.  
Lumbricals (1st/2nd, median; 3rd/4th, ulnar)—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** = Dorsals **AB**duct.  
**PAD** = Palmars **AD**duct.

**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.

SIGN	“Ulnar claw”	“Hand of benediction”	“Median claw”	“OK gesture”
PRESENTATION				
CONTEXT	Extending fingers/at rest	Making a fist	Extending fingers/at rest	Making a fist
LOCATION OF LESION	Distal ulnar nerve	Proximal median nerve	Distal median nerve	Proximal ulnar nerve

Note: Atrophy of the thenar eminence can be seen in median nerve lesions, while atrophy of the hypothenar eminence can be seen in ulnar nerve lesions.

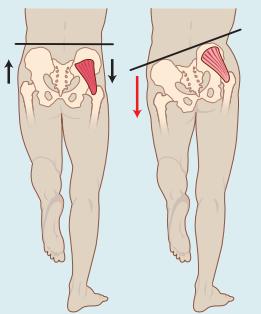
**Actions of hip muscles**

ACTION	MUSCLES
<b>Abductors</b>	Gluteus medius, gluteus minimus
<b>Adductors</b>	Adductor magnus, adductor longus, adductor brevis
<b>Extensors</b>	Gluteus maximus, semitendinosus, semimembranosus
<b>Flexors</b>	Iliopsoas, rectus femoris, tensor fascia lata, pectineus, sartorius
<b>Internal rotation</b>	Gluteus medius, gluteus minimus, tensor fascia latae
<b>External rotation</b>	Iliopsoas, gluteus maximus, piriformis, obturator

**Lower extremity nerves**

NERVE	INNERVATION	CAUSE OF INJURY	PRESNTATION/COMMENTS
<b>Iliohypogastric (T12-L1)</b>	Sensory—suprapubic region Motor—transversus abdominis and internal oblique	Abdominal surgery	Burning or tingling pain in surgical incision site radiating to inguinal and suprapubic region
<b>Genitofemoral nerve (L1-L2)</b>	Sensory—scrotum/labia majora, medial thigh Motor—cremaster	Laparoscopic surgery	↓ upper medial thigh and anterior thigh sensation beneath the inguinal ligament (lateral part of the femoral triangle); absent cremasteric reflex
<b>Lateral femoral cutaneous (L2-L3)</b>	Sensory—anterior and lateral thigh	Tight clothing, obesity, pregnancy, pelvic procedures	↓ thigh sensation (anterior and lateral)
<b>Obturator (L2-L4)</b>	Sensory—medial thigh Motor—obturator externus, adductor longus, adductor brevis, gracilis, pectenue, adductor magnus	Pelvic surgery	↓ thigh sensation (medial) and adduction
<b>Femoral (L2-L4)</b>	Sensory—anterior thigh, medial leg Motor—quadriceps, iliacus, pectenue, sartorius	Pelvic fracture	↓ leg extension (↓ patellar reflex)
<b>Sciatic (L4-S3)</b>	Motor—semitendinosus, semimembranosus, biceps femoris, adductor magnus	Herniated disc, posterior hip dislocation	Splits into common peroneal and tibial nerves
<b>Common (fibular) peroneal (L4-S2)</b>	Superficial peroneal nerve: <ul style="list-style-type: none"><li>▪ Sensory—dorsum of foot (except webspace between hallux and 2nd digit)</li><li>▪ Motor—peroneus longus and brevis</li></ul> Deep peroneal nerve: <ul style="list-style-type: none"><li>▪ Sensory—webspace between hallux and 2nd digit</li><li>▪ Motor—tibialis anterior</li></ul>	Trauma or compression of lateral aspect of leg, fibular neck fracture	<b>PED</b> = Peroneal Everts and Dorsiflexes; if injured, foot drop <b>PED</b> Loss of sensation on dorsum of foot <b>Foot drop</b> —inverted and plantarflexed at rest, loss of eversion and dorsiflexion; “steppage gait”

**Lower extremity nerves (continued)**

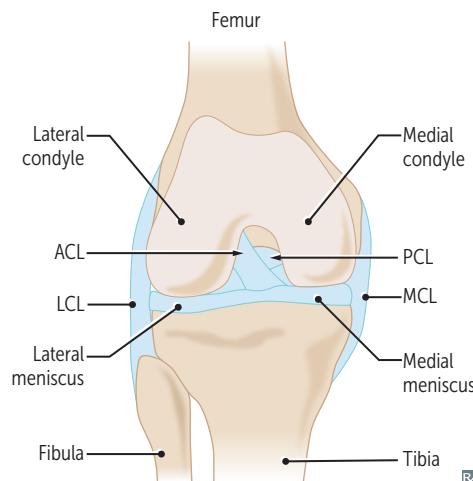
NERVE	INNERVATION	CAUSE OF INJURY	PRESENTATION/COMMENTS
<b>Tibial (L4-S3)</b> 	Sensory—sole of foot Motor—biceps femoris (long head), triceps surae, plantaris, popliteus, flexor muscles of foot	Knee trauma, Baker cyst (proximal lesion); tarsal tunnel syndrome (distal lesion)	<b>TIP</b> = Tibial Inverts and Plantarflexes; if injured, can't stand on <b>TIP</b> toes Inability to curl toes and loss of sensation on sole; in proximal lesions, foot everted at rest with weakened inversion and plantar flexion
<b>Superior gluteal (L4-S1)</b>  Normal      Trendelenburg sign 	Motor—gluteus medius, gluteus minimus, tensor fascia latae	Iatrogenic injury during intramuscular injection to superomedial gluteal region (prevent by choosing superolateral quadrant, preferably anterolateral region)	Trendelenburg sign/gait—pelvis tilts because weight-bearing leg cannot maintain alignment of pelvis through hip abduction Lesion is contralateral to the side of the hip that drops, ipsilateral to extremity on which the patient stands
<b>Inferior gluteal (L5-S2)</b>	Motor—gluteus maximus	Posterior hip dislocation	Difficulty climbing stairs, rising from seated position; loss of hip extension
<b>Pudendal (S2-S4)</b>	Sensory—perineum Motor—external urethral and anal sphincters	Stretch injury during childbirth, prolonged cycling, horseback riding	↓ sensation in perineum and genital area; can cause fecal and/or urinary incontinence Can be blocked with local anesthetic during childbirth using ischial spine as a landmark for injection

**Knee exam**

Lateral femoral condyle to anterior tibia: **ACL**.

Medial femoral condyle to posterior tibia: **PCL**.

**LAMP.**



TEST	PROCEDURE
<b>Anterior drawer sign</b>	Bending knee at 90° angle, ↑ anterior gliding of tibia (relative to femur) due to ACL injury Lachman test also tests ACL, but is more sensitive (↑ anterior gliding of tibia [relative to femur] with knee bent at 30° angle)
<b>Posterior drawer sign</b>	Bending knee at 90° angle, ↑ posterior gliding of tibia due to PCL injury
<b>Abnormal passive abduction</b>	Also called valgus stress test. Knee either extended or at ~ 30° angle, lateral (valgus) force → medial space widening of tibia → MCL injury
<b>Abnormal passive adduction</b>	Also called varus stress test. Knee either extended or at ~ 30° angle, medial (varus) force → lateral space widening of tibia → LCL injury
<b>McMurray test</b>	During flexion and extension of knee with rotation of tibia/foot ( <b>LIME</b> ): <ul style="list-style-type: none"><li>▪ Pain, “popping” on internal rotation and varus force → <b>Lateral meniscal tear</b> (Internal rotation stresses lateral meniscus)</li><li>▪ Pain, “popping” on external rotation and valgus force → <b>Medial meniscal tear</b> (External rotation stresses medial meniscus)</li></ul>

ACL tear

PCL tear

MCL tear

LCL tear

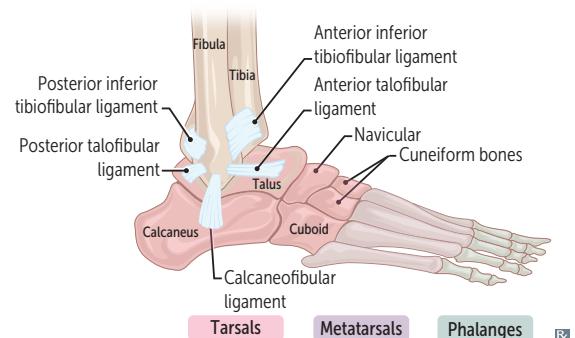
Lateral meniscal tear

Medial meniscal tear

**Ankle sprains**

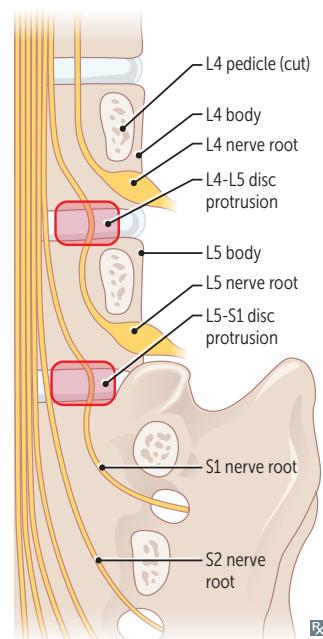
Anterior talofibular ligament—most common ankle sprain overall, classified as a low ankle sprain. Due to overinversion/supination of foot. Always tears first.

Anterior inferior tibiofibular ligament—most common high ankle sprain.

**Signs of lumbosacral radiculopathy**

Paresthesia and weakness related to specific lumbosacral spinal nerves. Intervertebral disc (nucleus pulposus) herniates posterolaterally through annulus fibrosus (outer ring) into central canal due to thin posterior longitudinal ligament and thicker anterior longitudinal ligament along midline of vertebral bodies. Nerve affected is usually below the level of herniation.

Disc level herniation Nerve root affected	L3-L4	L4-L5	L5-S1
	L4	L5	S1
Dermatome affected			
Clinical findings	Weakness of knee extension ↓ patellar reflex	Weakness of dorsiflexion Difficulty in heel walking	Weakness of plantar flexion Difficulty in toe walking ↓ Achilles reflex

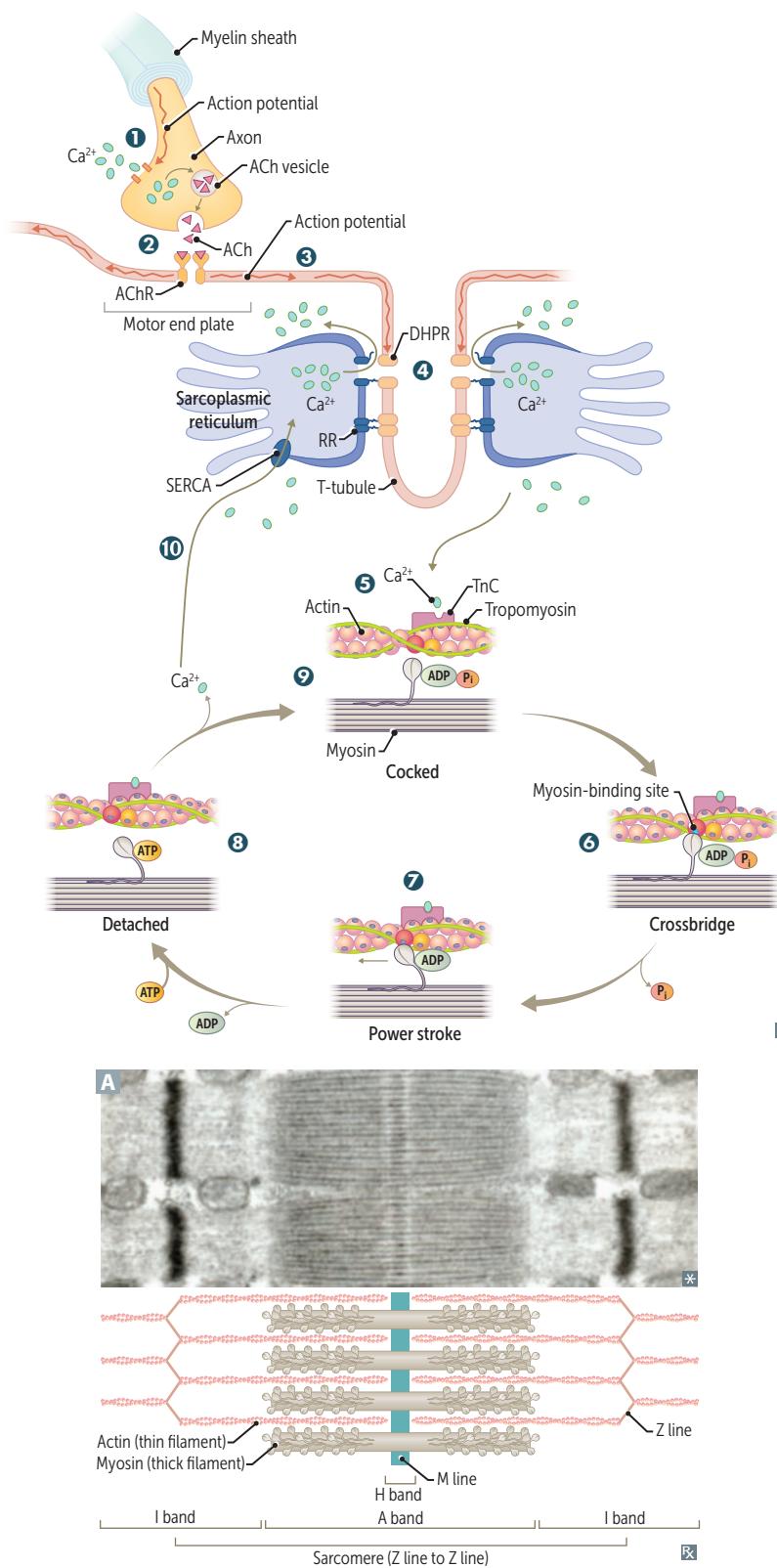
**Neurovascular pairing**

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
<b>Axilla/lateral thorax</b>	Long thoracic	Lateral thoracic
<b>Surgical neck of humerus</b>	Axillary	Posterior circumflex
<b>Midshaft of humerus</b>	Radial	Deep brachial
<b>Distal humerus/cubital fossa</b>	Median	Brachial
<b>Popliteal fossa</b>	Tibial	Popliteal
<b>Posterior to medial malleolus</b>	Tibial	Posterior tibial

### Motoneuron action potential to muscle contraction

T-tubules are extensions of plasma membrane in contact with the sarcoplasmic reticulum, allowing for coordinated contraction of striated muscles.



- 1 Action potential opens presynaptic voltage-gated Ca<sup>2+</sup> channels, inducing acetylcholine (ACh) release.
- 2 Postsynaptic ACh binding leads to muscle cell depolarization at the motor end plate.
- 3 Depolarization travels over the entire muscle cell and deep into the muscle via the T-tubules.
- 4 Membrane depolarization induces conformational changes in the voltage-sensitive dihydropyridine receptor (DHPR) and its mechanically coupled ryanodine receptor (RR) → Ca<sup>2+</sup> release from the sarcoplasmic reticulum into the cytoplasm.
- 5 Tropomyosin is blocking myosin-binding sites on the actin filament. Released Ca<sup>2+</sup> binds to troponin C (TnC), shifting tropomyosin to expose the myosin-binding sites.
- 6 The myosin head binds strongly to actin, forming a crossbridge. P<sub>i</sub> is then released, initiating the power stroke.
- 7 During the power stroke, force is produced as myosin pulls on the thin filament **A**. Muscle shortening occurs, with shortening of **H** and **I** bands and between **Z** lines (**HIZ** shrinkage). The **A** band remains the same length (**A** band is **Always** the same length). ADP is released at the end of the power stroke.
- 8 Binding of new ATP molecule causes detachment of myosin head from actin filament. Ca<sup>2+</sup> is resequestered.
- 9 ATP hydrolysis into ADP and P<sub>i</sub> results in myosin head returning to high-energy position (cocked). The myosin head can bind to a new site on actin to form a crossbridge if Ca<sup>2+</sup> remains available.
- 10 Reuptake of calcium by sarco(endo)plasmic reticulum Ca<sup>2+</sup> ATPase (SERCA) → muscle relaxation.

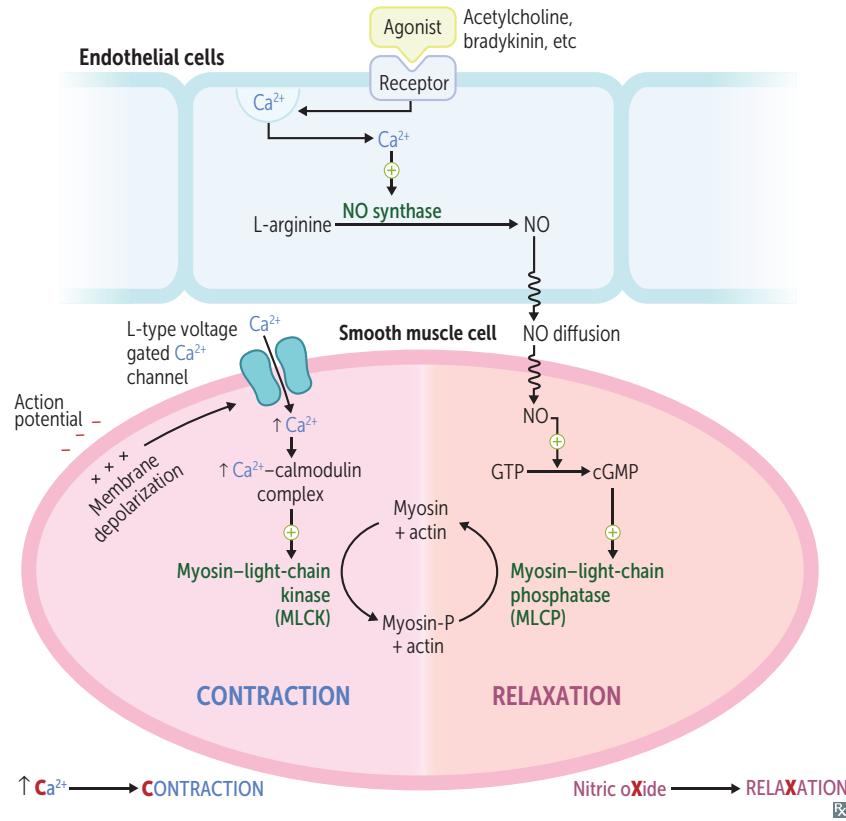
### Types of skeletal muscle fibers

	Type I	Type II
CONTRACTION VELOCITY	Slow	Fast
FIBER COLOR	Red	White
PREDOMINANT METABOLISM	Oxidative phosphorylation → sustained contraction	Anaerobic glycolysis
MITOCHONDRIA, MYOGLOBIN	↑	↓
TYPE OF TRAINING	Endurance training	Weight/resistance training, sprinting
NOTES	Think “1 slow red ox”	Think “2 fast white antelopes”

### Skeletal muscle adaptations

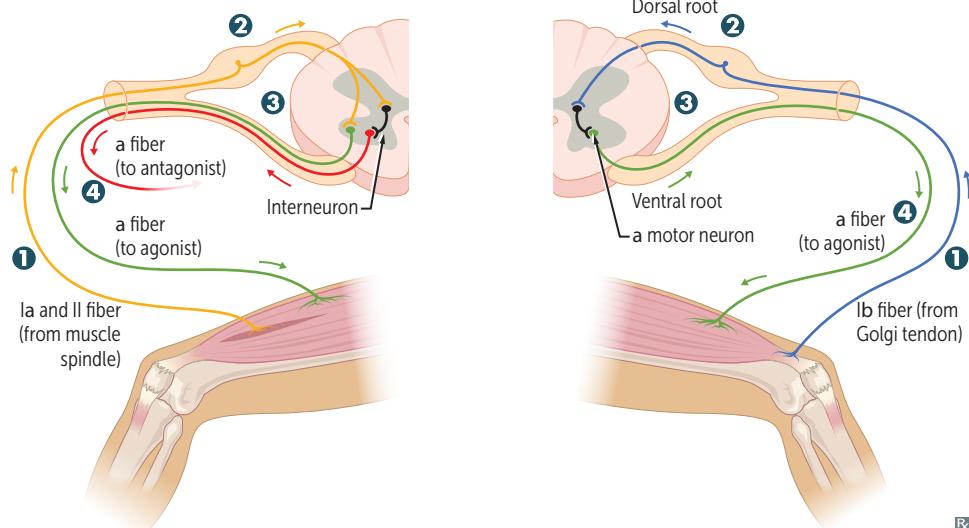
	Atrophy	Hypertrophy
MYOFIBRILS	↓ (removal via ubiquitin-proteasome system)	↑ (addition of sarcomeres in parallel)
MYONUCLEI	↓ (selective apoptosis)	↑ (fusion of satellite cells)

### Vascular smooth muscle contraction and relaxation



**Muscle proprioceptors** Specialized sensory receptors that relay information about muscle dynamics.

	<b>Muscle stretch receptors</b>	<b>Golgi tendon organ</b>
<b>PATHWAY</b>	① ↑ length and speed of stretch → ② via dorsal root ganglion (DRG) → ③ activation of inhibitory interneuron and $\alpha$ motor neuron → ④ simultaneous inhibition of antagonist muscle (prevents overstretching) and activation of agonist muscle (contraction).	① ↑ tension → ② via DRG → ③ activation of inhibitory interneuron → ④ inhibition of agonist muscle (reduced tension within muscle and tendon)
<b>LOCATION/INNERVATION</b>	Body of muscle/type Ia and II sensory axons	Tendons/type Ib sensory axons
<b>ACTIVATION BY</b>	↑ muscle stretch. Responsible for deep tendon reflexes	↑ muscle tension

**Bone formation****Endochondral ossification**

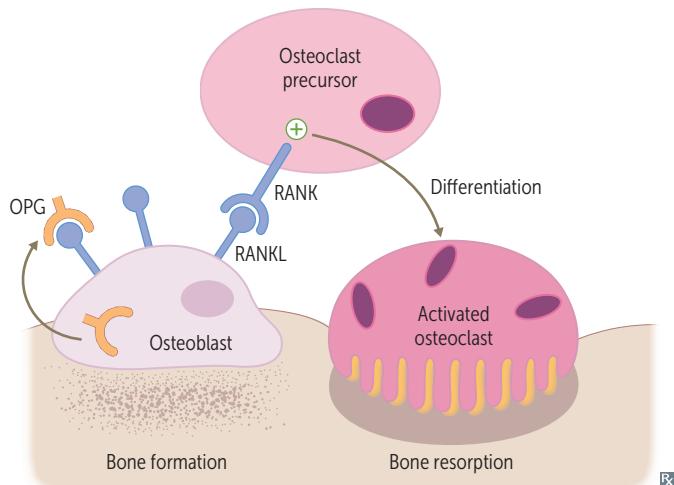
Bones of axial skeleton, appendicular skeleton, and base of skull. Cartilaginous model of bone is first made by chondrocytes. Osteoclasts and osteoblasts later replace with woven bone and then remodel to lamellar bone. In adults, woven bone occurs after fractures and in Paget disease. Defective in achondroplasia.

**Membranous ossification**

Bones of calvarium, facial bones, and clavicle. Woven bone formed directly without cartilage. Later remodeled to lamellar bone.

### Cell biology of bone

<b>Osteoblast</b>	Builds bone by secreting collagen and catalyzing mineralization in alkaline environment via ALP. Differentiates from mesenchymal stem cells in periosteum. Osteoblastic activity measured by bone ALP, osteocalcin, propeptides of type I procollagen.
<b>Osteoclast</b>	Dissolves (“crushes”) bone by secreting H <sup>+</sup> and collagenases. Differentiates from a fusion of monocyte/macrophage lineage precursors. RANK receptors on osteoclasts are stimulated by RANKL (RANK ligand, expressed on osteoblasts). OPG (osteoprotegerin, a RANKL decoy receptor) binds RANKL to prevent RANK-RANKL interaction → ↓ osteoclast activity.
<b>Parathyroid hormone</b>	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).
<b>Estrogen</b>	Inhibits apoptosis in bone-forming osteoblasts and induces apoptosis in bone-resorbing osteoclasts. Causes closure of epiphyseal plate during puberty. Estrogen deficiency (surgical or postmenopausal) → ↑ cycles of remodeling and bone resorption → ↑ risk of osteoporosis.



### ► MUSCULOSKELETAL, SKIN, AND CONNECTIVE TISSUE—PATHOLOGY

#### Overuse injuries of the elbow

<b>Medial epicondylitis (golfer's elbow)</b>	Repetitive flexion or idiopathic → pain near medial epicondyle.
<b>Lateral epicondylitis (tennis elbow)</b>	Repetitive extension (backhand shots) or idiopathic → pain near lateral epicondyle.

**Clavicle fractures**

Common in children and as birth trauma. Usually caused by a fall on outstretched hand or by direct trauma to shoulder. Weakest point at the junction of middle and lateral thirds; fractures at the middle third segment are most common **A**. Presents as shoulder drop, shortened clavicle (lateral fragment is depressed due to arm weight and medially rotated by arm adductors [eg, pectoralis major]).

**Wrist and hand injuries****Guyon canal syndrome**

Compression of ulnar nerve at wrist. Classically seen in cyclists due to pressure from handlebars.

**Carpal tunnel syndrome**

Entrapment of median nerve in carpal tunnel (between transverse carpal ligament and carpal bones) → nerve compression → paresthesia, pain, and numbness in distribution of median nerve. Thenar eminence atrophies **A** but sensation spared, because palmar cutaneous branch enters hand external to carpal tunnel.

Suggested by  $\oplus$  Tinel sign (percussion of wrist causes tingling) and Phalen maneuver ( $90^\circ$  flexion of wrist causes tingling). Associated with pregnancy (due to edema), rheumatoid arthritis, hypothyroidism, diabetes, acromegaly, dialysis-related amyloidosis; may be associated with repetitive use.

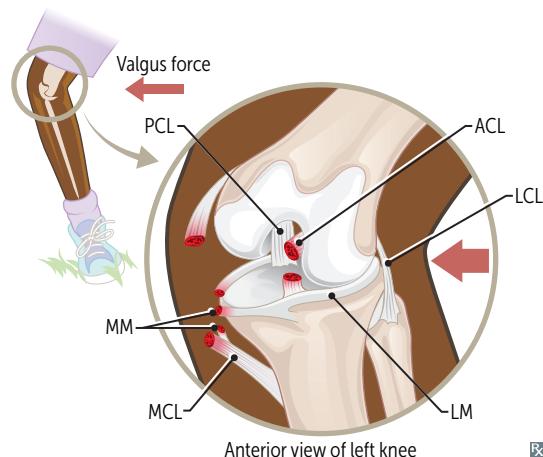
**Metacarpal neck fracture**

Also called boxer's fracture. Common fracture caused by direct blow with a closed fist (eg, from punching a wall). Most commonly seen in the 5th metacarpal **B**.

### Common knee conditions

#### "Unhappy triad"

Common injury in contact sports due to laterally directed force to a planted foot. Consists of damage to the ACL **A**, MCL, and medial meniscus (attached to MCL). However, lateral meniscus involvement is more common than medial meniscus involvement in conjunction with ACL and MCL injury. Presents with acute pain and signs of joint instability.



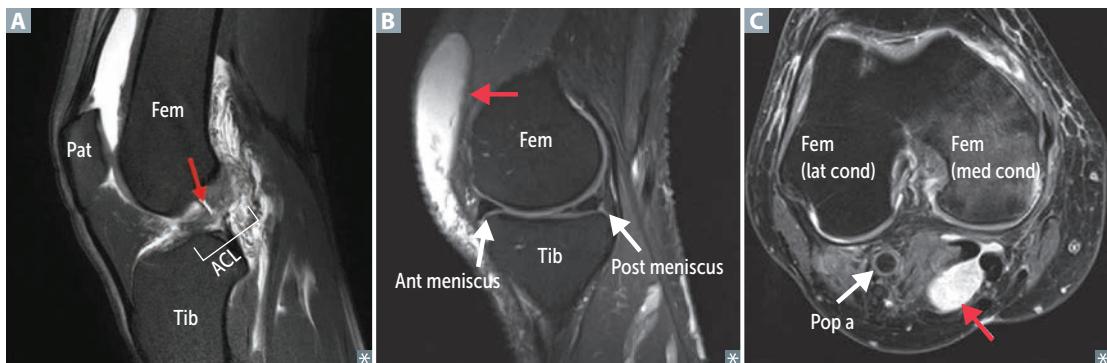
Anterior view of left knee

#### Prepatellar bursitis

Inflammation of the prepatellar bursa in front of the kneecap (red arrow in **B**). Can be caused by repeated trauma or pressure from excessive kneeling (also called "housemaid's knee").

#### Popliteal cyst

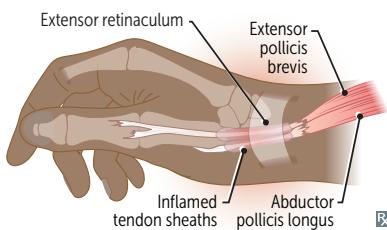
Also called Baker cyst. Popliteal fluid collection (red arrow in **C**) in gastrocnemius-semimembranosus bursa commonly communicating with synovial space and related to chronic joint disease (eg, osteoarthritis, rheumatoid arthritis).



### Common musculoskeletal conditions

#### De Quervain tenosynovitis

Noninflammatory thickening of abductor pollicis longus and extensor pollicis brevis tendons → pain or tenderness at radial styloid.  
 ⊕ Finkelstein test (pain at radial styloid with active or passive stretch of thumb tendons).  
 ↑ risk in new parent (lifting baby), golfers, racquet sport players, “thumb” texters.



#### Ganglion cyst

Fluid-filled swelling overlying joint or tendon sheath, most commonly at dorsal side of wrist. Arises from herniation of dense connective tissue. Usually resolves spontaneously.

#### Iliotibial band syndrome

Overuse injury of lateral knee that occurs primarily in runners. Pain develops 2° to friction of iliotibial band against lateral femoral epicondyle.

#### Limb compartment syndrome

↑ pressure within fascial compartment of a limb → venous outflow obstruction and arteriolar collapse → anoxia and necrosis. Causes include significant long bone fractures, reperfusion injury, animal venoms. Presents with severe pain and tense, swollen compartments with passive stretch of muscles in the affected compartment. Increased serum creatine kinase and motor deficits are late signs of irreversible muscle and nerve damage. **5 Ps:** pain, palor, paresthesia, pulselessness, paralysis.

#### Medial tibial stress syndrome

Also called shin splints. Common cause of shin pain and diffuse tenderness in runners and military recruits. Caused by bone resorption that outpaces bone formation in tibial cortex.

#### Plantar fasciitis

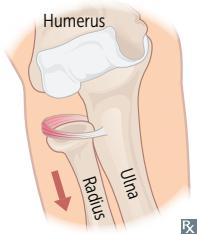
Inflammation of plantar aponeurosis characterized by heel pain (worse with first steps in the morning or after period of inactivity) and tenderness.

#### Temporomandibular disorders

Group of disorders that involve the temporomandibular joint (TMJ) and muscles of mastication. Multifactorial etiology; associated with TMJ trauma, poor head and neck posture, abnormal trigeminal nerve pain processing, psychological factors. Present with dull, constant unilateral facial pain that worsens with jaw movement, otalgia, headache, TMJ dysfunction (eg, limited range of motion).

### Childhood musculoskeletal conditions

#### Radial head subluxation



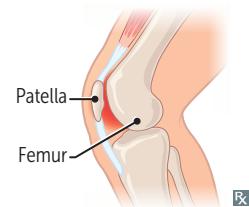
Also called nursemaid's elbow. Common elbow injury in children < 5 years. Caused by a sudden pull on the arm → immature annular ligament slips over head of radius. Injured arm held in slightly flexed and pronated position.

#### Osgood-Schlatter disease



Also called traction apophysitis. Overuse injury caused by repetitive strain and chronic avulsion of the secondary ossification center of proximal tibial tubercle. Occurs in adolescents after growth spurt. Common in running and jumping athletes. Presents with progressive anterior knee pain.

#### Patellofemoral syndrome



Overuse injury that commonly presents in young, female athletes as anterior knee pain. Exacerbated by prolonged sitting or weight-bearing on a flexed knee.

#### Developmental dysplasia of the hip

Abnormal acetabulum development in newborns. Risk factor is breech presentation. Results in hip instability/dislocation. Commonly tested with Ortolani and Barlow maneuvers (manipulation of newborn hip reveals a “clunk”). Confirmed via ultrasound (x-ray not used until ~4–6 months because cartilage is not ossified).

#### Legg-Calvé-Perthes disease

Idiopathic avascular necrosis of femoral head. Commonly presents between 5–7 years with insidious onset of hip pain that may cause child to limp. More common in males (4:1 ratio). Initial x-ray often normal.

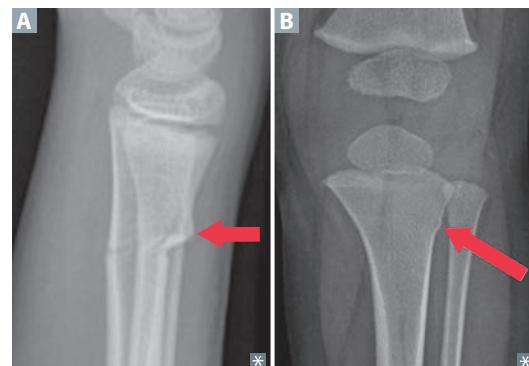
#### Slipped capital femoral epiphysis

Classically presents in an obese young adolescent with hip/knee pain and altered gait. Increased axial force on femoral head → epiphysis displaces relative to femoral neck (like a scoop of ice cream slipping off a cone). Diagnosed via x-ray.

### Common pediatric fractures

#### Greenstick fracture

Incomplete fracture extending partway through width of bone **A** following bending stress; bone fails on tension side; compression side intact (compare to torus fracture). Bone is bent like a **green twig**.



#### Torus (buckle) fracture

Axial force applied to immature bone → cortex buckles on compression (concave) side and fractures **B**. Tension (convex) side remains solid (intact).



### Achondroplasia

Failure of longitudinal bone growth (endochondral ossification) → short limbs. Membranous ossification is not affected → large head relative to limbs. Constitutive activation of fibroblast growth factor receptor (FGFR3) actually inhibits chondrocyte proliferation. > 85% of mutations occur sporadically; autosomal dominant with full penetrance (homozygosity is lethal). Associated with ↑ paternal age. Most common cause of short-limbed dwarfism.

### Osteoporosis



Trabecular (spongy) and cortical bone lose mass despite normal bone mineralization and lab values (serum Ca<sup>2+</sup> and PO<sub>4</sub><sup>3-</sup>).

Most commonly due to ↑ bone resorption related to ↓ estrogen levels and old age. Can be 2° to drugs (eg, steroids, alcohol, anticonvulsants, anticoagulants, thyroid replacement therapy) or other conditions (eg, hyperparathyroidism, hyperthyroidism, multiple myeloma, malabsorption syndromes, anorexia).

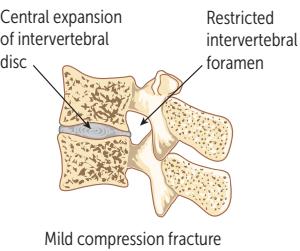
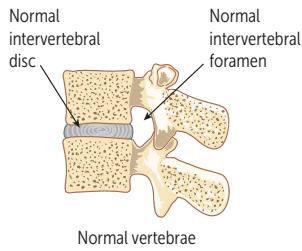
Diagnosed by bone mineral density measurement by DEXA (dual-energy X-ray absorptiometry) at the lumbar spine, total hip, and femoral neck, with a T-score of ≤ -2.5 or by a fragility fracture (eg, fall from standing height, minimal trauma) at hip or vertebra. One-time screening recommended in females ≥ 65 years old.

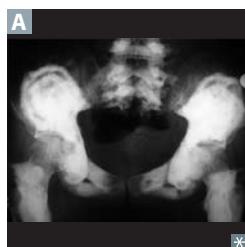
Prophylaxis: regular weight-bearing exercise and adequate Ca<sup>2+</sup> and vitamin D intake throughout adulthood.

Treatment: bisphosphonates, teriparatide, SERMs, rarely calcitonin; denosumab (monoclonal antibody against RANKL).

Can lead to **vertebral compression fractures**

**A**—acute back pain, loss of height, kyphosis. Also can present with fractures of femoral neck, distal radius (Colles fracture).



**Osteopetrosis**

Failure of normal bone resorption due to defective osteoclasts → thickened, dense bones that are prone to fracture. Mutations (eg, carbonic anhydrase II) impair ability of osteoclast to generate acidic environment necessary for bone resorption. Overgrowth of cortical bone fills marrow space → pancytopenia, extramedullary hematopoiesis. Can result in cranial nerve impingement and palsies due to narrowed foramina.

X-rays show diffuse symmetric sclerosis (bone-in-bone, “stone bone” **A**). Bone marrow transplant is potentially curative as osteoclasts are derived from monocytes.

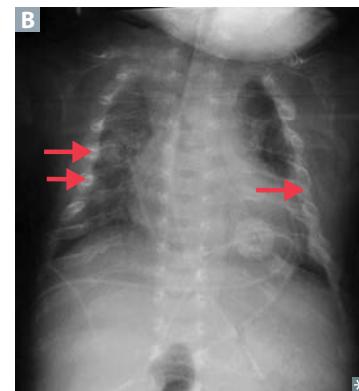
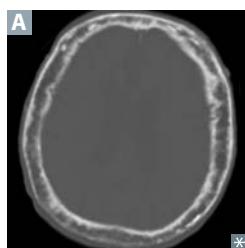
**Osteomalacia/rickets**

Defective mineralization of osteoid (osteomalacia) or cartilaginous growth plates (rickets, only in children). Most commonly due to vitamin D deficiency.

X-rays show osteopenia and pseudofractures in osteomalacia, epiphyseal widening and metaphyseal cupping/fraying in rickets. Children with rickets have pathologic bow legs (genu varum **A**), bead-like costochondral junctions (rachitic rosary **B**), craniotabes (soft skull).

↓ vitamin D → ↓ serum  $\text{Ca}^{2+}$  → ↑ PTH secretion  
→ ↓ serum  $\text{PO}_4^{3-}$ .

Hyperactivity of osteoblasts → ↑ ALP.

**Osteitis deformans**

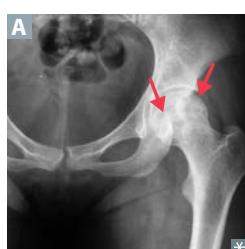
Also called Paget disease of bone. Common, localized disorder of bone remodeling caused by ↑ osteoclastic activity followed by ↑ osteoblastic activity that forms poor-quality bone. Serum  $\text{Ca}^{2+}$ , phosphorus, and PTH levels are normal. ↑ ALP. Mosaic pattern of woven and lamellar bone (osteocytes within lacunae in chaotic juxtapositions); long bone chalk-stick fractures. ↑ blood flow from ↑ arteriovenous shunts may cause high-output heart failure. ↑ risk of osteosarcoma.

Hat size can be increased due to skull thickening **A**; hearing loss is common due to skull deformity.

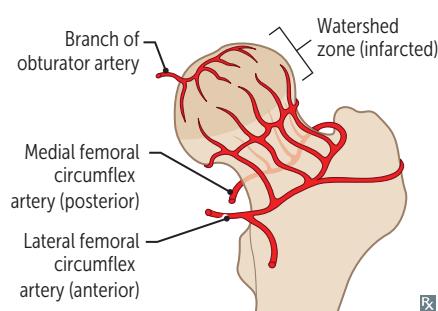
Stages of Paget disease:

- Lytic—osteoclasts
- Mixed—osteoclasts + osteoblasts
- Sclerotic—osteoblasts
- Quiescent—minimal osteoclast/osteoblast activity

Treatment: bisphosphonates.

**Avascular necrosis of bone**

Infarction of bone and marrow, usually very painful. Most common site is femoral head (watershed zone) **A** (due to insufficiency of medial circumflex femoral artery). Causes include **C**orticosteroids, chronic **A**lcohol overuse, **S**ickle cell disease, **T**rauma, **SLE**, “the **B**ends” (caisson/decompression disease), **L**Egg-Calvé-Perthes disease (idiopathic), **G**aucher disease, **S**lipped capital femoral epiphysis—**CASTS Bend LEGS**.



**Lab values in bone disorders**

DISORDER	SERUM Ca <sup>2+</sup>	PO <sub>4</sub> <sup>3-</sup>	ALP	PTH	COMMENTS
Osteoporosis	—	—	—	—	↓ bone mass
Osteopetrosis	—/↓	—	—	—	Dense, brittle bones. Ca <sup>2+</sup> ↓ in severe, malignant disease
Paget disease of bone	—	—	↑	—	Abnormal “mosaic” bone architecture
Osteitis fibrosa cystica					
Primary hyperparathyroidism	↑	↓	↑	↑	“Brown tumors” due to fibrous replacement of bone, subperiosteal thinning Idiopathic or parathyroid hyperplasia, adenoma, carcinoma
Secondary hyperparathyroidism	↓	↑	↑	↑	Often as compensation for CKD (↓ PO <sub>4</sub> <sup>3-</sup> 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)

↑ ↓ = 1° change.

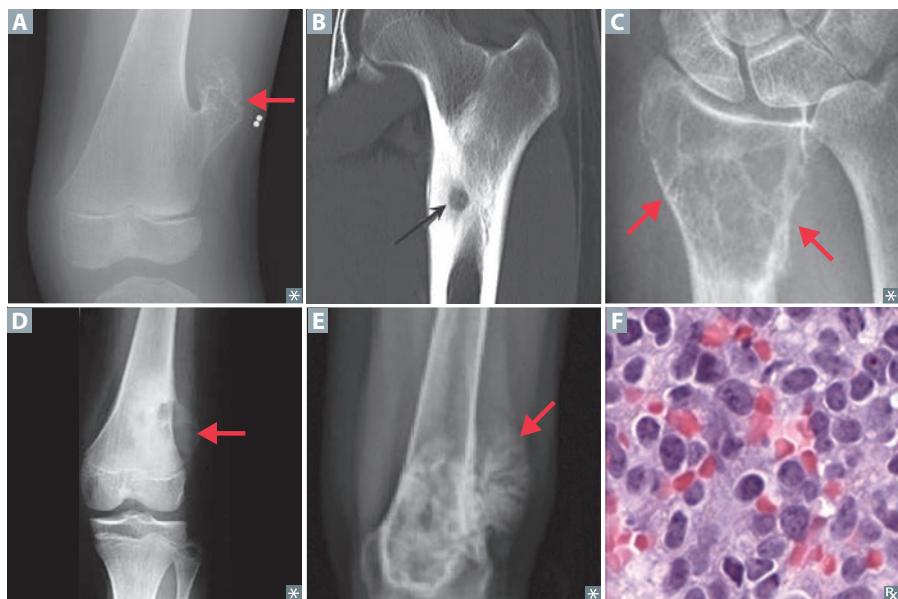
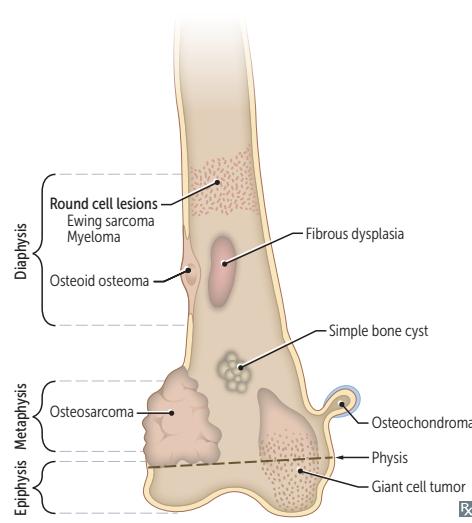
**Primary bone tumors**

Metastatic disease is more common than 1° bone tumors. Benign bone tumors that start with **o** are more common in boys.

TUMOR TYPE	EPIDEMIOLOGY	LOCATION	CHARACTERISTICS
<b>Benign tumors</b>			
<b>Osteochondroma</b>	Most common benign bone tumor Males < 25 years old	Metaphysis of long bones	Lateral bony projection of growth plate (continuous with marrow space) covered by cartilaginous cap <b>A</b> Rarely transforms to chondrosarcoma
<b>Osteoma</b>	Middle age	Surface of facial bones	Associated with Gardner syndrome
<b>Osteoid osteoma</b>	Adults < 25 years old Males > females	Cortex of long bones	Presents as bone pain (worse at night) that is relieved by NSAIDs Bony mass (< 2 cm) with radiolucent osteoid core <b>B</b>
<b>Osteoblastoma</b>	Males > females	Vertebrae	Similar histology to osteoid osteoma Larger size (> 2 cm), pain unresponsive to NSAIDs
<b>Chondroma</b>		Medulla of small bones of hand and feet	Benign tumor of cartilage
<b>Giant cell tumor</b>	20–40 years old	Epiphysis of long bones (often in knee region)	Locally aggressive benign tumor Neoplastic mononuclear cells that express RANKL and reactive multinucleated giant (osteoclast-like) cells. “Osteoclastoma” “Soap bubble” appearance on x-ray <b>C</b>

**Primary bone tumors (continued)**

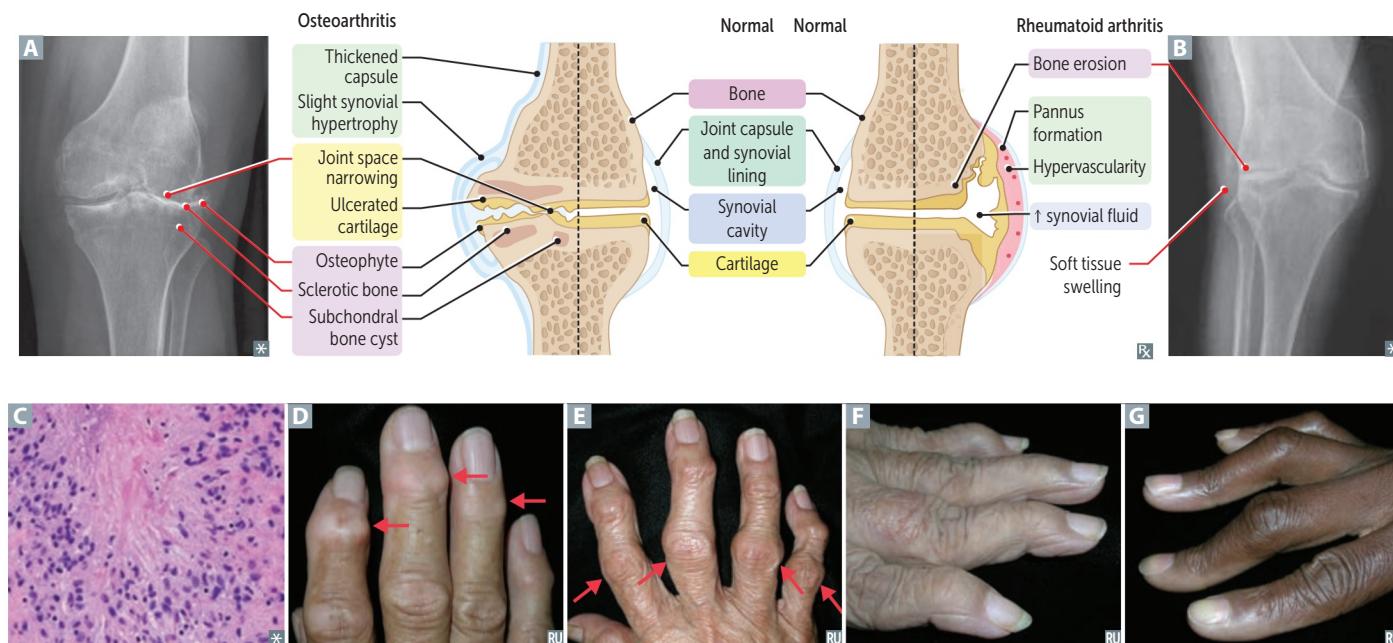
TUMOR TYPE	EPIDEMIOLOGY	LOCATION	CHARACTERISTICS
<b>Malignant tumors</b>			
<b>Osteosarcoma (osteogenic sarcoma)</b>	Accounts for 20% of 1° bone cancers. Peak incidence of 1° tumor in males < 20 years. Less common in elderly; usually 2° to predisposing factors, such as Paget disease of bone, bone infarcts, radiation, familial retinoblastoma, Li-Fraumeni syndrome.	Metaphysis of long bones (often in knee region).	Pleiomorphic osteoid-producing cells (malignant osteoblasts). Presents as painful enlarging mass or pathologic fractures. <b>Codman triangle</b> <b>D</b> (from elevation of periosteum) or <b>sunburst pattern</b> on x-ray <b>E</b> (think of an <b>osteocod</b> [bone fish] swimming in the <b>sun</b> ). Aggressive. 1° usually responsive to treatment (surgery, chemotherapy), poor prognosis for 2°.
<b>Chondrosarcoma</b>		Medulla of pelvis, proximal femur and humerus.	Tumor of malignant chondrocytes.
<b>Ewing sarcoma</b>	Most common in White patients. Generally males < 15 years old.	Diaphysis of long bones (especially femur), pelvic flat bones.	Anaplastic small blue cells of neuroectodermal origin (resemble lymphocytes) <b>F</b> . Differentiate from conditions with similar morphology (eg, lymphoma, chronic osteomyelitis) by testing for <b>t(11;22)</b> (fusion protein EWS-FLI1). “Onion skin” periosteal reaction in bone. Aggressive with early metastases, but responsive to chemotherapy. <b>11 + 22 = 33</b> (Patrick <b>Ewing’s</b> jersey number).



**Osteoarthritis vs rheumatoid arthritis**

	<b>Osteoarthritis A</b>	<b>Rheumatoid arthritis B</b>
<b>PATHOGENESIS</b>	Mechanical—wear and tear destroys articular cartilage (degenerative joint disorder) → inflammation with inadequate repair. Chondrocytes mediate degradation and inadequate repair.	Autoimmune—inflammation <b>C</b> induces formation of pannus (proliferative granulation tissue), which erodes articular cartilage and bone.
<b>PREDISPOSING FACTORS</b>	Age, female, obesity, joint trauma.	Female, HLA-DR4 (4-walled “ <b>rheum</b> ”), tobacco smoking. $\oplus$ rheumatoid factor (IgM antibody that targets IgG Fc region; in 80%), anti-cyclic citrullinated peptide antibody (more specific).
<b>PRESENTATION</b>	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.*
<b>JOINT FINDINGS</b>	Osteophytes (bone spurs), joint space narrowing, subchondral sclerosis and cysts. Synovial fluid noninflammatory ( $WBC < 2000/mm^3$ ). Development of Heberden nodes <b>D</b> (at DIP) and Bouchard nodes <b>E</b> (at PIP), and 1st CMC; not MCP.	Erosions, juxta-articular osteopenia, soft tissue swelling, subchondral cysts, joint space narrowing. Deformities: cervical subluxation, ulnar finger deviation, swan neck <b>F</b> , boutonniere <b>G</b> . Involves MCP, PIP, wrist; not DIP or 1st CMC.
<b>TREATMENT</b>	Activity modification, acetaminophen, NSAIDs, intra-articular glucocorticoids.	NSAIDs, glucocorticoids, disease-modifying agents (eg, methotrexate, sulfasalazine), biologic agents (eg, TNF- $\alpha$ 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**. Risk factors: male sex, hypertension, obesity, diabetes, dyslipidemia, alcohol use. Strongest risk factor is hyperuricemia, which can be caused by:

- Underexcretion of uric acid (90% of patients)—largely idiopathic, potentiated by renal failure; can be exacerbated by certain medications (eg, thiazide diuretics).
- Overproduction of uric acid (10% of patients)—Lesch-Nyhan syndrome, PRPP excess, ↑ cell turnover (eg, tumor lysis syndrome), von Gierke disease.

Crystals are needle shaped and ⊖ birefringent under polarized light (yellow under parallel light, blue under perpendicular light **B**). Serum uric acid levels may be normal during an acute attack.

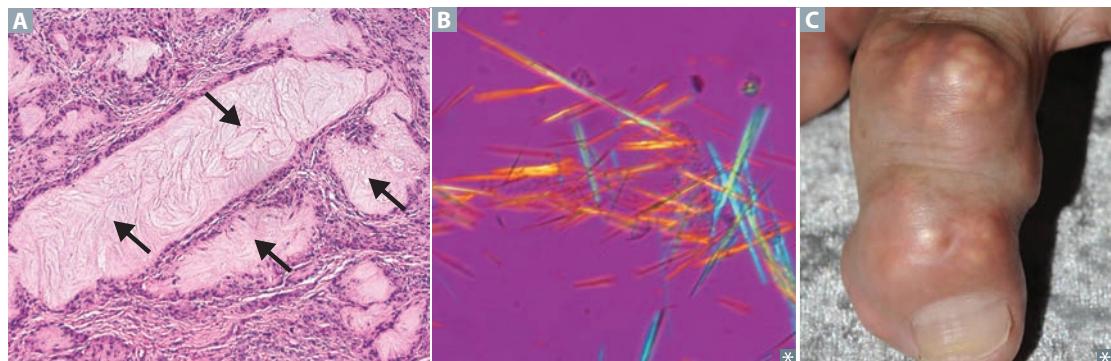
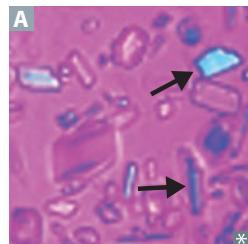
**SYMPTOMS**

Asymmetric joint distribution. Joint is swollen, red, and painful. Classic manifestation is painful MTP joint of big toe (podagra). Tophus formation **C** (often on external ear, olecranon bursa, or Achilles tendon). Acute attack tends to occur after a large meal with foods rich in purines (eg, red meat, seafood), trauma, surgery, dehydration, diuresis, or alcohol consumption (alcohol metabolites compete for same excretion sites in kidney as uric acid → ↓ uric acid secretion and subsequent buildup in blood).

**TREATMENT**

Acute: NSAIDs (eg, indomethacin), glucocorticoids, colchicine.

Chronic (preventive): xanthine oxidase inhibitors (eg, allopurinol, febuxostat).

**Calcium pyrophosphate deposition disease**

Previously called pseudogout. Deposition of calcium pyrophosphate crystals within the joint space. Occurs in patients > 50 years old; both sexes affected equally. Usually idiopathic, sometimes associated with hemochromatosis, hyperparathyroidism, joint trauma.

Pain and swelling with acute inflammation (pseudogout) and/or chronic degeneration (pseudo-osteoarthritis). Most commonly affected joint is the knee.

Chondrocalcinosis (cartilage calcification) on x-ray.

Crystals are rhomboid and weakly ⊕ birefringent under polarized light (blue when parallel to light) **A**.

Acute treatment: NSAIDs, colchicine, glucocorticoids.

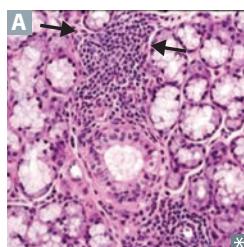
Prophylaxis: colchicine.

The **blue P's—blue** (when parallel), **positive birefringence**, **calcium pyrophosphate**, **pseudogout**

### Systemic juvenile idiopathic arthritis

Systemic arthritis seen in < 16 year olds. Usually presents with daily spiking fevers, salmon-pink macular rash, arthritis (commonly 2+ joints). Associated with anterior uveitis. Frequently presents with leukocytosis, thrombocytosis, anemia, ↑ ESR, ↑ CRP. Treatment: NSAIDs, steroids, methotrexate, TNF inhibitors.

### Sjögren syndrome



Autoimmune disorder characterized by destruction of exocrine glands (especially lacrimal and salivary) by lymphocytic infiltrates **A**. Predominantly affects females 40–60 years old.

#### Findings:

- Inflammatory joint pain
- Keratoconjunctivitis sicca (↓ tear production and subsequent corneal damage)
- Xerostomia (↓ saliva production) → mucosal atrophy, fissuring of the tongue **B**
- Presence of antinuclear antibodies, rheumatoid factor (can be positive in the absence of rheumatoid arthritis), antiribonucleoprotein antibodies: SS-A (anti-Ro) and/or SS-B (anti-La)
- Bilateral parotid enlargement

Anti-SSA and anti-SSB may also be seen in SLE.

A common 1° disorder or a 2° syndrome associated with other autoimmune disorders (eg, rheumatoid arthritis, SLE, systemic sclerosis).

Complications: dental caries; mucosa-associated lymphoid tissue (MALT) lymphoma (may present as parotid enlargement); ↑ risk of giving birth to baby with neonatal lupus.

Focal lymphocytic sialadenitis on labial salivary gland biopsy can confirm diagnosis.

### Septic arthritis



*S aureus*, *Streptococcus*, and *Neisseria gonorrhoeae* are common causes. Affected joint is swollen **A**, red, and painful. Synovial fluid purulent (WBC > 50,000/mm<sup>3</sup>).

**Disseminated gonococcal infection**—STI that presents as either purulent arthritis (eg, knee) or triad of polyarthralgia, tenosynovitis (eg, hand), dermatitis (eg, pustules).

<b>Seronegative spondyloarthritis</b>	Arthritis without rheumatoid factor (no anti-IgG antibody). Strong association with HLA-B27 (MHC class I serotype). Subtypes ( <b>PAIR</b> ) 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.	
<b>Psoriatic arthritis</b>	Associated with skin psoriasis and nail lesions. Asymmetric and patchy involvement <b>A</b> . Dactylitis and “pencil-in-cup” deformity of DIP on x-ray <b>B</b> .	Seen in fewer than 1/3 of patients with psoriasis.
<b>Ankylosing spondylitis</b>	Symmetric involvement of spine and sacroiliac joints → ankylosis (joint fusion), uveitis, aortic regurgitation.	Bamboo spine (vertebral fusion) <b>C</b> . Costovertebral and costosternal ankylosis may cause restrictive lung disease. Monitor degree of reduced chest wall expansion to assess disease severity. More common in males.
<b>Inflammatory bowel disease</b>	Crohn disease and ulcerative colitis are often associated with spondyloarthritis.	
<b>Reactive arthritis</b>	Classic triad: <ul style="list-style-type: none"><li>▪ <b>Conjunctivitis</b></li><li>▪ <b>Urethritis</b></li><li>▪ <b>Arthritis</b></li></ul>	“Can’t <b>see</b> , can’t <b>pee</b> , can’t <b>bend my knee</b> .” Associated with infections by <i>Shigella</i> , <i>Campylobacter</i> , <i>E. coli</i> , <i>Salmonella</i> , <i>Chlamydia</i> , <i>Yersinia</i> . “She Caught Every Student Cheating Yesterday and over <b>reacted</b> .”



**Systemic lupus erythematosus**

Systemic, remitting, and relapsing autoimmune disease. Organ damage primarily due to a type III hypersensitivity reaction and, to a lesser degree, a type II hypersensitivity reaction. Associated with deficiency of early complement proteins (eg, C1q, C4, C2) → ↓ clearance of immune complexes. Classic presentation: rash, joint pain, and fever in a female of reproductive age. ↑ prevalence in Black, Caribbean, Asian, and Hispanic populations.



**Libman-Sacks Endocarditis**—nonbacterial, verrucous thrombi usually on mitral or aortic valve and can be present on either surface of the valve (but usually on undersurface). **LSE** in **SLE**.

Lupus nephritis (glomerular deposition of DNA-anti-DNA immune complexes) can be nephritic or nephrotic (causing hematuria or proteinuria). Most common and severe type is diffuse proliferative.

Common causes of death in SLE: **infections**, **cardiovascular disease** (accelerated CAD), **kidney disease** (most common). **Immune complexes kill**.

In an anti-SSA + pregnant patient, ↑ risk of newborn developing **neonatal lupus**  
→ congenital heart block, periorbital/diffuse rash, transaminitis, and cytopenias at birth.

Features of SLE, systemic sclerosis, and/or polymyositis. Associated with anti-U1 RNP antibodies (speckled ANA).

**RASH OR PAIN:**

Rash (malar **A** or discoid **B**)

Arthritis (nonerosive)

Serositis (eg, pleuritis, pericarditis)

Hematologic disorders (eg, cytopenias)

Oral/nasopharyngeal ulcers (usually painless)

Renal disease

Photosensitivity

Antinuclear antibodies

Immunologic disorder (anti-dsDNA, anti-Sm, antiphospholipid)

Neurologic disorders (eg, seizures, psychosis)

**Mixed connective tissue disease****Antiphospholipid syndrome**

1° or 2° autoimmune disorder (most commonly in SLE).

Diagnosed based on clinical criteria including history of thrombosis (arterial or venous) or spontaneous abortion along with laboratory findings of lupus anticoagulant, anticardiolipin, anti-β<sub>2</sub> glycoprotein I antibodies.

Treatment: systemic anticoagulation.

Anticardiolipin antibodies can cause false-positive VDRL/RPR.

Lupus anticoagulant can cause prolonged PTT that is not corrected by the addition of normal platelet-free plasma.

**Polymyalgia rheumatica**

<b>SYMPTOMS</b>	Pain and stiffness in proximal muscles (eg, shoulders, hips), often with fever, malaise, weight loss. Does not cause muscular weakness. More common in females > 50 years old; associated with giant cell (temporal) arteritis.
<b>FINDINGS</b>	↑ ESR, ↑ CRP, normal CK.
<b>TREATMENT</b>	Rapid response to low-dose corticosteroids.

**Fibromyalgia**

Most common in females 20–50 years old. Chronic, widespread musculoskeletal pain associated with “tender points,” stiffness, paresthesias, poor sleep, fatigue, cognitive disturbance (“fibro fog”). Treatment: regular exercise, antidepressants (TCAs, SNRIs), neuropathic pain agents (eg, gabapentin).

**Polymyositis/  
dermatomyositis**

Nonspecific: + ANA, ↑ CK. Specific: + anti-Jo-1 (histidyl-tRNA synthetase), + anti-SRP (signal recognition particle), + anti-Mi-2 (helicase).

**Polymyositis**

Progressive symmetric proximal muscle weakness, characterized by endomysial inflammation with CD8+ T cells. Most often involves shoulders.

**Dermatomyositis**

Clinically similar to polymyositis, but also involves Gottron papules **A**, photodistributed facial erythema (eg, heliotrope [violaceous] edema of the eyelids **B**), “shawl and face” rash **C**, darkening and thickening of fingertips and sides resulting in irregular, “dirty”-appearing marks. ↑ risk of occult malignancy. Perimysial inflammation and atrophy with CD4+ T cells.

**Myositis ossificans**

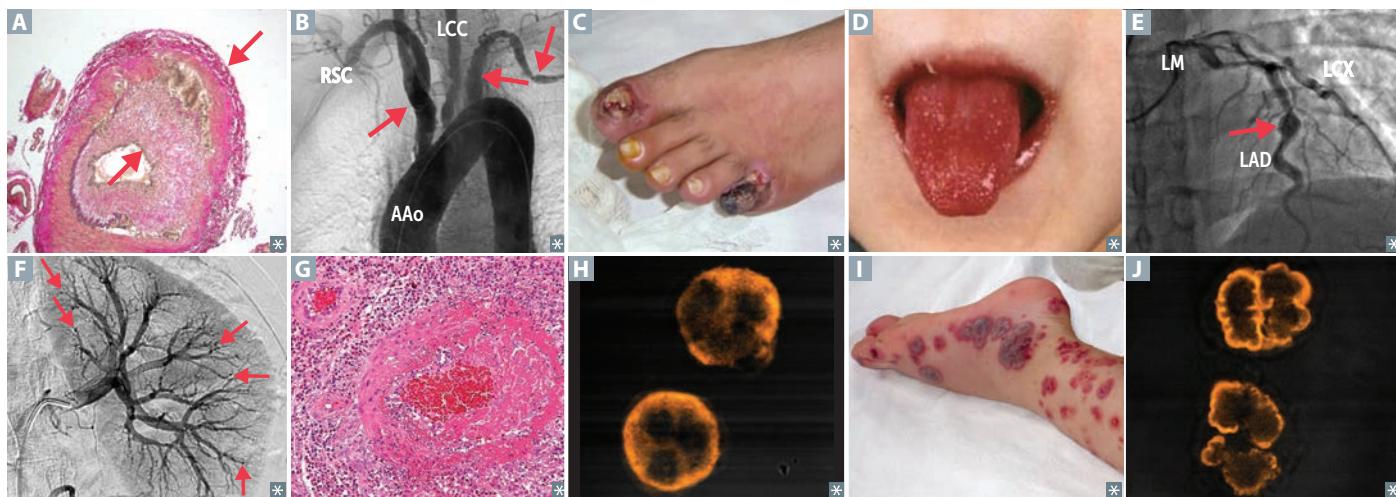
Heterotopic ossification involving skeletal muscle (eg, quadriceps). Associated with blunt muscle trauma. Presents as painful soft tissue mass. Imaging shows eggshell calcification. Histology shows metaplastic bone surrounding area of fibroblastic proliferation. Benign, but may be mistaken for sarcoma.

**Vasculitides**

	EPIDEMIOLOGY/PRESENTATION	NOTES
<b>Large-vessel vasculitis</b>		
<b>Giant cell (temporal) arteritis</b>	Females > 50 years old. Unilateral headache, possible temporal artery tenderness, jaw claudication. May lead to irreversible blindness due to anterior ischemic optic neuropathy. Associated with polymyalgia rheumatica.	Most commonly affects branches of carotid artery. Focal granulomatous inflammation <b>A</b> . ↑ ESR. Treat with high-dose corticosteroids prior to temporal artery biopsy to prevent blindness.
<b>Takayasu arteritis</b>	Usually Asian females < 40 years old. “Pulseless disease” (weak upper extremity pulses), fever, night sweats, arthritis, myalgias, skin nodules, ocular disturbances.	Granulomatous thickening and narrowing of aortic arch and proximal great vessels <b>B</b> . ↑ ESR. Treatment: corticosteroids.
<b>Medium-vessel vasculitis</b>		
<b>Buerger disease (thromboangiitis obliterans)</b>	Heavy tobacco smoking history, males < 40 years old. Intermittent claudication. May lead to gangrene <b>C</b> , autoamputation of digits, superficial nodular phlebitis. Raynaud phenomenon is often present.	Segmental thrombosing vasculitis with vein and nerve involvement. Treatment: smoking cessation.
<b>Kawasaki disease (mucocutaneous lymph node syndrome)</b>	Usually Asian children < 4 years old. <b>Conjunctival injection</b> , <b>Rash</b> (polymorphous → desquamating), <b>Adenopathy</b> (cervical), <b>Strawberry tongue</b> (oral mucositis) <b>D</b> , <b>Hand-foot changes</b> (edema, erythema), <b>fever</b> .	<b>CRASH</b> and <b>burn</b> on a <b>Kawasaki</b> . May develop coronary artery aneurysms <b>E</b> ; thrombosis or rupture can cause death. Treatment: IV immunoglobulin and aspirin.
<b>Polyarteritis nodosa</b>	Usually middle-aged males. Hepatitis B seropositivity in 30% of patients. Fever, weight loss, malaise, headache. GI: abdominal pain, melena. Hypertension, neurologic dysfunction, cutaneous eruptions, renal damage.	Typically involves renal and visceral vessels, not pulmonary arteries. Different stages of transmural inflammation with fibrinoid necrosis. Innumerable renal microaneurysms <b>F</b> and spasms on arteriogram (string of pearls appearance). Treatment: corticosteroids, cyclophosphamide.
<b>Small-vessel vasculitis</b>		
<b>Behçet syndrome</b>	↑ incidence in people of Turkish and eastern Mediterranean descent. Recurrent aphthous ulcers, genital ulcerations, uveitis, erythema nodosum. Can be precipitated by HSV or parvovirus. Flares last 1–4 weeks.	Immune complex vasculitis. Associated with HLA-B51.
<b>Cutaneous small-vessel vasculitis</b>	Occurs 7-10 days after certain medications (penicillin, cephalosporins, phenytoin, allopurinol) or infections (eg, HCV, HIV). Palpable purpura, no visceral involvement.	Immune complex-mediated leukocytoclastic vasculitis; late involvement indicates systemic vasculitis.

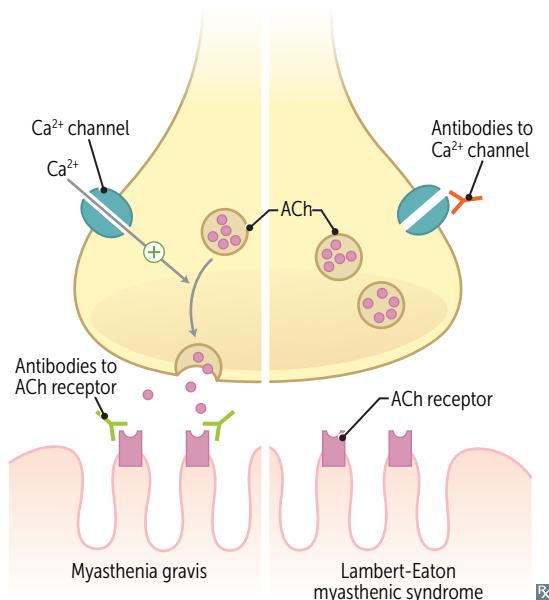
**Vasculitides (continued)**

	EPIDEMIOLOGY/PRESENTATION	NOTES
<b>Small-vessel vasculitis (continued)</b>		
<b>Eosinophilic granulomatosis with polyangiitis</b>	Asthma, sinusitis, skin nodules or purpura, peripheral neuropathy (eg, wrist/foot drop). Can also involve heart, GI, kidneys (pauci-immune glomerulonephritis).	Formerly called Churg-Strauss syndrome. Granulomatous, necrotizing vasculitis with eosinophilia <b>G</b> . MPO-ANCA/p-ANCA, ↑ IgE level.
<b>Granulomatosis with polyangiitis</b>	Upper respiratory tract: perforation of nasal septum, chronic sinusitis, otitis media, mastoiditis. Lower respiratory tract: hemoptysis, cough, dyspnea. Renal: hematuria, red cell casts.	Triad: <ul style="list-style-type: none"><li>▪ Focal necrotizing vasculitis</li><li>▪ Necrotizing granulomas in lung and upper airway</li><li>▪ Necrotizing glomerulonephritis</li></ul> PR3-ANCA/c-ANCA <b>H</b> (anti-proteinase 3). CXR: large nodular densities. Treatment: corticosteroids in combination with rituximab or cyclophosphamide.
<b>Immunoglobulin A vasculitis</b>	Most common childhood systemic vasculitis. Often follows URI. Classic triad of <b>Henoch-Schönlein purpura</b> <ul style="list-style-type: none"><li>▪ Hinge pain (arthralgias)</li><li>▪ Stomach pain (abdominal pain associated with intussusception)</li><li>▪ Palpable purpura on buttocks/legs <b>I</b></li></ul>	Formerly called Henoch-Schönlein purpura. Vasculitis 2° to IgA immune complex deposition. Associated with IgA nephropathy (Berger disease). Treatment: supportive care, possibly corticosteroids.
<b>Microscopic polyangiitis</b>	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 <b>J</b> (anti-myeloperoxidase). Treatment: cyclophosphamide, corticosteroids.
<b>Mixed cryoglobulinemia</b>	Often due to viral infections, especially HCV. Triad of palpable purpura, weakness, arthralgias. May also have peripheral neuropathy and renal disease (eg, glomerulonephritis).	Cryoglobulins are immunoglobulins that precipitate in the Cold. Vasculitis due to mixed IgG and IgM immune complex deposition.



### Neuromuscular junction diseases

	<b>Myasthenia gravis</b>	<b>Lambert-Eaton myasthenic syndrome</b>
<b>FREQUENCY</b>	Most common NMJ disorder	Uncommon
<b>PATHOPHYSIOLOGY</b>	Autoantibodies to postsynaptic ACh receptor	Autoantibodies to presynaptic $\text{Ca}^{2+}$ channel → ↓ ACh release
<b>CLINICAL</b>	Fatigable muscle weakness—ptosis; diplopia; proximal weakness; respiratory muscle involvement → dyspnea; bulbar muscle involvement → dysphagia, difficulty chewing Spared reflexes Worsens with muscle use	Proximal muscle weakness, autonomic symptoms (dry mouth, constipation, impotence)  Hyporeflexia Improves with muscle use
<b>ASSOCIATED WITH</b>	Thymoma, thymic hyperplasia	Small cell lung cancer
<b>AChE INHIBITOR ADMINISTRATION</b>	Reverses symptoms (pyridostigmine for treatment)	Minimal effect



### Raynaud phenomenon



↓ blood flow to skin due to arteriolar (small vessel) vasospasm in response to cold or stress: color change from white (ischemia) to blue (hypoxia) to red (reperfusion). Most often in the fingers **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 syndrome (limited form of systemic sclerosis). Digital ulceration (critical ischemia) seen in 2° Raynaud syndrome. Treat with calcium channel blockers.

**Scleroderma**

Systemic sclerosis. Triad of autoimmunity, noninflammatory vasculopathy, and collagen deposition with fibrosis. Commonly sclerosis of skin, manifesting as puffy, taut skin **A** without wrinkles, fingertip pitting **B**. Can involve other systems, eg, renal (scleroderma renal crisis; treat with ACE inhibitors), pulmonary (interstitial fibrosis, pulmonary HTN), GI (esophageal dysmotility and reflux), cardiovascular. 75% female. 2 major types:

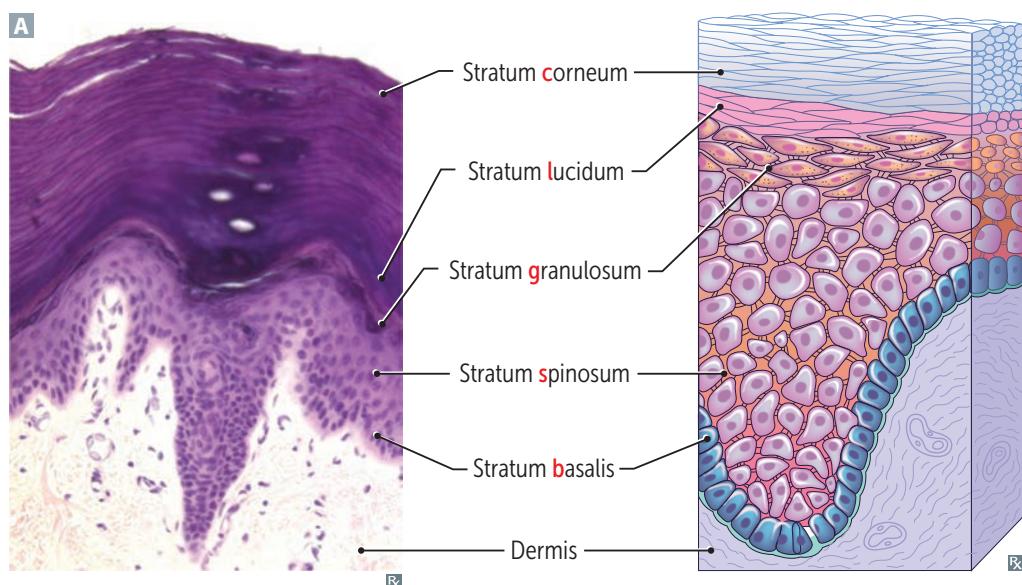
- **Diffuse scleroderma**—widespread skin involvement, rapid progression, early visceral involvement. Associated with anti-Scl-70 antibody (anti-DNA topoisomerase-I antibody) and anti-RNA polymerase III.
- **Limited scleroderma**—limited skin involvement confined to fingers and face. Also with **CREST** syndrome: **C**alcinosis cutis **C**, anti-**C**entromere antibody, **R**aynaud phenomenon, **E**sophageal dysmotility, **S**clerodactyly, and **T**elangiectasia. More benign clinical course.



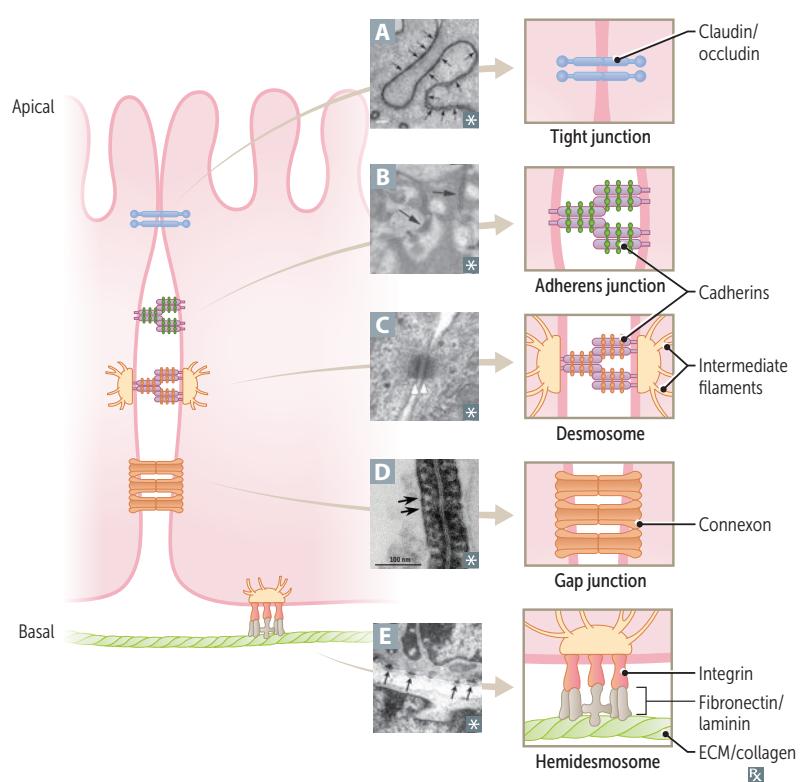
## ▶ MUSCULOSKELETAL, SKIN, AND CONNECTIVE TISSUE—DERMATOLOGY

**Skin layers**

Skin has 3 layers: epidermis, dermis, subcutaneous fat (hypodermis, subcutis).  
Epidermal layers: **come, let's get sunburned.**



### Epithelial cell junctions



Tight junctions (zonula occludens) **A**—prevents paracellular movement of solutes; composed of claudins and occludins.

Adherens junction (belt desmosome, zonula adherens) **B**—forms “belt” connecting actin cytoskeletons of adjacent cells with **cad**herins ( $\text{Ca}^{2+}$ -dependent **ad**hesion proteins). Loss of E-cadherin promotes metastasis.

Desmosome (spot desmosome, macula adherens) **C**—structural support via intermediate filament interactions. Autoantibodies to desmoglein 1 and/or 3 → pemphigus vulgaris.

Gap junction **D**—channel proteins called connexons permit electrical and chemical communication between cells.

Hemidesmosome **E**—connects keratin in basal cells to underlying basement membrane. Autoantibodies → **bullo**us pemphigoid. (Hemidesmosomes are down “**bullo**w.”)

**Integrins**—membrane proteins that maintain **integrity** of basolateral membrane by binding to collagen, laminin, and fibronectin in basement membrane.

**Dermatologic macroscopic terms**

LESION	CHARACTERISTICS	EXAMPLES
<b>Macule</b>	Flat lesion with well-circumscribed change in skin color < 1 cm	Freckle (ephelide), labial macule <b>A</b>
<b>Patch</b>	Macule > 1 cm	Large birthmark (congenital nevus) <b>B</b>
<b>Papule</b>	Elevated solid skin lesion < 1 cm	Mole (nevus) <b>C</b> , acne
<b>Plaque</b>	Papule > 1 cm	Psoriasis <b>D</b>
<b>Vesicle</b>	Small fluid-containing blister < 1 cm	Chickenpox (varicella), shingles (zoster) <b>E</b>
<b>Bulla</b>	Large fluid-containing blister > 1 cm	Bullous pemphigoid <b>F</b>
<b>Pustule</b>	Vesicle containing pus	Pustular psoriasis <b>G</b>
<b>Wheal</b>	Transient smooth papule or plaque	Hives (urticaria) <b>H</b>
<b>Scale</b>	Flaking off of stratum corneum	Eczema, psoriasis, SCC <b>I</b>
<b>Crust</b>	Dry exudate	Impetigo <b>J</b>

**Dermatologic microscopic terms**

LESION	CHARACTERISTICS	EXAMPLES
<b>Dyskeratosis</b>	Abnormal premature keratinization	Squamous cell carcinoma
<b>Hyperkeratosis</b>	↑ thickness of stratum corneum	Psoriasis, calluses
<b>Parakeratosis</b>	Retention of nuclei in stratum corneum	Psoriasis, actinic keratosis
<b>Hypergranulosis</b>	↑ thickness of stratum granulosum	Lichen planus
<b>Spongiosis</b>	Epidermal accumulation of edematous fluid in intercellular spaces	Eczematous dermatitis
<b>Acantholysis</b>	Separation of epidermal cells	Pemphigus vulgaris
<b>Acanthosis</b>	Epidermal hyperplasia (↑ spinosum)	Acanthosis nigricans, psoriasis

**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)**

Acquired hyperpigmentation associated with pregnancy (“mask of pregnancy” **B**) or OCP use. More common in pregnant patients with darker skin tones.

**Vitiligo**

Irregular patches of complete depigmentation **C**. Caused by destruction of melanocytes (believed to be autoimmune). Associated with other autoimmune disorders.

**Seborrheic dermatitis**

Erythematous, well-demarcated plaques **A** with greasy yellow scales in areas rich in sebaceous glands, such as scalp, face, and periocular region. Common in both infants (cradle cap) and adults, associated with Parkinson disease. Sebaceous glands are not inflamed, but play a role in disease development. Possibly associated with *Malassezia* spp. Treatment: topical antifungals and corticosteroids.

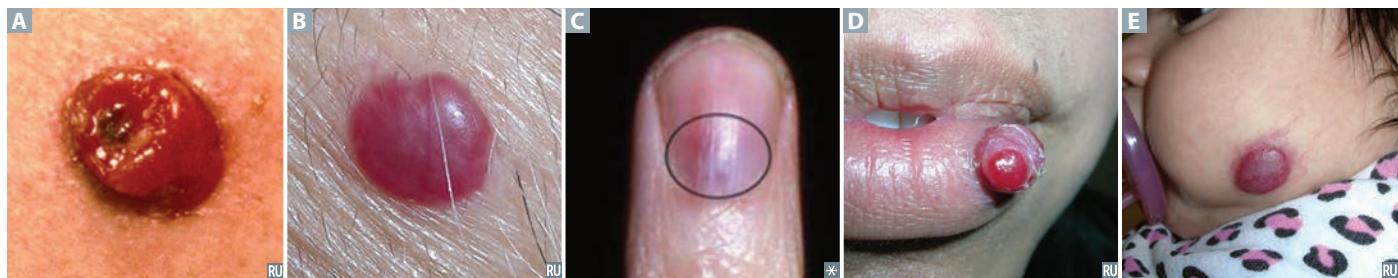
**Common skin disorders**

<b>Acne</b>	Multifactorial etiology—↑ sebum/androgen production, abnormal keratinocyte desquamation, <i>Cutibacterium acnes</i> colonization of the pilosebaceous unit (comedones), and inflammation (papules/pustules <b>A</b> , nodules, cysts). Treatment: retinoids, benzoyl peroxide, and antibiotics.
<b>Atopic dermatitis (eczema)</b>	Type I hypersensitivity reaction. Pruritic eruption, commonly on skin flexures. Associated with other atopic diseases (asthma, allergic rhinitis, food allergies); ↑ serum IgE. Mutations in filaggrin gene predispose (via skin barrier dysfunction). Often appears on face in infancy <b>B</b> and then in antecubital fossa <b>C</b> in children and adults.
<b>Allergic contact dermatitis</b>	Type IV hypersensitivity reaction secondary to contact allergen (eg, nickel <b>D</b> , poison ivy, neomycin <b>E</b> ).
<b>Melanocytic nevus</b>	Common mole. Benign, but melanoma can arise in congenital or atypical moles. Intradermal nevi are papular <b>F</b> . Junctional nevi are flat macules <b>G</b> .
<b>Pseudofolliculitis barbae</b>	Foreign body inflammatory facial skin disorder characterized by firm, hyperpigmented papules and pustules that are painful and pruritic. Located on cheeks, jawline, and neck. Commonly occurs as a result of shaving (“razor bumps”), primarily affects Black males.
<b>Psoriasis</b>	Papules and plaques with silvery scaling <b>H</b> , especially on knees and elbows. Acanthosis with parakeratotic scaling (nuclei still in stratum corneum), Munro microabscesses. ↑ stratum spinosum, ↓ stratum granulosum. Auspitz sign ( <b>I</b> )—pinpoint bleeding spots from exposure of dermal papillae when scales are scraped off. Associated with nail pitting and psoriatic arthritis.
<b>Rosacea</b>	Inflammatory facial skin disorder characterized by erythematous papules and pustules <b>J</b> , but no comedones. May be associated with facial flushing in response to external stimuli (eg, alcohol, heat). Complications include ocular involvement, rhinophyma (bulbous deformation of nose).
<b>Seborrheic keratosis</b>	Flat, greasy, pigmented squamous epithelial proliferation of immature keratinocytes with keratin-filled cysts (horn cysts) <b>K</b> . Looks “stuck on.” Lesions occur on head, trunk, and extremities. Common benign neoplasm of older persons. Leser-Trélat sign <b>L</b> —rapid onset of multiple seborrheic keratoses, indicates possible malignancy (eg, GI adenocarcinoma).
<b>Verrucae</b>	Warts; caused by low-risk HPV strains. Soft, tan-colored, cauliflower-like papules <b>M</b> . Epidermal hyperplasia, hyperkeratosis, koilicytosis. Condyloma acuminatum on anus or genitals <b>N</b> .
<b>Urticaria</b>	Hives. Pruritic wheals that form after mast cell degranulation <b>O</b> . Characterized by superficial dermal edema and lymphatic channel dilation.



**Vascular tumors of skin**

<b>Angiosarcoma</b>	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.
<b>Bacillary angiomatosis</b>	Benign capillary skin papules <b>A</b> found in patients with AIDS. Caused by <i>Bartonella</i> infections. Frequently mistaken for Kaposi sarcoma, but has neutrophilic infiltrate.
<b>Cherry hemangioma</b>	Benign capillary hemangioma <b>B</b> commonly appearing in middle-aged adults. Does not regress. Frequency ↑ with age.
<b>Glomus tumor</b>	Benign, painful, red-blue tumor, commonly under fingernails <b>C</b> . Arises from modified smooth muscle cells of the thermoregulatory glomus body.
<b>Kaposi sarcoma</b>	Endothelial malignancy most commonly affecting the skin, mouth, GI tract, respiratory tract. Classically seen in older Eastern European males, patients with AIDS, and organ transplant patients. Associated with HHV-8 and HIV. Lymphocytic infiltrate, unlike bacillary angiomatosis.
<b>Pyogenic granuloma</b>	Polypoid lobulated capillary hemangioma <b>D</b> that can ulcerate and bleed. Associated with trauma and pregnancy.
<b>Strawberry hemangioma</b>	Benign capillary hemangioma of infancy <b>E</b> . Appears in first few weeks of life (1/200 births); grows rapidly and regresses spontaneously by 5–8 years old.



**Skin infections****Bacterial infections**

<b>Impetigo</b>	Skin infection involving superficial epidermis. Usually from <i>S aureus</i> or <i>S pyogenes</i> . Highly contagious. Honey-colored crusting <b>A</b> . Bullous impetigo <b>B</b> has bullae and is usually caused by <i>S aureus</i> .
<b>Erysipelas</b>	Infection involving upper dermis and superficial lymphatics, usually from <i>S pyogenes</i> . Presents with well-defined, raised demarcation between infected and normal skin <b>C</b> .
<b>Cellulitis</b>	Acute, painful, spreading infection of deeper dermis and subcutaneous tissues. Usually from <i>S pyogenes</i> or <i>S aureus</i> . Often starts with a break in skin from trauma or another infection <b>D</b> .
<b>Abscess</b>	Collection of pus from a walled-off infection within deeper layers of skin <b>E</b> . Offending organism is almost always <i>S aureus</i> .
<b>Necrotizing fascitis</b>	Deeper tissue injury, usually from anaerobic bacteria or <i>S pyogenes</i> . Pain may be out of proportion to exam findings. Results in crepitus from methane and CO <sub>2</sub> production. “Flesh-eating bacteria.” Causes bullae and skin necrosis → violaceous color of bullae, surrounding skin <b>F</b> . Surgical emergency.
<b>Staphylococcal scalded skin syndrome</b>	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 <b>G</b> that heals completely. ⊕ Nikolsky sign (separation of epidermis upon manual stroking of skin). Commonly seen in newborns and children/adults with renal insufficiency.

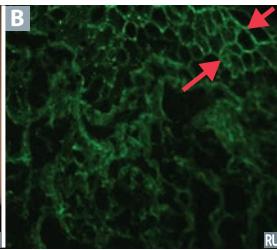
**Viral infections**

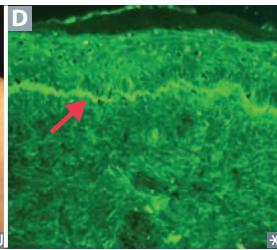
<b>Herpes</b>	Herpes virus infections (HSV1 and HSV2) of skin can occur anywhere from mucosal surfaces to normal skin. These include herpes labialis, herpes genitalis, herpetic whitlow <b>H</b> (finger).
<b>Molluscum contagiosum</b>	Umbilicated papules <b>I</b> caused by a poxvirus. While frequently seen in children, it may be sexually transmitted in adults.
<b>Varicella zoster virus</b>	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).
<b>Hairy leukoplakia</b>	Irregular, white, painless plaques on lateral tongue that cannot be scraped off <b>J</b> . EBV mediated. Occurs in patients living with HIV, organ transplant recipients. Contrast with thrush (scrapable) and leukoplakia (precancerous).

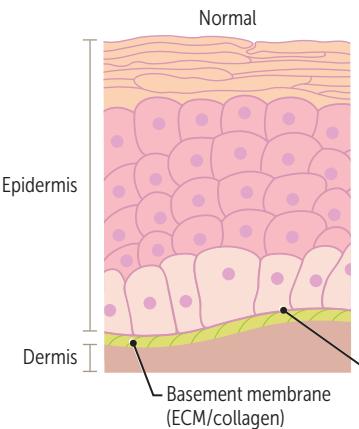
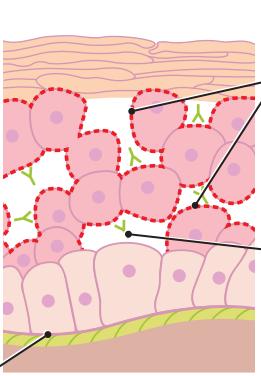
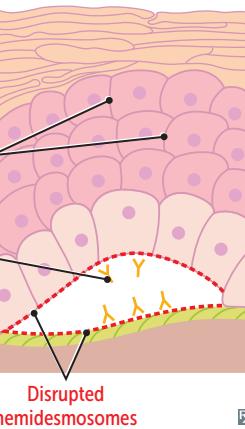


**Autoimmune blistering skin disorders**

	<b>Pemphigus vulgaris</b>	<b>Bullous pemphigoid</b>
<b>PATHOPHYSIOLOGY</b>	Potentially fatal. Most commonly seen in older adults. Type II hypersensitivity reaction. IgG antibodies against desmoglein-1 and/or desmoglein-3 (component of desmosomes, which connect keratinocytes in the stratum spinosum).	Less severe than pemphigus vulgaris. Most commonly seen in older adults. Type II hypersensitivity reaction. IgG antibodies against hemidesmosomes (epidermal basement membrane; antibodies are “bulow” the epidermis).
<b>GROSS MORPHOLOGY</b>	Flaccid intraepidermal bullae <b>A</b> caused by acantholysis (separation of keratinocytes, “row of tombstones” on H&E stain); oral mucosa is involved. Nikolsky sign $\oplus$ .	Tense blisters <b>C</b> containing eosinophils; oral mucosa spared. Nikolsky sign $\ominus$ .
<b>IMMUNOFLUORESCENCE</b>	Reticular pattern around epidermal cells <b>B</b> .	Linear pattern at epidermal-dermal junction <b>D</b> .



### Other blistering skin disorders

<b>Dermatitis herpetiformis</b>	Pruritic papules, vesicles, and bullae (often found on elbows, knees, buttocks) <b>A</b> . Deposits of IgA at tips of dermal papillae. Associated with celiac disease. Treatment: dapsone, gluten-free diet.
<b>Erythema multiforme</b>	Associated with infections (eg, <i>Mycoplasma pneumoniae</i> , HSV), drugs (eg, sulfa drugs, $\beta$ -lactams, phenytoin). Presents with multiple types of lesions—macules, papules, vesicles, target lesions (look like targets with multiple rings and dusky center showing epithelial disruption) <b>B</b> .
<b>Stevens-Johnson syndrome</b>	Characterized by fever, bullae formation and necrosis, sloughing of skin at dermal-epidermal junction ( $\oplus$ Nikolsky), high mortality rate. Typically mucous membranes are involved <b>C D</b> . Targetoid skin lesions may appear, as seen in erythema multiforme. Usually associated with adverse drug reaction. <b>Toxic epidermal necrolysis (TEN)</b> <b>E F</b> is more severe form of SJS involving $> 30\%$ body surface area. 10–30% involvement denotes SJS-TEN.



### Lower extremity ulcers

	<b>Venous ulcer</b>	<b>Arterial ulcer</b>	<b>Neuropathic ulcer</b>
<b>ETIOLOGY</b>	Chronic venous insufficiency; most common ulcer type	Peripheral artery disease (eg, atherosclerotic stenosis)	Peripheral neuropathy (eg, diabetic foot)
<b>LOCATION</b>	Gaiter area (ankle to midcalf), typically over malleoli	Distal toes, anterior shin, pressure points	Bony prominences (eg, metatarsal heads, heel)
<b>APPEARANCE</b>	Irregular border, shallow, exudative <b>A</b>	Symmetric with well-defined punched out appearance <b>B</b>	Hyperkeratotic edge with undermined borders <b>C</b>
<b>PAIN</b>	Mild to moderate	Severe	Absent
<b>ASSOCIATED SIGNS</b>	Telangiectasias, varicose veins, edema, stasis dermatitis (erythematous eczematous patches)	Signs of arterial insufficiency including cold, pale, atrophic skin with hair loss and nail dystrophy, absent pulses	Claw toes, Charcot joints, absent reflexes



### Miscellaneous skin disorders

#### Acanthosis nigricans

Epidermal hyperplasia causing symmetric, hyperpigmented thickening of skin, especially in axilla or on neck **A B**. Associated with insulin resistance (eg, diabetes, obesity, Cushing syndrome, PCOS), visceral malignancy (eg, gastric adenocarcinoma).

#### Actinic keratosis

Premalignant lesions caused by sun exposure. Small, rough, erythematous or brownish papules or plaques **C D**. Risk of squamous cell carcinoma is proportional to degree of epithelial dysplasia.

#### Erythema nodosum

Painful, raised inflammatory lesions of subcutaneous fat (panniculitis), usually on anterior shins. Often idiopathic, but can be associated with sarcoidosis, coccidioidomycosis, histoplasmosis, TB, streptococcal infections **E**, leprosy **F**, inflammatory bowel disease.

#### Lichen Planus

Pruritic, purple, polygonal planar papules and plaques are the **6 P's** of lichen Planus **G H**. Mucosal involvement manifests as Wickham striae (reticular white lines) and hypergranulosis. Sawtooth infiltrate of lymphocytes at dermal-epidermal junction. Associated with hepatitis C.

#### Pityriasis rosea

“Herald patch” **I** followed days later by other scaly erythematous plaques, often in a “Christmas tree” distribution on trunk **J**. Multiple pink plaques with collarette scale. Self-resolving in 6–8 weeks.

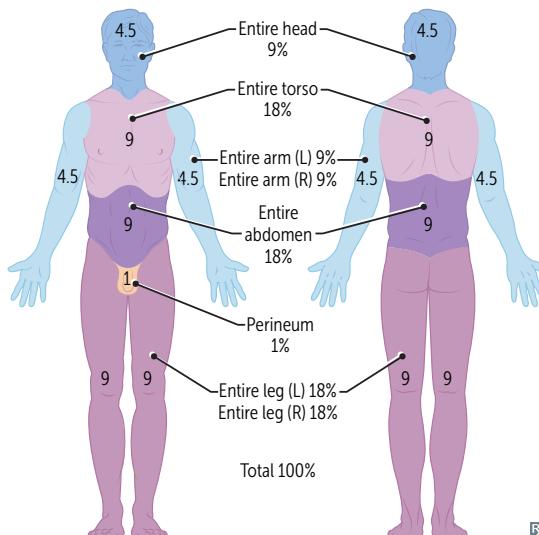
#### Sunburn

Acute cutaneous inflammatory reaction due to excessive UV irradiation. Causes DNA mutations, inducing apoptosis of keratinocytes. UVB is dominant in sunBurn, UVA in tAnning and photoAging. Exposure to UVA and UVB ↑ risk of skin cancer.



**Rule of 9's**

The extent of a burn injury can be estimated as a percentage of the body surface area.

**Burn classification**

DEPTH	INVOLVEMENT	APPEARANCE	SENSATION
<b>Superficial burn</b>	Epidermis only	Similar to sunburn; localized, dry, blanching redness with no blisters	Painful
<b>Superficial partial-thickness burn</b>	Epidermis and papillary dermis	Blisters, blanches with pressure, swollen, warm	Painful to temperature and air
<b>Deep partial-thickness burn</b>	Epidermis and reticular dermis	Blisters (easily unroofed), does not blanch with pressure	Painless; perception of pressure only
<b>Full-thickness burn</b>	Epidermis and full-thickness dermis	White, waxy, dry, inelastic, leathery, does not blanch with pressure	Painless; perception of deep pressure only
<b>Deeper injury burn</b>	Epidermis, dermis, and involvement of underlying tissue (eg, fascia, muscle)	White, dry, inelastic, does not blanch with pressure	Painless; some perception of deep pressure

**Skin cancer**

Basal cell carcinoma more common above **upper lip**

Squamous cell carcinoma more common below **lower lip**

Sun exposure strongly predisposes to skin cancer.

**Basal cell carcinoma**

Most common skin cancer. Found in sun-exposed areas of body (eg, face). Locally invasive, but rarely metastasizes. Waxy, pink, pearly nodules, commonly with telangiectasias, rolled borders **A**, central crusting or ulceration. BCCs also appear as nonhealing ulcers with infiltrating growth **B** or as a scaling plaque (superficial BCC) **C**. Basal cell tumors have “palisading” (aligned) nuclei **D**.

**Keratoacanthoma**

Seen in middle-aged and elderly individuals. Rapidly growing, resembles squamous cell carcinoma. Presents as dome-shaped nodule with keratin-filled center. Grows rapidly (4-6 weeks) and may spontaneously regress **E**.

**Melanoma**

Common tumor with significant risk of metastasis. S-100 tumor marker. Associated with dysplastic nevi; people with lighter skin tones are at ↑ risk. Depth of tumor (Breslow thickness) 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 **F**, nodular **G**, lentigo maligna **H**, and acral lentiginous (highest prevalence in people with darker skin tones) **I**. Often driven by activating mutation in BRAF kinase. Primary treatment is excision with appropriately wide margins. Advanced melanoma also treated with immunotherapy (eg, ipilimumab) and/or BRAF inhibitors (eg, vemurafenib).

**Squamous cell carcinoma**

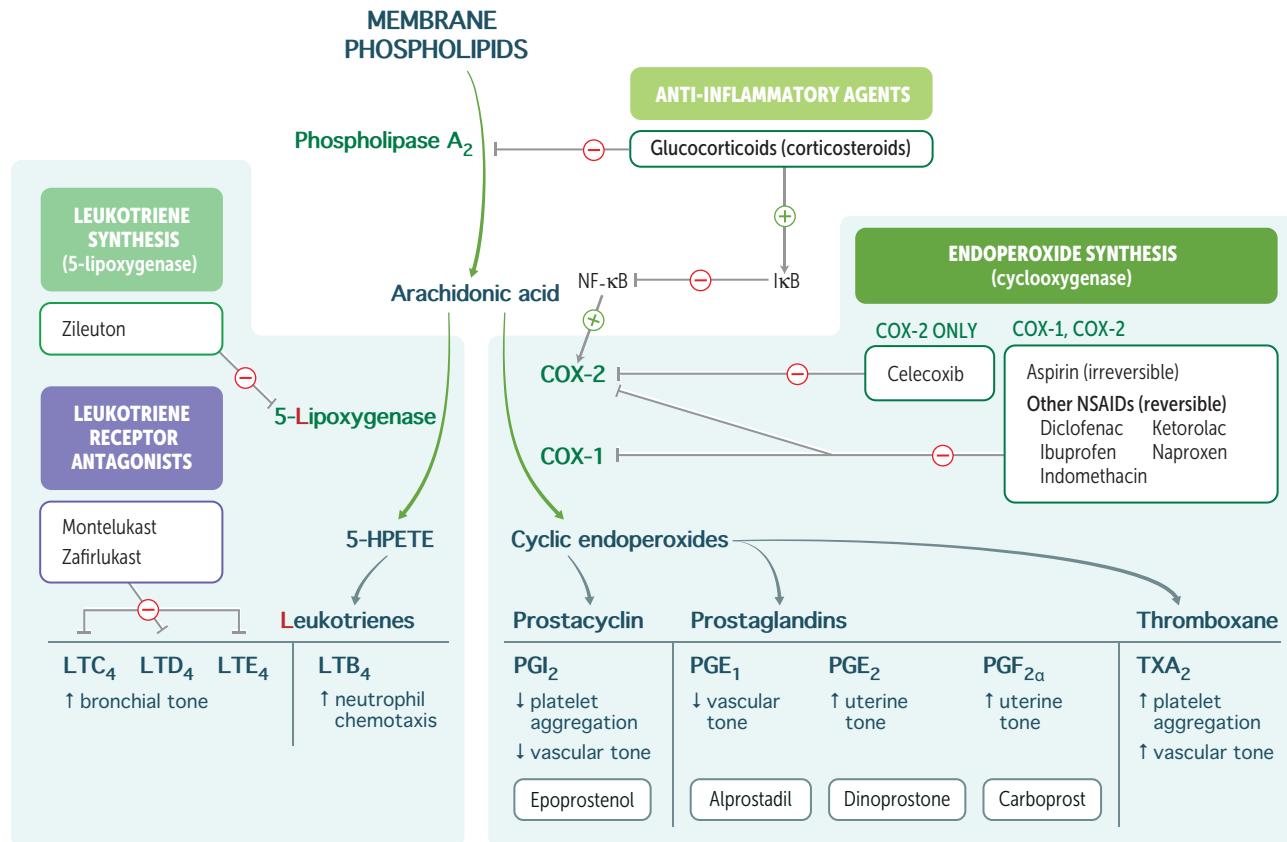
Second most common skin cancer. Associated with immunosuppression, chronic nonhealing wounds, and occasionally arsenic exposure. Commonly appears on face **J**, lower lip **K**, ears, hands. Locally invasive, may spread to lymph nodes, and will rarely metastasize. Ulcerative red lesions. Histopathology: keratin “pearls” **L**.

**Actinic keratosis**, a scaly plaque, is a precursor to squamous cell carcinoma.



## ► MUSCULOSKELETAL, SKIN, AND CONNECTIVE TISSUE—PHARMACOLOGY

## Arachidonic acid pathways



LTB<sub>4</sub> is a **neutrophil** chemotactic agent.

PGI<sub>2</sub> inhibits platelet aggregation and promotes vasodilation.

Neutrophils arrive “B4” others.

Platelet-Gathering Inhibitor.

## Acetaminophen

MECHANISM	Reversibly inhibits cyclooxygenase, mostly in CNS. Inactivated peripherally.
CLINICAL USE	Antipyretic, analgesic, but not anti-inflammatory. Used instead of aspirin to avoid Reye syndrome in children with viral infection.
ADVERSE EFFECTS	Overdose produces hepatic necrosis; acetaminophen metabolite (NAPQI) depletes glutathione and forms toxic tissue byproducts in liver. N-acetylcysteine is antidote—regenerates glutathione.

**Aspirin**

MECHANISM	NSAID that irreversibly inhibits cyclooxygenase (both COX-1 and COX-2) by covalent acetylation → ↓ synthesis of TXA <sub>2</sub> 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), allergic reactions (especially in patients with asthma or nasal polyps). Chronic use can lead to acute kidney injury, interstitial nephritis, GI bleeding. Risk of Reye syndrome in children treated with aspirin for viral infection. Toxic doses cause respiratory alkalosis early, but transitions to mixed metabolic acidosis-respiratory alkalosis. Treatment of overdose: NaHCO <sub>3</sub> .

**Celecoxib**

MECHANISM	Reversibly and <b>selectively</b> inhibits the cyclooxygenase ( <b>COX</b> ) isoform 2 (“ <b>Selecoxib</b> ”), which is found in inflammatory cells and vascular endothelium and mediates inflammation and pain; spares COX-1, which helps maintain gastric mucosa. Thus, does not have the corrosive effects of other NSAIDs on the GI lining. Spares platelet function as TXA <sub>2</sub> production is dependent on COX-1.
CLINICAL USE	Rheumatoid arthritis, osteoarthritis.
ADVERSE EFFECTS	↑ risk of thrombosis, sulfa allergy.

**Nonsteroidal anti-inflammatory drugs**

Ibuprofen, naproxen, indomethacin, ketorolac, diclofenac, meloxicam, piroxicam.

MECHANISM	Reversibly inhibit cyclooxygenase (both COX-1 and COX-2). Block prostaglandin synthesis.
CLINICAL USE	Antipyretic, analgesic, anti-inflammatory. Indomethacin is used to close a PDA.
ADVERSE EFFECTS	Interstitial nephritis, gastric ulcer (prostaglandins protect gastric mucosa), renal ischemia (prostaglandins vasodilate afferent arteriole), aplastic anemia.

**Leflunomide**

MECHANISM	Reversibly inhibits dihydroorotate dehydrogenase, preventing pyrimidine synthesis. Suppresses T-cell proliferation.
CLINICAL USE	Rheumatoid arthritis, psoriatic arthritis.
ADVERSE EFFECTS	Diarrhea, hypertension, hepatotoxicity, teratogenicity.

**Bisphosphonates**

Alendronate, ibandronate, risedronate, zoledronate.

MECHANISM	Pyrophosphate analogs; bind hydroxyapatite in bone, inhibiting osteoclast activity.
CLINICAL USE	Osteoporosis, hypercalcemia, Paget disease of bone, metastatic bone disease, osteogenesis imperfecta.
ADVERSE EFFECTS	Esophagitis (if taken orally, patients are advised to take with water and remain upright for 30 minutes), osteonecrosis of jaw, atypical femoral stress fractures.

**Teriparatide**

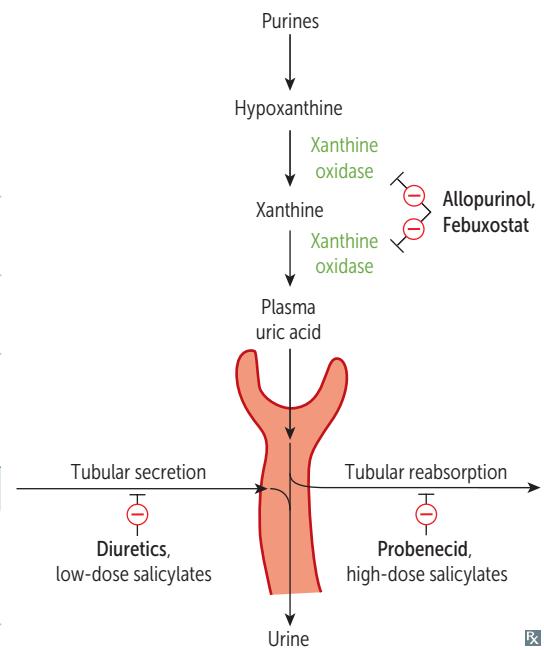
MECHANISM	Recombinant PTH analog. ↑ osteoblastic activity when administered in pulsatile fashion.
CLINICAL USE	Osteoporosis. Causes ↑ bone growth compared to antiresorptive therapies (eg, bisphosphonates).
ADVERSE EFFECTS	↑ risk of osteosarcoma (avoid use in patients with Paget disease of the bone or unexplained elevation of alkaline phosphatase). Avoid in patients who have had prior cancers or radiation therapy. Transient hypercalcemia.

**Gout drugs****Chronic gout drugs (preventive)**

<b>Allupurinol</b>	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 xanthine oxidase active metabolites, azathioprine, and 6-MP.	All painful flares are preventable.
<b>Pegloticase</b>	Recombinant uricase catalyzing uric acid to allantoin (a more water-soluble product).	
<b>Febuxostat</b>	Inhibits xanthine oxidase. Think, “febu-xo-stat makes Xanthine Oxidase static.”	
<b>Probenecid</b>	Inhibits reabsorption of uric acid in proximal convoluted tubule (also inhibits secretion of penicillin). Can precipitate uric acid calculi.	

**Acute gout drugs**

<b>NSAIDs</b>	Any NSAID. Use salicylates with caution (may decrease uric acid excretion, particularly at low doses).
<b>Glucocorticoids</b>	Oral, intra-articular, or parenteral.
<b>Colchicine</b>	Binds and stabilizes tubulin to inhibit microtubule polymerization, impairing neutrophil chemotaxis and degranulation. Acute and prophylactic value. GI, neuromyopathic side effects. Can also cause myelosuppression, nephrotoxicity.



**TNF- $\alpha$  inhibitors**

DRUG	MECHANISM	CLINICAL USE	ADVERSE EFFECTS
<b>Etanercept</b>	Fusion protein (decoy receptor for TNF- $\alpha$ + IgG <sub>1</sub> Fc), produced by recombinant DNA.  Etanercept intercepts TNF.	Rheumatoid arthritis, psoriasis, ankylosing spondylitis	Predisposition to infection, including reactivation of latent TB, since TNF is important in granuloma formation and stabilization.
<b>Infliximab, adalimumab, certolizumab, golimumab</b>	Anti-TNF- $\alpha$ monoclonal antibody.	Inflammatory bowel disease, rheumatoid arthritis, ankylosing spondylitis, psoriasis	Can also lead to drug-induced lupus.

# Neurology and Special Senses

*“We are all now connected by the Internet, like neurons in a giant brain.”*  
—Stephen Hawking

*“Anything’s possible if you’ve got enough nerve.”*  
—J.K. Rowling, *Harry Potter and the Order of the Phoenix*

*“I like nonsense; it wakes up the brain cells.”*  
—Dr. Seuss

*“I believe in an open mind, but not so open that your brains fall out.”*  
—Arthur Hays Sulzberger

*“The chief function of the body is to carry the brain around.”*  
—Thomas Edison

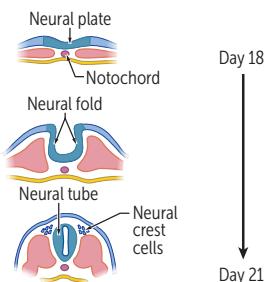
*“Exactly how [the brain] operates remains one of the biggest unsolved mysteries, and it seems the more we probe its secrets, the more surprises we find.”*

—Neil deGrasse Tyson

Understand the difference between the findings and underlying anatomy of upper motor neuron and lower motor neuron lesions. Know the major motor, sensory, cerebellar and visual pathways and their respective locations in the CNS. Connect key neurological associations with certain pathologies (eg, cerebellar lesions, stroke manifestations, Brown-Séquard syndrome). Recognize common findings on MRI/CT (eg, ischemic and hemorrhagic stroke) and on neuropathology (eg, neurofibrillary tangles and Lewy bodies). High-yield medications include those used to treat epilepsy, Parkinson disease, migraine, and pain (eg, opioids).

► Embryology	504
► Anatomy and Physiology	507
► Pathology	528
► Otology	551
► Ophthalmology	553
► Pharmacology	564

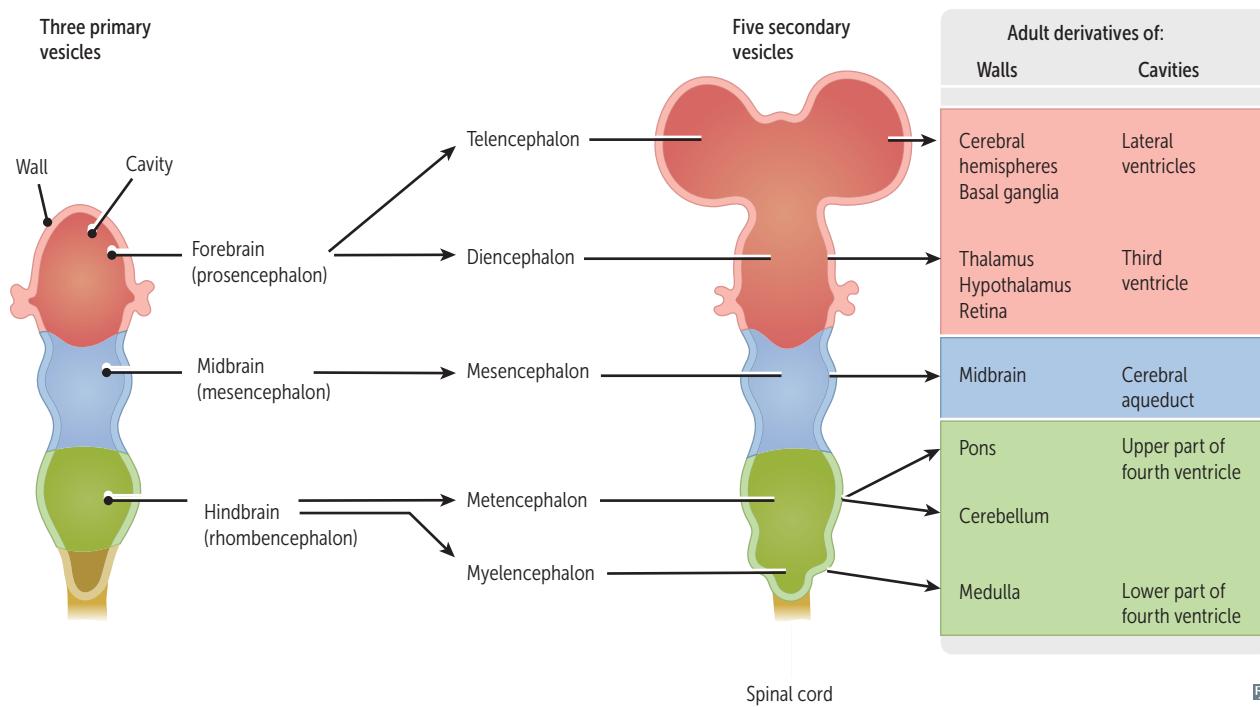
## ▶ NEUROLOGY—EMBRYOLOGY

**Neural development**

Notochord induces overlying ectoderm to differentiate into neuroectoderm and form neural plate.  
 Neural plate gives rise to neural tube and neural crest cells.  
 Notochord becomes nucleus pulposus of intervertebral disc in adults.  
 Alar plate (dorsal): sensory; regulated by TGF- $\beta$  (including bone morphogenetic protein [BMP])  
 Basal plate (ventral): motor; regulated by sonic hedgehog gene (*SHH*) ] Same orientation as spinal cord

**Regional specification of developing brain**

Telencephalon is the 1st part. Diencephalon is the 2nd part. The rest are arranged alphabetically: mesencephalon, metencephalon, myelencephalon.

**Central and peripheral nervous systems origins**

Neuroepithelia in neural tube—CNS neurons, CNS glial cells (astrocytes, oligodendrocytes, ependymal cells).  
 Neural crest—PNS neurons (dorsal root ganglia, autonomic ganglia [sympathetic, parasympathetic, enteric]), PNS glial cells (Schwann cells, satellite cells), adrenal medulla, melanocytes, face/branchial arch mesenchyme.  
 Mesoderm—microglia (like macrophages).

**Neural tube defects**

Neuropores fail to fuse by the 4th week of development → persistent connection between amniotic cavity and spinal canal. Associated with diabetes and folate deficiency during pregnancy.  
 ↑ α-fetoprotein (AFP) in amniotic fluid and serum (except spina bifida occulta = normal AFP).  
 ↑ acetylcholinesterase (AChE) in amniotic fluid is a helpful confirmatory test.

**Spina bifida occulta**

Failure of caudal neuropore to close, but no herniation. Usually seen at lower vertebral levels. Dura is intact. Associated with tuft of hair or skin dimple at level of bony defect.

**Meningocele**

Meninges (but no neural tissue) herniate through bony defect.

**Myelomeningocele**

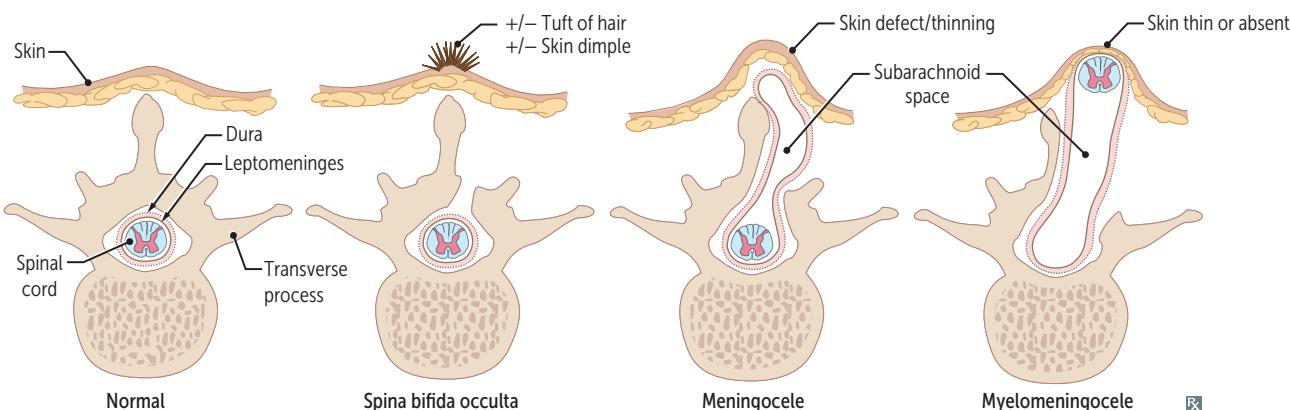
Meninges and neural tissue (eg, cauda equina) herniate through bony defect.

**Myeloschisis**

Also called rachischisis. Exposed, unfused neural tissue without skin/meningeal covering.

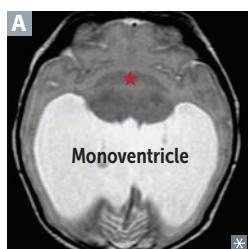
**Anencephaly**

Failure of rostral neuropore to close → no forebrain, open calvarium. Clinical findings: polyhydramnios (no swallowing center in brain).

**Holoprosencephaly**

Developmental field defect characterized by failure of embryonic forebrain (prosencephalon) to separate into 2 cerebral hemispheres; usually occurs during weeks 3–4 of development. May be related to mutations in sonic hedgehog signaling pathway. Associated with other midline defects including cleft lip/palate (moderate form) and cyclopia (severe form). ↑ risk for pituitary dysfunction (eg, diabetes insipidus). May be seen with Patau syndrome (trisomy 13) and maternal alcohol use.

MRI reveals monoventricle **A** and fusion of basal ganglia (star in **A**).

**Lissencephaly**

Failure of neuronal migration resulting in a “smooth brain” that lacks sulci and gyri **A**. May be associated with microcephaly, ventriculomegaly, hydrocephalus.



### Posterior fossa malformations

#### Chiari I malformation

Ectopia of cerebellar tonsils inferior to foramen magnum (1 structure) **A**. Congenital, usually asymptomatic in childhood, manifests in adulthood with headaches and cerebellar symptoms. Associated with spinal cavitations (eg, syringomyelia).

#### Chiari II malformation

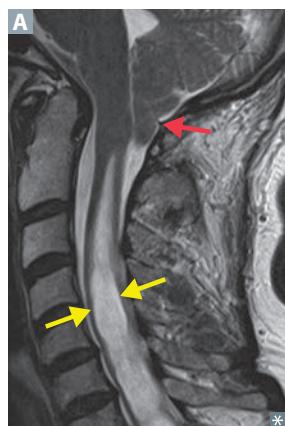
Herniation of cerebellum (vermis and tonsils) and medulla (2 structures) through foramen magnum → noncommunicating hydrocephalus. Usually associated with aqueductal stenosis, lumbosacral myelomeningocele (may present as paralysis/sensory loss at and below the level of the lesion). More severe than Chiari I, usually presents early in life.

#### Dandy-Walker malformation

Agenesis of cerebellar vermis → cystic enlargement of 4th ventricle (arrow in **B**) that fills the enlarged posterior fossa. Associated with noncommunicating hydrocephalus, spina bifida.

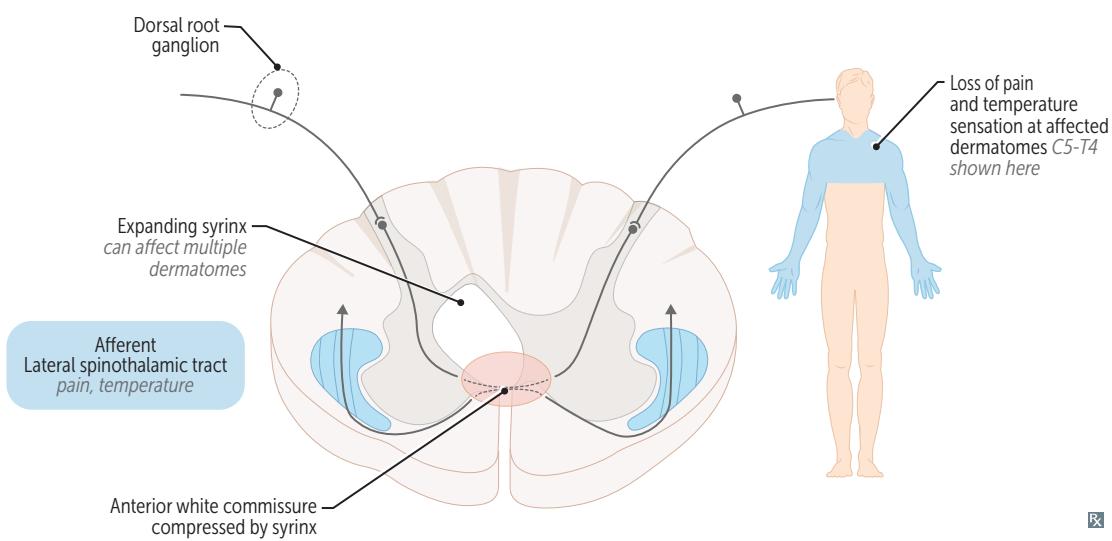


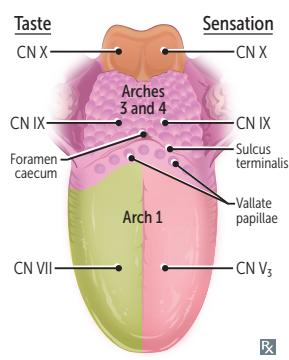
### Syringomyelia



Cystic cavity (syrinx) within central canal of spinal cord (yellow arrows in **A**). Fibers crossing in anterior white commissure (spinothalamic tract) are typically damaged first. Results in a “cape-like,” bilateral, symmetrical loss of pain and temperature sensation in upper extremities (fine touch sensation is preserved).

Associated with Chiari I malformation (red arrow in **A** shows low-lying cerebellar tonsils), scoliosis and other congenital malformations; acquired causes include trauma and tumors. Most common location cervical > thoracic > lumbar. **Syrinx** = tube, as in “**syringe**.”



**Tongue development**

1st pharyngeal arch forms anterior 2/3 of tongue (sensation via CN V<sub>3</sub>, taste via CN VII).

3rd and 4th pharyngeal arches form posterior 1/3 of tongue (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 V<sub>3</sub>, IX, X.

Motor—CN X, XII.

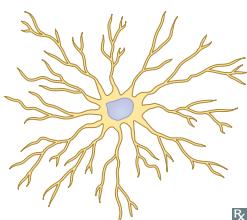
The **genie** comes **out** of the lamp in **style**.

CN **10** innervates **palaten****glossus**.

## ▶ NEUROLOGY—ANATOMY AND PHYSIOLOGY

**Neurons**

Signal-transmitting cells of the nervous system. Permanent cells—do not divide in adulthood. Signal-relaying cells with dendrites (receive input), cell bodies, and axons (send output). Cell bodies and dendrites can be seen on Nissl staining (stains RER). RER is not present in the axon. Neuron markers: neurofilament protein, synaptophysin.

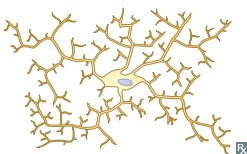
**Astrocytes**

Most common glial cell type in CNS.

Physical support, repair, removal of excess neurotransmitter, component of blood-brain barrier, glycogen fuel reserve buffer. Reactive gliosis in response to neural injury.

Derived from neuroectoderm.

Astrocyte marker: GFAP.

**Microglia**

Phagocytic scavenger cells of CNS. Activation in response to tissue damage → release of inflammatory mediators (eg, nitric oxide, glutamate). Not readily discernible by Nissl stain.

Derived from mesoderm.

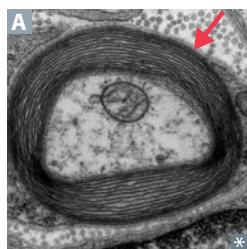
HIV-infected microglia fuse to form multinucleated giant cells in CNS seen in HIV-associated dementia.

**Ependymal cells**

Ciliated simple columnar glial cells lining ventricles and central canal of spinal cord. Apical surfaces are covered with cilia (which circulate CSF) and microvilli (which help with CSF absorption).

Derived from neuroectoderm.

Specialized ependymal cells (choroid plexus) produce CSF.

**Myelin**

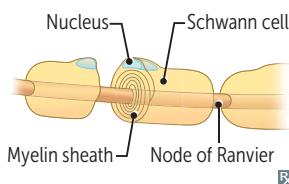
↑ conduction velocity of signals transmitted down axons → saltatory conduction of action potential at the nodes of Ranvier, where there are high concentrations of  $\text{Na}^+$  channels.

In CNS (including CN II), myelin is synthesized by oligodendrocytes; in PNS (including CN III-XII), myelin is synthesized by Schwann cells.

Myelin (arrow in A) wraps and insulates axons:  
 ↓ membrane capacitance, ↑ membrane resistance, ↑ space (length) constant, ↓ time constant.

CNS: Oligodendrocytes.

PNS: Schwann cells. COPS

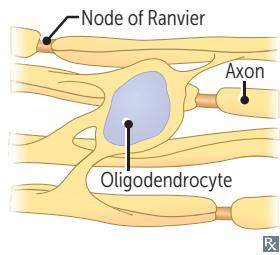
**Schwann cells**

Promote axonal regeneration. Derived from neural crest.

Each “Schwone” cell myelinates only 1 PNS axon.

Injured in Guillain-Barré syndrome.

Schwann cell marker: S100.

**Oligodendrocytes**

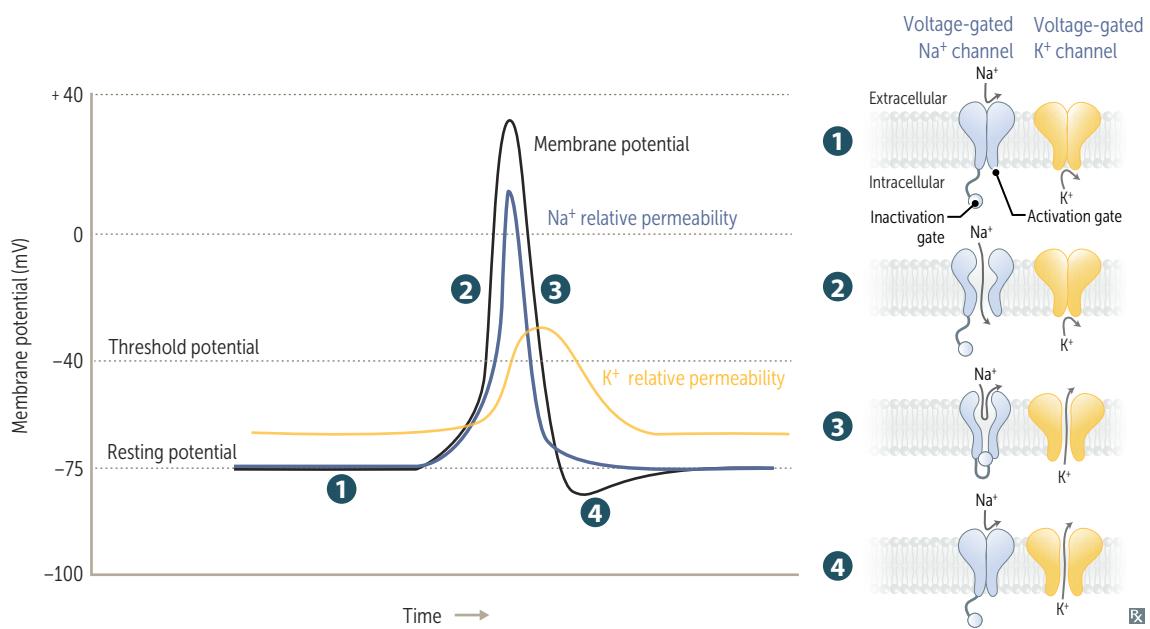
Myelinate axons of neurons in CNS. Each oligodendrocyte can myelinate many axons (~ 30). Predominant type of glial cell in white matter.

Derived from neuroectoderm.

“Fried egg” appearance histologically.

Injured in multiple sclerosis, progressive multifocal leukoencephalopathy (PML), leukodystrophies.

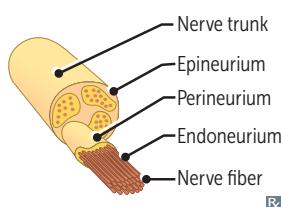
### Neuron action potential



- ① Resting membrane potential: membrane is more permeable to K<sup>+</sup> than Na<sup>+</sup> at rest. Voltage-gated Na<sup>+</sup> and K<sup>+</sup> channels are closed.
- ② Membrane depolarization: Na<sup>+</sup> activation gate opens → Na<sup>+</sup> flows inward.
- ③ Membrane repolarization: Na<sup>+</sup> inactivation gate closes at peak potential, thus stopping Na<sup>+</sup> inflow. K<sup>+</sup> activation gate opens → K<sup>+</sup> flows outward.
- ④ Membrane hyperpolarization: K<sup>+</sup> activation gates are slow to close → excess K<sup>+</sup> efflux and brief period of hyperpolarization. Voltage-gated Na<sup>+</sup> channels switch back to resting state. Na<sup>+</sup>/K<sup>+</sup> pump restores ions concentration.

### Sensory receptors

RECEPTOR TYPE	SENSORY NEURON FIBER TYPE	LOCATION	SENSES
<b>Free nerve endings</b>	Aδ—fast, myelinated fibers C—slow, unmyelinated A Delta plane is fast, but a taxC is slow	All tissues except cartilage and eye lens; numerous in skin	Pain, temperature
<b>Meissner corpuscles</b>	Large, myelinated fibers; adapt quickly	Glabrous (hairless) skin	Dynamic, fine/light touch, position sense, low-frequency vibration, skin indentation
<b>Pacinian corpuscles</b>	Large, myelinated fibers; adapt quickly	Deep skin layers, ligaments, joints	High-frequency vibration, pressure
<b>Merkel discs</b>	Large, myelinated fibers; adapt slowly	Finger tips, superficial skin	Pressure, deep static touch (eg, shapes, edges)
<b>Ruffini corpuscles</b>	Large, myelinated fiber intertwined among collagen fiber bundles; adapt slowly	Finger tips, joints	Stretch, joint angle change

**Peripheral nerve**

Endoneurium—thin, supportive connective tissue that ensheathes and supports individual myelinated nerve fibers. May be affected in Guillain-Barré syndrome.

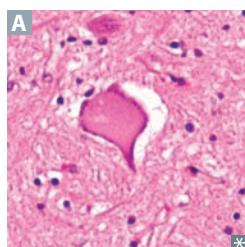
*Endo* = inner

*Peri* = around

*Epi* = outer

Perineurium (blood-nerve permeability barrier)—surrounds a fascicle of nerve fibers.

Epineurium—dense connective tissue that surrounds entire nerve (fascicles and blood vessels).

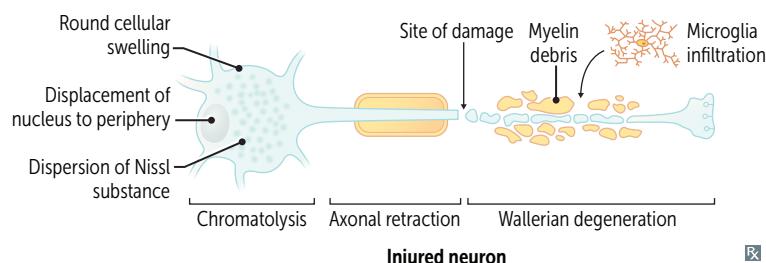
**Chromatolysis**

Reaction of neuronal cell body to axonal injury. Changes reflect ↑ protein synthesis in effort to repair the damaged axon. Characterized by:

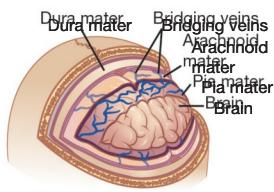
- Round cellular swelling **A**
- Displacement of the nucleus to the periphery
- Dispersion of Nissl substance throughout cytoplasm

**Wallerian degeneration**—disintegration of the axon and myelin sheath distal to site of axonal injury with macrophages removing debris.

Proximal to the injury, the axon retracts, and the cell body sprouts new protrusions that grow toward other neurons for potential reinnervation. Serves as a preparation for axonal regeneration and functional recovery.

**Neurotransmitter changes with disease**

	LOCATION OF SYNTHESIS	ANXIETY	DEPRESSION	SCHIZOPHRENIA	ALZHEIMER DISEASE	HUNTINGTON DISEASE	PARKINSON DISEASE
<b>Acetylcholine</b>	Basal nucleus of Meynert (forebrain)				↓	↓	↑
<b>Dopamine</b>	Ventral tegmentum, SNc (midbrain)		↓	↑		↑	↓
<b>GABA</b>	Nucleus accumbens (basal ganglia)	↓				↓	
<b>Norepinephrine</b>	Locus ceruleus (pons)	↑	↓				
<b>Serotonin</b>	Raphe nuclei (brain stem)	↓	↓				↓

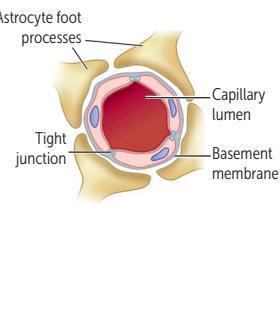
**Meninges**

Three membranes that surround and protect the brain and spinal cord:

- Dura mater—thick outer layer closest to skull. Derived from mesoderm.
- Arachnoid mater—middle layer, contains web-like connections. Derived from neural crest.
- Pia mater—thin, fibrous inner layer that firmly adheres to brain and spinal cord. Derived from neural crest.

CSF flows in the subarachnoid space, located between arachnoid and pia mater.

Epidural space—potential space between dura mater and skull/vertebral column containing fat and blood vessels. Site of blood collection associated with middle meningeal artery injury.

**Blood-brain barrier**

Prevents circulating blood substances (eg, bacteria, drugs) from reaching the CSF/CNS. Formed by 4 structures:

- Tight junctions between nonfenestrated capillary endothelial cells
- Basement membrane
- Astrocyte foot processes
- Pericytes

Glucose and amino acids cross slowly by carrier-mediated transport mechanisms.

Nonpolar/lipid-soluble substances cross rapidly via diffusion.

Circumventricular organs with fenestrated capillaries and no blood-brain barrier allow molecules in blood to affect brain function (eg, area postrema—vomiting after chemotherapy; OVLT [organum vasculosum lamina terminalis]—osmoreceptors or neurosecretory products to enter circulation (eg, neurohypophysis—ADH release).

Infarction and/or neoplasm destroys endothelial cell tight junctions → vasogenic edema.

Hyperosmolar agents (eg, mannitol) can disrupt the BBB → ↑ permeability of medications.

**Vomiting center**

Coordinated by nucleus tractus solitarius (NTS) in the medulla, which receives information from the chemoreceptor trigger zone (CTZ, located within area postrema (pronounce “puke”-stremma) in 4th ventricle), GI tract (via vagus nerve), vestibular system, and CNS.

CTZ and adjacent vomiting center nuclei receive input from 5 major receptors: muscarinic ( $M_1$ ), dopamine ( $D_2$ ), histamine ( $H_1$ ), serotonin ( $5-HT_3$ ), and neurokinin (NK-1) receptors.

- $5-HT_3$ ,  $D_2$ , and NK-1 antagonists used to treat chemotherapy-induced vomiting.
- $H_1$  and  $M_1$  antagonists treat motion sickness;  $H_1$  antagonists treat hyperemesis gravidarum.

**Sleep physiology**

Sleep cycle is regulated by the circadian rhythm, which is driven by suprachiasmatic nucleus (SCN) of the hypothalamus. Circadian rhythm controls nocturnal release of ACTH, prolactin, melatonin, norepinephrine: SCN → norepinephrine release → pineal gland → ↑ melatonin. SCN is regulated by environment (eg, light).

Two stages: rapid-eye movement (REM) and non-REM.

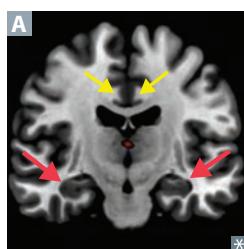
Alcohol, benzodiazepines, and barbiturates are associated with ↓ REM sleep and N3 sleep; norepinephrine also ↓ REM sleep.

Benzodiazepines are useful for night terrors and sleepwalking by ↓ N3 and REM sleep.

SLEEP STAGE (% OF TOTAL SLEEP TIME IN YOUNG ADULTS)	DESCRIPTION	EEG WAVEFORM AND NOTES
<b>Awake (eyes open)</b>	Alert, active mental concentration.	Beta (highest frequency, lowest amplitude).
<b>Awake (eyes closed)</b>		Alpha.
<b>Non-REM sleep</b>		
<b>Stage N1 (5%)</b>	Light sleep.	Theta.
<b>Stage N2 (45%)</b>	Deeper sleep; when bruxism (“ <b>twoth<td>Sleep spindles and K complexes.</td></b>	Sleep spindles and K complexes.
<b>Stage N3 (25%)</b>	Deepest non-REM sleep (slow-wave sleep); <b>sleepwalking</b> , night terrors, and <b>bedwetting</b> occur ( <b>wee</b> and <b>flee</b> in N3).	Delta (lowest frequency, highest amplitude), deepest sleep stage.
<b>REM sleep (25%)</b>	Loss of motor tone, ↑ brain O <sub>2</sub> use, variable pulse/BP, ↑ ACh. REM is when dreaming, nightmares, and penile/clitoral tumescence occur; may serve memory processing function. Extraocular movements due to activity of PPRF (paramedian pontine reticular formation/conjugate gaze center). Occurs every 90 minutes, and duration ↑ through the night.	Beta. Changes in elderly: ↓ REM, ↓ N3, ↑ sleep latency, ↑ early awakenings. Changes in depression: ↑ REM sleep time, ↓ REM latency, ↓ N3, repeated nighttime awakenings, early morning awakening (terminal insomnia). Change in narcolepsy: ↓ REM latency. At night, <b>BATS</b> Drink Blood.

<b>Hypothalamus</b>	Maintains homeostasis by regulating Thirst and water balance, controlling Adenohypophysis (anterior pituitary) and Neurohypophysis (posterior pituitary) release of hormones produced in the hypothalamus, and regulating Hunger, Autonomic nervous system, Temperature, and Sexual urges ( <b>TAN HATS</b> ). Inputs (areas not protected by blood-brain barrier): OVLT (senses change in osmolarity), area postrema (found in dorsal medulla, responds to emetics).	
<b>Lateral nucleus</b>	Hunger. Destruction → anorexia, failure to thrive (infants). Stimulated by ghrelin, inhibited by leptin.	Lateral injury makes you lean.
<b>Ventromedial nucleus</b>	Satiety. Destruction (eg, craniopharyngioma) → hyperphagia. Stimulated by leptin.	Ventromedial injury makes you very massive.
<b>Anterior nucleus</b>	Cooling, parasympathetic.	<b>A/C</b> = Anterior Cooling.
<b>Posterior nucleus</b>	Heating, sympathetic.	<b>Heating</b> controlled by posterior nucleus (“hot pot”).
<b>Suprachiasmatic nucleus</b>	Circadian rhythm.	<b>SCN</b> is a Sun-Censing Nucleus.
<b>Supraoptic and paraventricular nuclei</b>	Synthesize ADH and oxytocin.	<b>SAD POX:</b> Supraoptic = ADH, Paraventricular = OXytocin. ADH and oxytocin are carried by neurophysins down axons to posterior pituitary, where these hormones are stored and released.
<b>Preoptic nucleus</b>	Thermoregulation, sexual behavior. Releases GnRH.	Failure of GnRH-producing neurons to migrate from olfactory pit → Kallmann syndrome.

Thalamus				
NUCLEI	INPUT	SENSES	DESTINATION	MNEMONIC
<b>Ventral postero-lateral nucleus</b>	Spinothalamic and dorsal columns/medial lemniscus	Vibration, pain, pressure, proprioception (conscious), light touch, temperature	1° somatosensory cortex (parietal lobe)	
<b>Ventral postero-medial nucleus</b>	Trigeminal and gustatory pathway	Face sensation, taste	1° somatosensory cortex (parietal lobe)	<b>V</b> ery pretty makeup goes on the <b>f</b> ace
<b>Lateral geniculate nucleus</b>	CN II, optic chiasm, optic tract	Vision	1° visual cortex (occipital lobe)	<b>L</b> ateral = <b>l</b> ight
<b>Medial geniculate nucleus</b>	Superior olive and inferior colliculus of tectum	Hearing	1° auditory cortex (temporal lobe)	<b>M</b> edial = <b>m</b> usic
<b>Ventral anterior and lateral nuclei</b>	Basal ganglia, cerebellum	Motor	Motor cortices (frontal lobe)	<b>V</b> enus astronauts love to <b>m</b> ove

**Limbic system**

Collection of neural structures involved in emotion, long-term memory, olfaction, behavior modulation, ANS function.

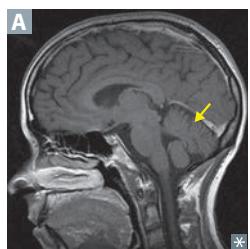
Consists of hippocampus (red arrows in A), amygdalae, mammillary bodies, anterior thalamic nuclei, cingulate gyrus (yellow arrows in A), entorhinal cortex. Responsible for feeding, fleeing, fighting, feeling, and sex.

The famous **5 F's**.

**Dopaminergic pathways**

Commonly altered by drugs (eg, antipsychotics) and movement disorders (eg, Parkinson disease).

PATHWAY	SYMPTOMS OF ALTERED ACTIVITY	NOTES
<b>Mesocortical</b>	↓ activity → “negative” symptoms (eg, anergia, apathy, lack of spontaneity)	Antipsychotic drugs have limited effect
<b>Mesolimbic</b>	↑ activity → “positive” symptoms (eg, delusions, hallucinations)	1° therapeutic target of antipsychotic drugs → ↓ positive symptoms (eg, in schizophrenia)
<b>Nigrostriatal</b>	↓ activity → extrapyramidal symptoms (eg, dystonia, akathisia, parkinsonism, tardive dyskinesia)	Major dopaminergic pathway in brain Significantly affected by movement disorders and antipsychotic drugs
<b>Tuberoinfundibular</b>	↓ activity → ↑ prolactin → ↓ libido, sexual dysfunction, galactorrhea, gynecomastia (in males)	

**Cerebellum**

Modulates movement; aids in coordination and balance **A**.

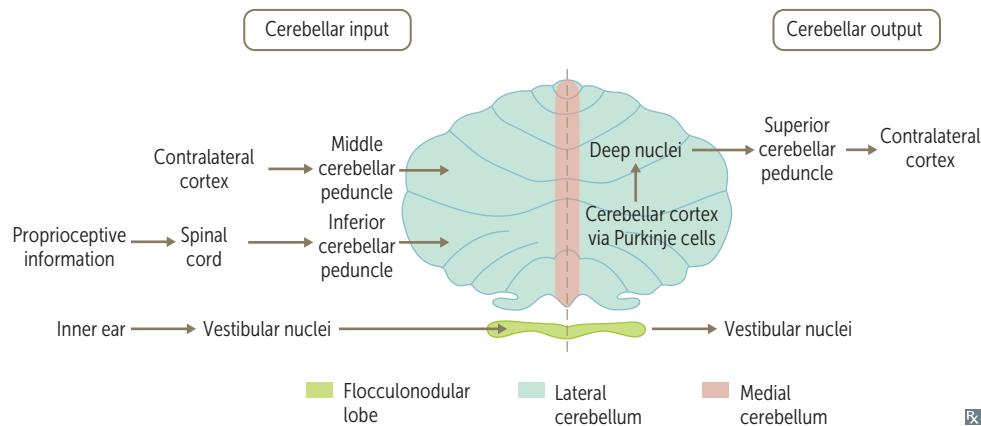
- Ipsilateral (unconscious) proprioceptive information via inferior cerebellar peduncle from spinal cord
- Deep nuclei (lateral → medial)—**d**entate, **e**mboliform, **g**lobose, **f**astigial

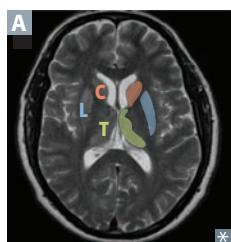
**Lateral** lesions—affect voluntary movement of extremities (**lateral** structures); when injured, propensity to fall toward injured (ipsilateral) side.

**Medial** lesions (eg, vermis, fastigial nuclei, flocculonodular lobe)—truncal ataxia (wide-based cerebellar gait), nystagmus, head tilting. Generally result in bilateral motor deficits affecting axial and proximal limb musculature (**medial structures**).

**Tests:** **f**inger-to-nose, gait, heel-to-shin, dysdiadochokinesis.

**Don't eat** greasy foods.



**Basal ganglia**

Important in voluntary movements and adjusting posture **A**. Receives cortical input, provides negative feedback to cortex to modulate movement.

Striatum = putamen (motor) + Caudate (cognitive).

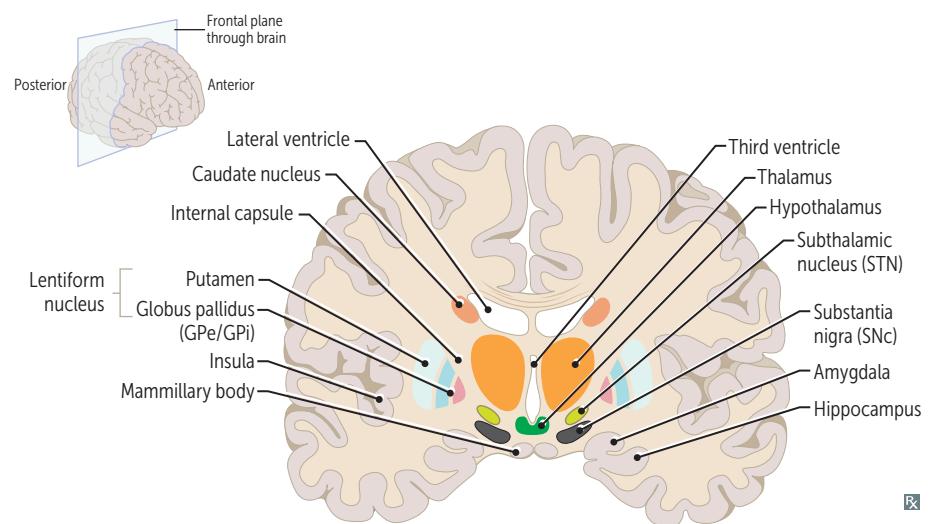
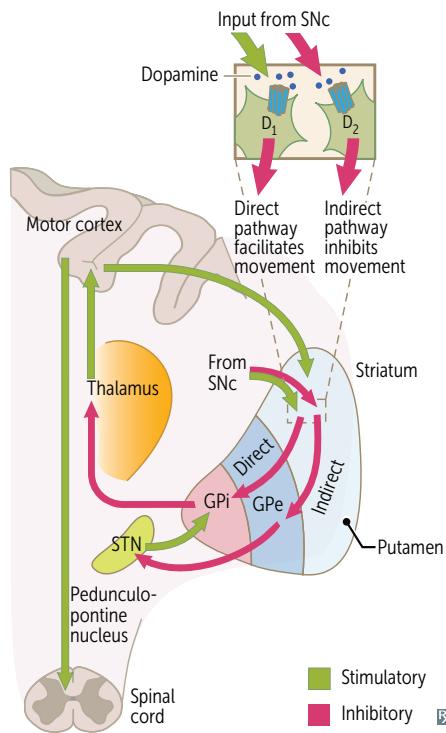
Lentiform = putamen + globus pallidus.

**D<sub>1</sub>** Receptor = **D**irect pathway.  
**Indirect (D<sub>2</sub>)** = **I**nhibitory.

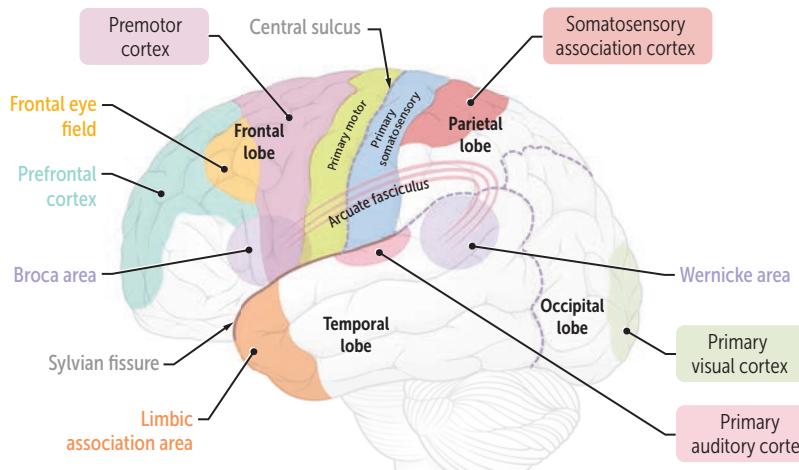
Direct (excitatory) pathway—SNc input to the striatum via the nigrostriatal dopaminergic pathway releases GABA, which inhibits GABA release from the GPi, disinhibiting the Thalamus via the GPi ( $\uparrow$  motion).

Indirect (inhibitory) pathway—SNc input to the striatum via the nigrostriatal dopaminergic pathway releases GABA that disinhibits STN via GPe inhibition, and STN stimulates GPi to inhibit the thalamus ( $\downarrow$  motion).

Dopamine binds to D<sub>1</sub>, stimulating the excitatory pathway, and to D<sub>2</sub>, inhibiting the inhibitory pathway  $\rightarrow \uparrow$  motion.



### Cerebral cortex regions

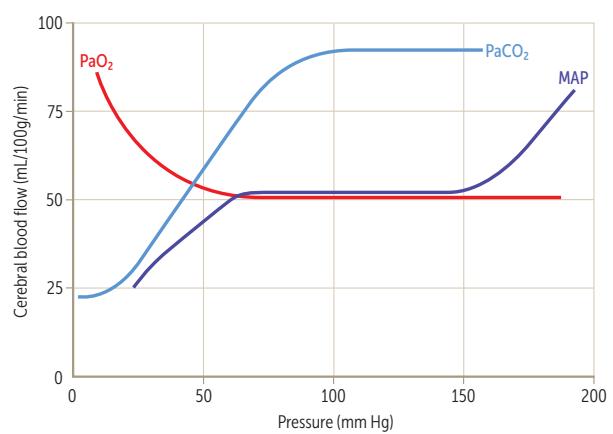


Rx

### Cerebral perfusion

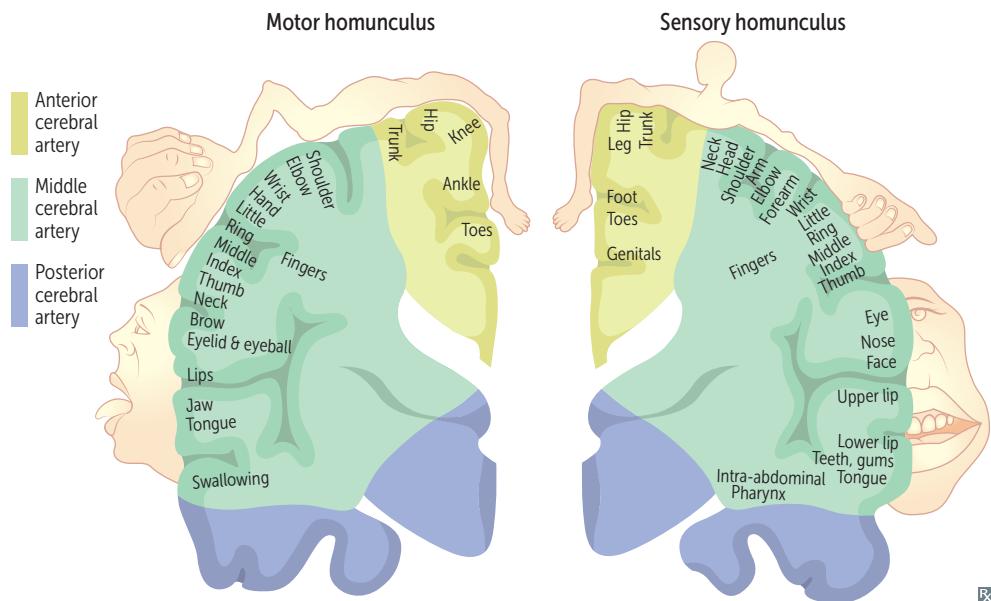
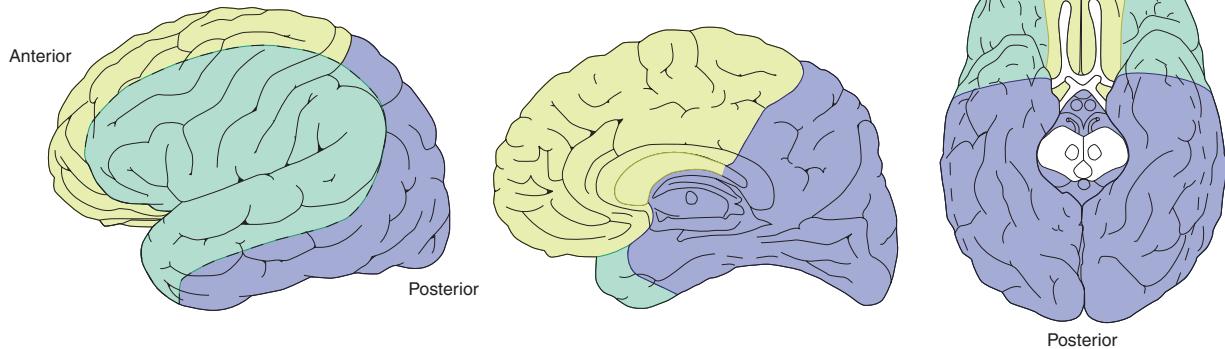
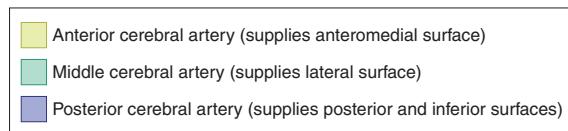
Relies on tight autoregulation. Primarily driven by  $\text{PCO}_2$  ( $\text{PO}_2$  also modulates perfusion in severe hypoxia).  
Also relies on a pressure gradient between mean arterial pressure (MAP) and intracranial pressure (ICP). ↓ blood pressure or ↑ ICP → ↓ cerebral perfusion pressure (CPP).  
Cushing reflex—triad of hypertension, bradycardia, and respiratory depression in response to ↑ ICP.

Therapeutic hyperventilation → ↓  $\text{PCO}_2$  → vasoconstriction → ↓ cerebral blood flow → ↓ 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.  
Hypoxemia increases CPP only if  $\text{PO}_2 < 50$  mm Hg.  
CPP is directly proportional to  $\text{PCO}_2$  until  $\text{PCO}_2 > 90$  mm Hg.



**Homunculus**

Topographic representation of motor and sensory areas in the cerebral cortex. Distorted appearance is due to certain body regions being more richly innervated and thus having ↑ cortical representation.

**Cerebral arteries—cortical distribution****Watershed zones**

Cortical border zones occur between anterior and middle cerebral arteries and posterior and middle cerebral arteries (blue areas in A). Internal border zones occur between the superficial and deep vascular territories of the middle cerebral artery (red areas in A).

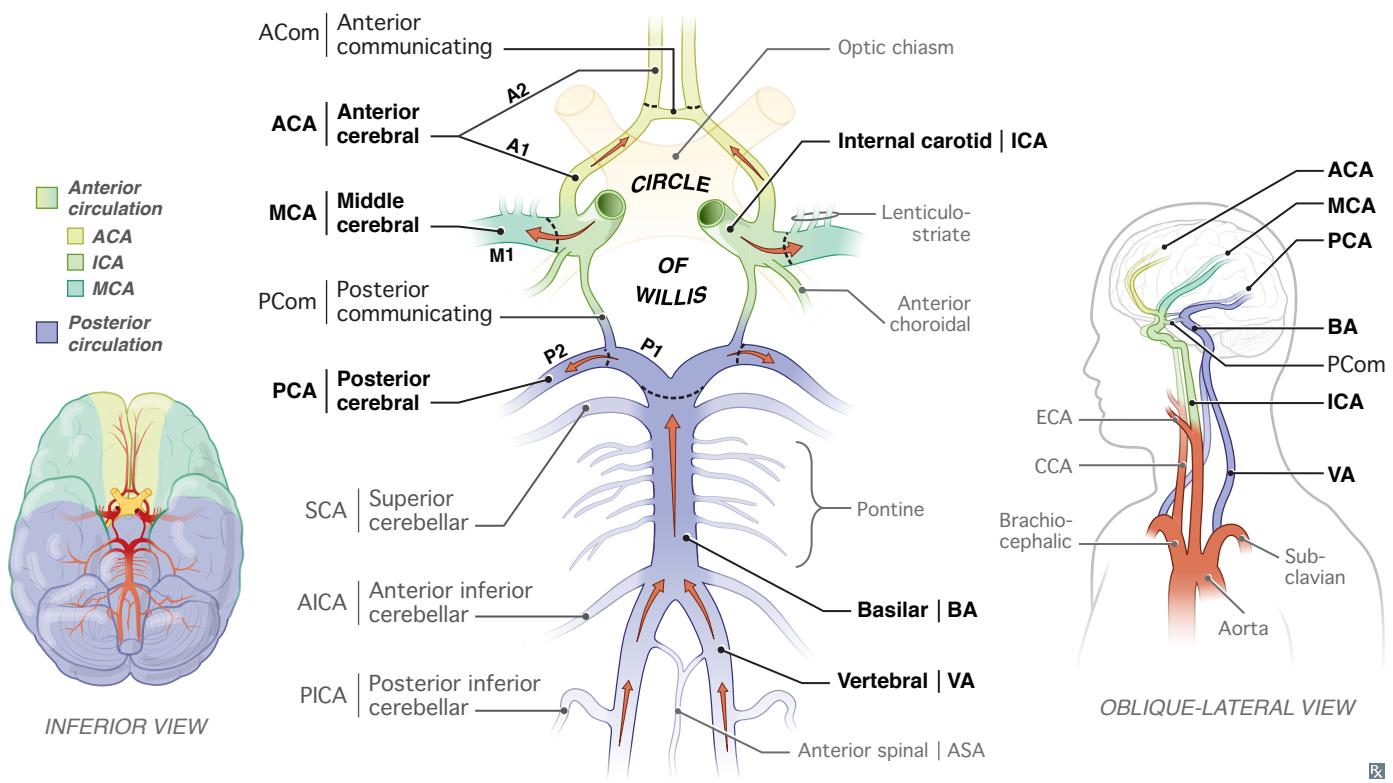
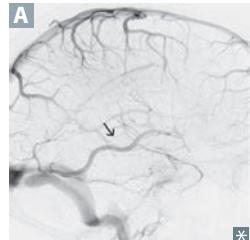
Common locations for brain metastases.

Infarct due to severe hypoperfusion:

- ACA-MCA watershed infarct—proximal upper and lower extremity weakness (“man-in-a-barrel syndrome”).
- PCA-MCA watershed infarct—higher-order visual dysfunction.

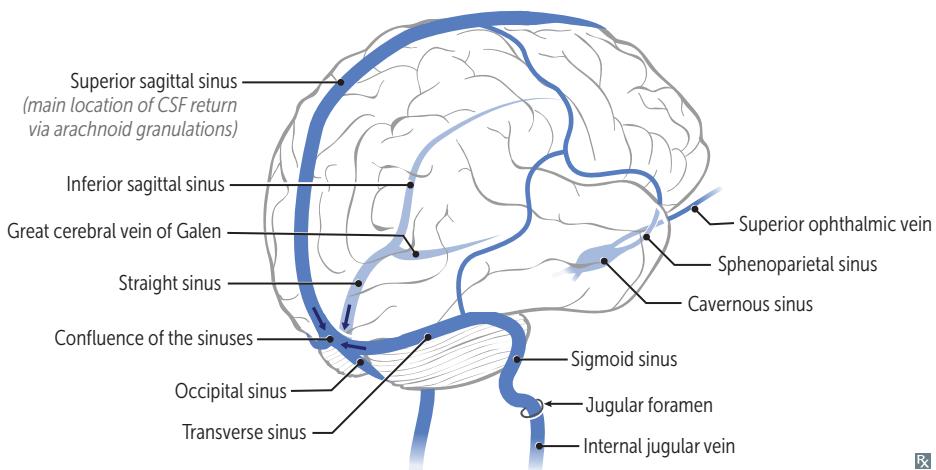
**Circle of Willis**

System of anastomoses between anterior and posterior blood supplies to brain.

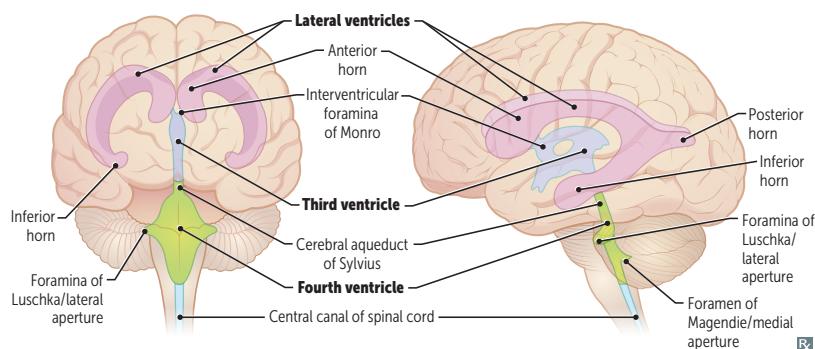
**Dural venous sinuses**

Large venous channels **A** that run through the periosteal and meningeal layers of the dura mater. Drain blood from cerebral veins (arrow) and receive CSF from arachnoid granulations. Empty into internal jugular vein.

**Venous sinus thrombosis**—presents with signs/symptoms of ↑ ICP (eg, headache, seizures, papilledema, focal neurologic deficits). May lead to venous hemorrhage. Associated with hypercoagulable states (eg, pregnancy, OCP use, factor V Leiden).



### Ventricular system



Lateral ventricles → 3rd ventricle via right and left interventricular foramina of Monro.

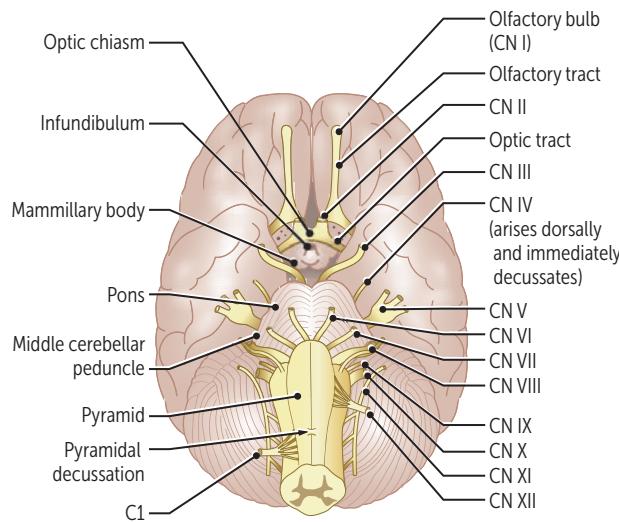
3rd ventricle → 4th ventricle via cerebral aqueduct of Sylvius.

4th ventricle → subarachnoid space via:

- Foramina of **Luschka** = lateral.
- Foramen of **Magendie** = medial.

CSF made by choroid plexuses located in the lateral and fourth ventricles. Travels to subarachnoid space via foramina of Luschka and Magendie, is reabsorbed by arachnoid granulations, and then drains into dural venous sinuses.

### Brain stem—ventral view



4 CN are above pons (I, II, III, IV).

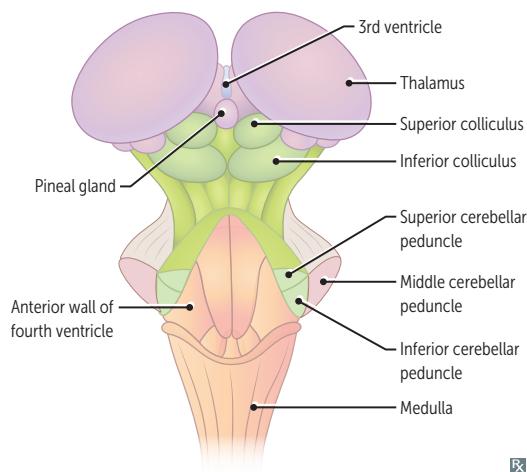
4 CN exit the pons (V, VI, VII, VIII).

4 CN are in medulla (IX, X, XI, XII).

4 CN nuclei are medial (III, IV, VI, XII).

“Factors of 12, except 1 and 2.”

### Brain stem—dorsal view (cerebellum removed)



Pineal gland—melatonin secretion, circadian rhythms.

Superior colliculi—direct eye movements to stimuli (noise/movements) or objects of interest.

Inferior colliculi—auditory.

Your eyes are **above** your ears, and the superior colliculus (visual) is **above** the inferior colliculus (auditory).

**Cranial nerve nuclei**

Located in tegmentum portion of brain stem (between dorsal and ventral portions):

- Midbrain—nuclei of CN III, IV
- Pons—nuclei of CN V, VI, VII, VIII
- Medulla—nuclei of CN IX, X, XII
- Spinal cord—nucleus of CN XI

Lateral nuclei = sensory (alar plate).

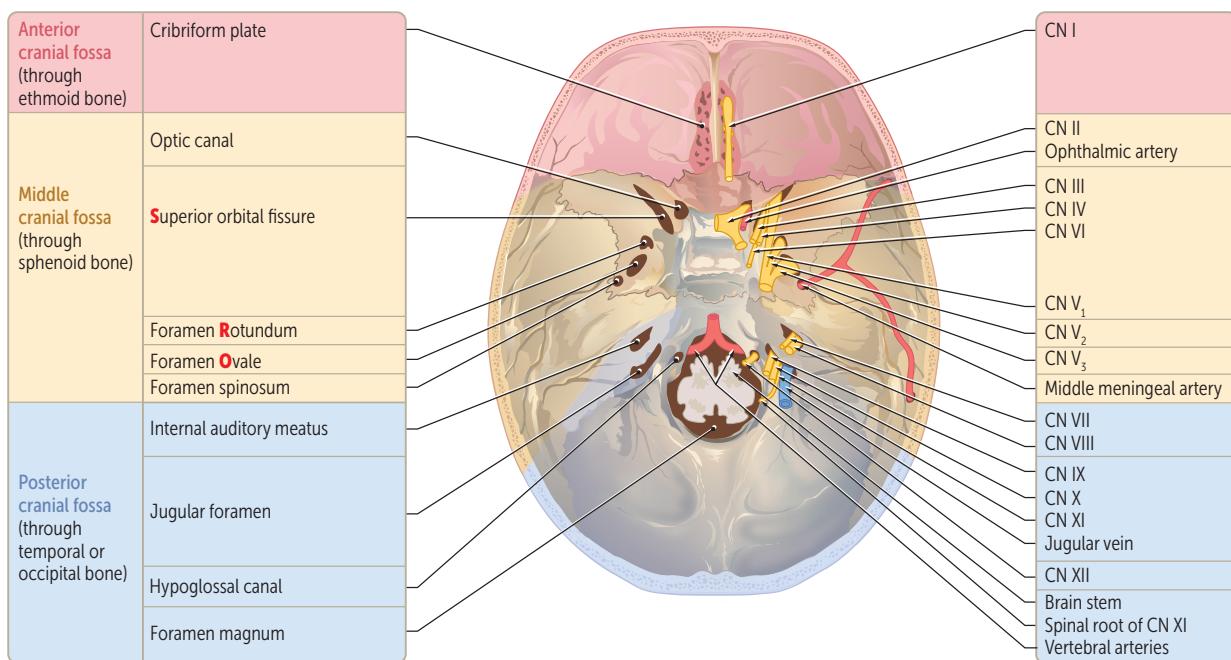
—Sulcus limitans—

Medial nuclei = motor (basal plate).

**Vagal nuclei**

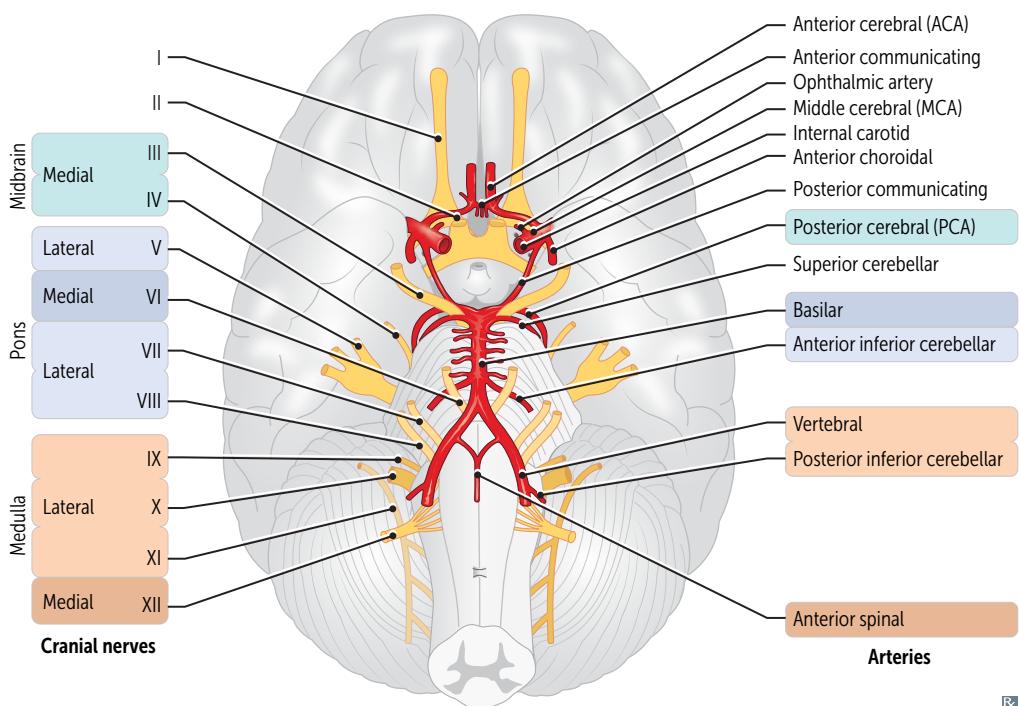
NUCLEUS	FUNCTION	CRANIAL NERVES
<b>Nucleus tractus solitarius</b>	Visceral <b>sensory</b> information (eg, taste, baroreceptors, gut distention) May play a role in vomiting	VII, IX, X
<b>Nucleus ambiguus</b>	<b>Motor</b> innervation of pharynx, larynx, upper esophagus (eg, swallowing, palate elevation)	IX, X, XI (cranial portion)
<b>Dorsal motor nucleus</b>	Sends autonomic (parasympathetic) fibers to heart, lungs, upper GI	X

### Cranial nerves and vessel pathways



Rx

### Cranial nerves and arteries



Rx

**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: pretectal nucleus, Edinger-Westphal nuclei, 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, dampening of loud noises (tensor tympani)	Both	But
Abducens	VI	Eye movement (LR)	Motor	My
Facial	VII	Facial movement, taste from anterior 2/3 of tongue (chorda tympani), lacrimation, salivation (submandibular and sublingual glands are innervated by CN seven), eye closing (orbicularis oculi), auditory volume modulation (stapedius)	Both	Brother
Vestibulocochlear	VIII	Hearing, balance	Sensory	Says
Glossopharyngeal	IX	Taste and sensation from posterior 1/3 of tongue, swallowing, salivation (parotid gland), monitoring carotid body and sinus chemo- and baroreceptors, and elevation of pharynx/larynx (stylopharyngeus)	Both	Big
Vagus	X	Taste from supraglottic region, swallowing, soft palate elevation, midline uvula, talking, cough reflex, parasympathetics to thoracoabdominal viscera, monitoring aortic arch chemo- and baroreceptors	Both	Brains
Accessory	XI	Head turning, shoulder shrugging (SCM, trapezius)	Motor	Matter
Hypoglossal	XII	Tongue movement	Motor	Most

**Cranial nerve reflexes**

REFLEX	AFFERENT	EFFECTIVE
Corneal	V <sub>1</sub> ophthalmic (nasociliary branch)	Bilateral VII (temporal branch—orbicularis oculi)
Cough	X	X (also phrenic and spinal nerves)
Gag	IX	X
Jaw jerk	V <sub>3</sub> (sensory—muscle spindle from masseter)	V <sub>3</sub> (motor—masseter)
Lacrimation	V <sub>1</sub> (loss of reflex does not preclude emotional tears)	VII
Pupillary	II	III

**Mastication muscles**

3 muscles close jaw: masseter, temporalis, medial pterygoid. Lateral pterygoids protrude the jaw. All are innervated by trigeminal nerve (V<sub>3</sub>).

**M's munch.**

**Spinal nerves**

There are 31 pairs of spinal nerves: 8 cervical, 12 thoracic, 5 lumbar, 5 sacral, 1 coccygeal. Nerves C1–C7 exit above the corresponding vertebrae (eg, C3 exits above the 3rd cervical vertebra). C8 spinal nerve exits below C7 and above T1. All other nerves exit below (eg, L2 exits below the 2nd lumbar vertebra).

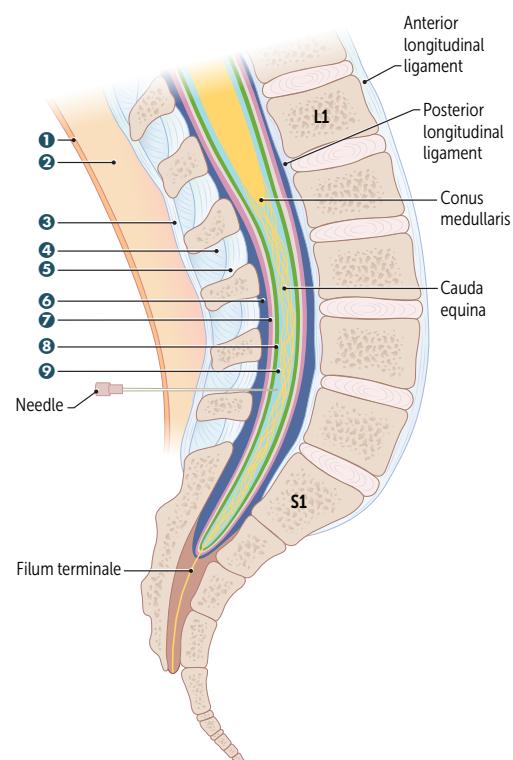
**Spinal cord—lower extent**

In adults, spinal cord ends at lower border of L1–L2 vertebrae. Subarachnoid space (which contains the CSF) extends to lower border of 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**.

Needle passes through:

- ① skin
- ② fascia and fat
- ③ supraspinous ligament
- ④ interspinous ligament
- ⑤ ligamentum flavum
- ⑥ epidural space  
(epidural anesthesia needle stops here)
- ⑦ dura mater
- ⑧ arachnoid mater
- ⑨ subarachnoid space  
(CSF collection occurs here)

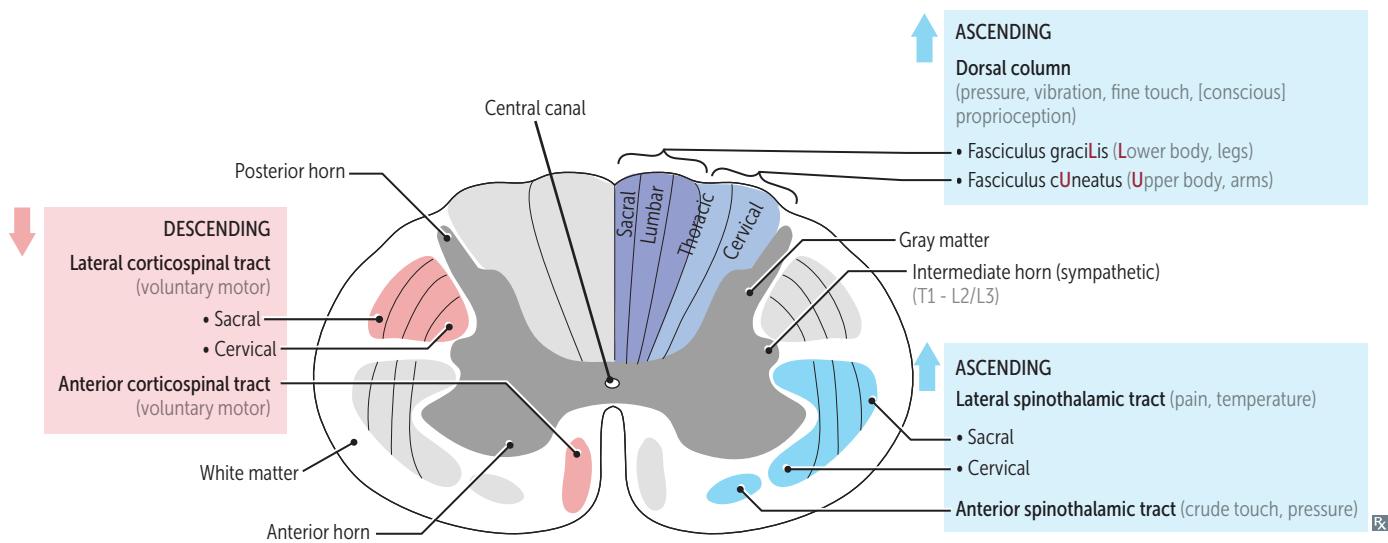
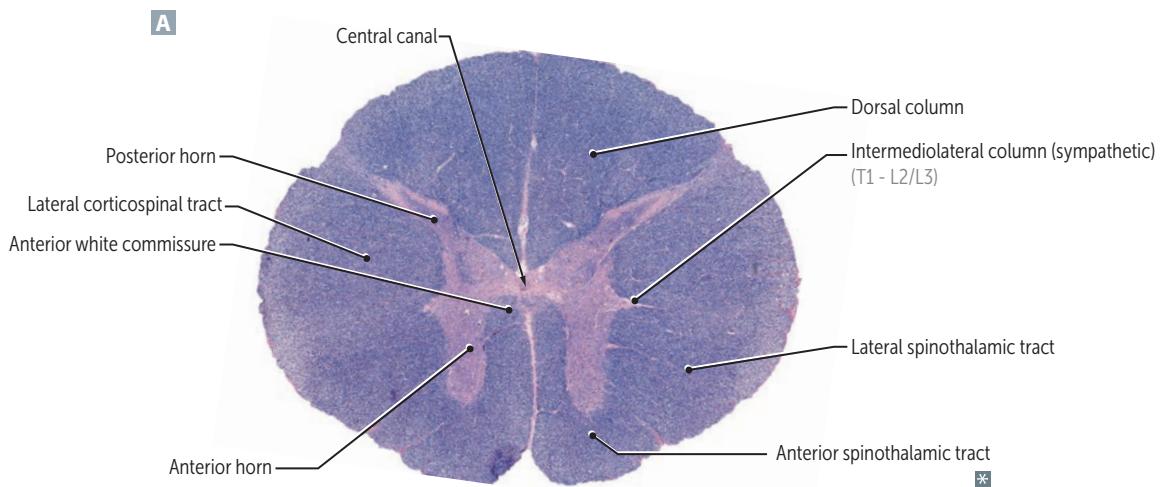


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**Spinal cord and associated tracts**

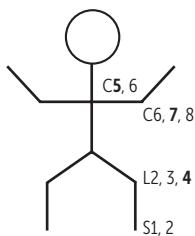
Legs (lumbosacral) are lateral in lateral corticospinal, spinothalamic tracts. Thoracic spinal cord section in **A**.

Dorsal columns are organized as you are, with hands at sides. “Arms outside, legs inside.”



**Spinal tract anatomy and functions** Ascending tracts synapse and then cross.

TRACT	FUNCTION	1ST-ORDER NEURON	SYNAPSE 1	2ND-ORDER NEURON	SYNAPSE 2 + PROJECTIONS
<b>Ascending tracts</b>					
<b>Dorsal column</b>	Pressure, vibration, fine touch, (conscious) proprioception	Sensory nerve ending → bypasses pseudounipolar cell body in dorsal root ganglion → enters spinal cord → ascends ipsilaterally in dorsal columns	Nucleus gracilis, nucleus cuneatus (ipsilateral medulla)	Decussates in medulla → ascends contralaterally as the medial lemniscus	VPL (thalamus) → sensory cortex
<b>Spinothalamic tract</b>	Lateral: pain, temperature Anterior: crude touch, pressure	Sensory nerve ending (A $\delta$ and C fibers) → bypasses pseudounipolar cell body in dorsal root ganglion → enters spinal cord	Ipsilateral gray matter (spinal cord)	Decussates in spinal cord as the anterior white commissure → ascends contralaterally	
<b>Descending tract</b>					
<b>Lateral corticospinal tract</b>	Voluntary movement of contralateral limbs	UMN: cell body in 1° motor cortex → descends ipsilaterally (through posterior limb of internal capsule and cerebral peduncle), most fibers decussate at caudal medulla (pyramidal decussation) → descends contralaterally	Cell body of anterior horn (spinal cord)	LMN: leaves spinal cord	NMJ → muscle fibers

**Clinical reflexes**

Reflexes count up in order (main nerve root in bold):

**Achilles reflex** = S1, S2 (“buckle my shoe”)

**Patellar reflex** = L2-L4 (“kick the door”)

**Biceps and brachioradialis reflexes** = C5, C6 (“pick up sticks”)

**Triceps reflex** = C6, C7, C8 (“lay them straight”)

Additional reflexes:

**Cremasteric reflex** = L1, L2 (“testicles move”)

**Anal wink reflex** = S3, S4 (“winks galore”)

Reflex grading:

0: absent

1: hypoactive

2: normal

3: hyperactive

4: clonus

**Primitive reflexes**

CNS reflexes that are present in a healthy infant, but are absent in a neurologically intact adult. Normally disappear within 1st year of life. These primitive reflexes are inhibited by a mature/developing frontal lobe. They may reemerge in adults following frontal lobe lesions → loss of inhibition of these reflexes.

**Moro reflex**

“Hang on for life” reflex—abduct/extend arms when startled, and then draw together.

**Rooting reflex**

Movement of head toward one side if cheek or mouth is stroked (nipple seeking).

**Sucking reflex**

Sucking response when roof of mouth is touched.

**Palmar reflex**

Curling of fingers if palm is stroked.

**Plantar reflex**

Dorsiflexion of large toe and fanning of other toes with plantar stimulation.

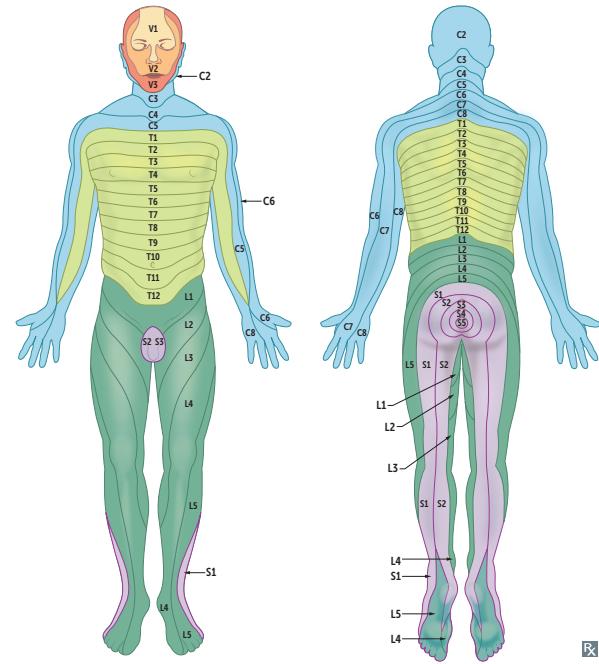
Babinski sign—presence of this reflex in an adult, which may signify a UMN lesion.

**Galant reflex**

Stroking along one side of the spine while newborn is in ventral suspension (face down) causes lateral flexion of lower body toward stimulated side.

**Landmark dermatomes**

DERMATOME	CHARACTERISTICS
C2	Posterior half of skull
C3	High turtleneck shirt Diaphragm and gallbladder pain referred to the right shoulder via phrenic nerve <b>C3, 4, 5</b> keeps the diaphragm <b>alive</b>
C4	Low-collar shirt
C6	Includes thumbs <b>Thumbs up</b> sign on left hand looks like a <b>6</b>
T4	At the <b>nipple</b> <b>T4</b> at the <b>teat pore</b>
T7	At the xiphoid process <b>7</b> letters in xiphoid
T10	At the umbilicus (belly button) Point of referred pain in early appendicitis
L1	At the <b>Inguinal Ligament</b>
L4	Includes the kneecaps Down on <b>ALL 4's</b>
S2, S3, S4	Sensation of penile and anal zones <b>S2, 3, 4</b> keep the penis off the <b>floor</b>



## ▶ NEUROLOGY—PATHOLOGY

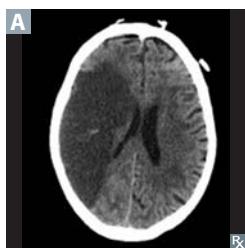
**Common brain lesions**

AREA OF LESION	CONSEQUENCE	EXAMPLES/COMMENTS
<b>Frontal lobe</b>	Disinhibition and deficits in concentration, orientation, judgment; may have reemergence of primitive reflexes	
<b>Frontal eye fields</b>	Destructive lesions (eg, MCA stroke): eyes look toward brain lesion (ie, away from side of hemiplegia)	
<b>Paramedian pontine reticular formation</b>	Eyes look away from brain lesion (ie, toward side of hemiplegia)	
<b>Medial longitudinal fasciculus</b>	Internuclear ophthalmoplegia (impaired adduction of ipsilateral eye; nystagmus of contralateral eye with abduction)	Multiple sclerosis
<b>Dominant parietal cortex</b>	Agraphia, acalculia, finger agnosia, left-right disorientation	Gerstmann syndrome
<b>Nondominant parietal cortex</b>	Agnosia of the contralateral side of the world	Hemispatial neglect syndrome
<b>Hippocampus (bilateral)</b>	Anterograde amnesia— inability to make new memories	
<b>Basal ganglia</b>	May result in tremor at rest, chorea, athetosis	Parkinson disease, Huntington disease, Wilson disease
<b>Subthalamic nucleus</b>	Contralateral hemiballismus	
<b>Mammillary bodies (bilateral)</b>	<b>Wernicke-Korsakoff syndrome</b> — Confusion, Ataxia, Nystagmus, Ophthalmoplegia, memory loss (anterograde and retrograde amnesia), confabulation, personality changes	Wernicke problems come in a <b>CAN O'</b> beer and other conditions associated with thiamine deficiency
<b>Amygdala (bilateral)</b>	<b>Klüver-Bucy syndrome</b> — disinhibited behavior (eg, hyperphagia, hypersexuality, hyperorality)	HSV-1 encephalitis
<b>Dorsal midbrain</b>	<b>Parinaud syndrome</b> — vertical gaze palsy, pupillary light-near dissociation, lid retraction, convergence-retraction nystagmus	Stroke, hydrocephalus, pinealoma
<b>Reticular activating system (midbrain)</b>	Reduced levels of arousal and wakefulness	Coma
<b>Cerebellar hemisphere</b>	Intention tremor, limb ataxia, loss of balance; damage to cerebellum → ipsilateral deficits; fall toward side of lesion	Cerebellar hemispheres are <b>laterally</b> located— affect <b>lateral</b> limbs
<b>Cerebellar vermis</b>	Truncal ataxia (wide-based, “drunken sailor” gait), nystagmus	Vermis is <b>centrally</b> located—affects <b>central</b> body Degeneration associated with chronic alcohol use
<b>Red nucleus (midbrain)</b>	Decorticate (flexor) posturing—lesion above red nucleus, presents with flexion of upper extremities and extension of lower extremities Decerebrate (extensor) posturing—lesion at or below red nucleus, presents with extension of upper and lower extremities	Worse prognosis with decerebrate posturing In <b>decorticate</b> posturing, your hands are near the <b>cor</b> (heart)

**Ischemic brain disease/stroke**

Irreversible neuronal injury begins after 5 minutes of hypoxia. Most **vulnerable**: hippocampus, neocortex, cerebellum (Purkinje cells), **watershed areas** (“**vulnerable hippos need pure water**”). Stroke imaging: noncontrast CT to exclude hemorrhage (before tPA can be given). CT detects ischemic changes in 6–24 hr. Diffusion-weighted MRI can detect ischemia within 3–30 min.

TIME SINCE ISCHEMIC EVENT	12–24 HOURS	24–72 HOURS	3–5 DAYS	1–2 WEEKS	> 2 WEEKS
<b>Histologic features</b>	Eosinophilic cytoplasm + pyknotic nuclei (red neurons)	Necrosis + neutrophils	Macrophages (microglia)	Reactive gliosis (astrocytes) + vascular proliferation	Glial scar

**Ischemic stroke**

Acute blockage of vessels → disruption of blood flow and subsequent ischemia → infarction → liquefactive necrosis.

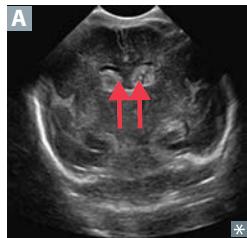
3 types:

- Thrombotic—due to a clot forming directly at site of infarction (commonly the MCA **A**), usually over a ruptured atherosclerotic plaque.
- Embolic—embolus from another part of the body obstructs vessel. Can affect multiple vascular territories. Examples: atrial fibrillation, carotid artery stenosis, DVT with patent foramen ovale (paradoxical embolism), infective endocarditis.
- Hypoxic—due to hypoperfusion or hypoxemia. Common during cardiovascular surgeries, tends to affect watershed areas.

Treatment: tPA (if within 3–4.5 hr of onset and no hemorrhage/risk of hemorrhage) and/or thrombectomy (if large artery occlusion). Reduce risk with medical therapy (eg, aspirin, clopidogrel); optimum control of blood pressure, blood sugars, lipids; smoking cessation; and treat conditions that ↑ risk (eg, atrial fibrillation, carotid artery stenosis).

**Transient ischemic attack**

Brief, reversible episode of focal neurologic dysfunction without acute infarction ( $\ominus$  MRI), with the majority resolving in < 15 minutes; ischemia (eg, embolus, small vessel stenosis). May present with amaurosis fugax (transient visual loss) due to retinal artery emboli from carotid artery disease.

**Neonatal  
intraventricular  
hemorrhage**

Bleeding into ventricles (arrows in A show blood in intraventricular spaces on ultrasound).

Increased risk in premature and low-birth-weight infants. Originates in germinal matrix, a highly vascularized layer within the subventricular zone. Due to reduced glial fiber support and impaired autoregulation of BP in premature infants. Can present with altered level of consciousness, bulging fontanelle, hypotension, seizures, coma.

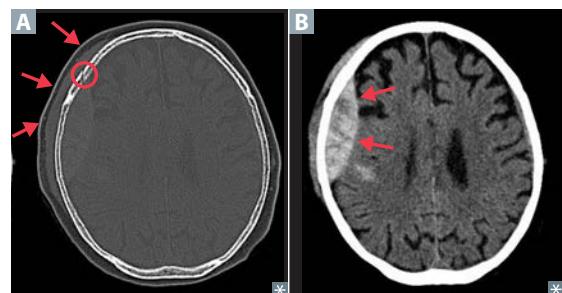
### Intracranial hemorrhage

#### Epidural hematoma

Rupture of middle meningeal artery (branch of maxillary artery), often 2° to skull fracture (circle in **A**) involving the pterion (thinnest area of the lateral skull). Might present with transient loss of consciousness → recovery (“lucid interval”) → rapid deterioration due to hematoma expansion.

Scalp hematoma (arrows in **A**) and rapid intracranial expansion (arrows in **B**) under systemic arterial pressure → transtentorial herniation, CN III palsy.

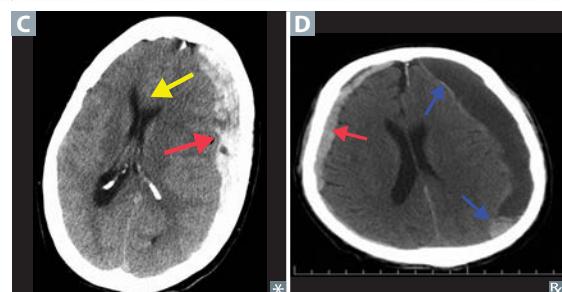
CT shows biconvex (lentiform), hyperdense blood collection **B** **not crossing suture lines**.



#### Subdural hematoma

Rupture of bridging veins. Can be acute (traumatic, high-energy impact → hyperdense on CT) or chronic (associated with mild trauma, cerebral atrophy, elderly, chronic alcohol overuse → hypodense on CT). Also seen in shaken babies. Predisposing factors: brain atrophy, trauma.

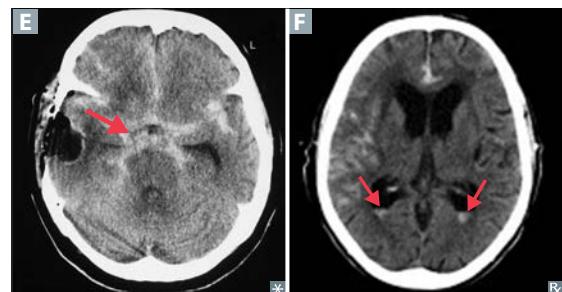
Crescent-shaped hemorrhage (red arrows in **C** and **D**) that **crosses suture lines**. Can cause midline shift (yellow arrow in **C**), findings of “acute on chronic” hemorrhage (blue arrows in **D**).



#### Subarachnoid hemorrhage

Bleeding **E F** due to trauma, or rupture of an aneurysm (such as a saccular aneurysm **E**) or arteriovenous malformation. Rapid time course. Patients complain of “worst headache of my life.” Bloody or yellow (xanthochromic) lumbar puncture.

Vasospasm can occur due to blood breakdown or rebleed 3–10 days after hemorrhage → ischemic infarct; nimodipine used to prevent/reduce vasospasm. ↑ risk of developing communicating and/or obstructive hydrocephalus.



#### Intraparenchymal hemorrhage

Most commonly caused by systemic hypertension. Also seen with amyloid angiopathy (recurrent lobar hemorrhagic stroke in elderly), vascular malformations, vasculitis, neoplasm. May be 2° to reperfusion injury in ischemic stroke.

Hypertensive hemorrhages (Charcot-Bouchard microaneurysm) most often occur in putamen of basal ganglia (lenticulostriate vessels **G**), followed by thalamus, pons, and cerebellum **H**.

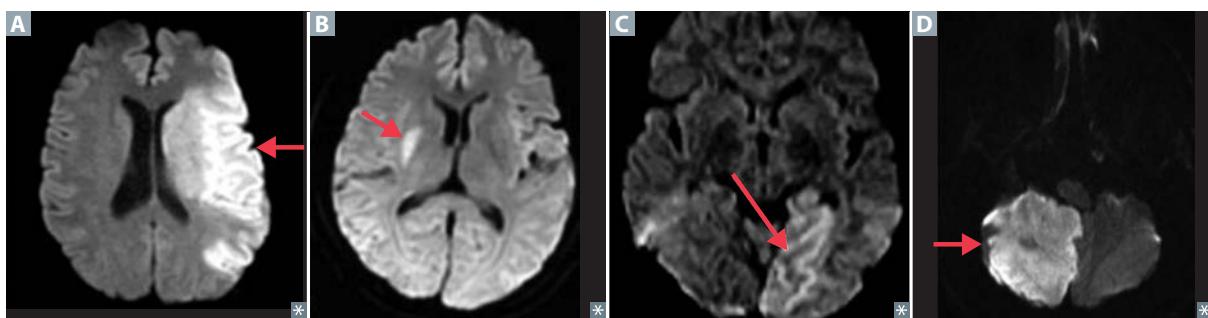


**Effects of strokes**

ARTERY	AREA OF LESION	SYMPTOMS	NOTES
<b>Anterior circulation</b>			
<b>Anterior cerebral artery</b>	Motor and sensory cortices—lower limb.	Contralateral paralysis and sensory loss—lower limb, urinary incontinence.	
<b>Middle cerebral artery</b>	Motor and sensory cortices <b>A</b> —upper limb and face. Temporal lobe (Wernicke area); frontal lobe (Broca area).	Contralateral paralysis and sensory loss—face and upper limb. Aphasia if in dominant (usually left) hemisphere. Hemineglect if lesion affects nondominant (usually right) hemisphere.	Wernicke aphasia is associated with right superior quadrant visual field defect due to temporal lobe involvement.
<b>Lenticulo-striate artery</b>	Striatum, internal capsule.	Contralateral paralysis. Absence of cortical signs (eg, neglect, aphasia, visual field loss).	Pure motor stroke (most common). Common location of lacunar infarcts <b>B</b> , due to microatheroma and hyaline arteriosclerosis (lipohyalinosis) $2^{\circ}$ to unmanaged hypertension.
<b>Posterior circulation</b>			
<b>Posterior cerebral artery</b>	Occipital lobe <b>C</b> .	Contralateral hemianopia with macular sparing; alexia without agraphia (dominant hemisphere, extending to splenium of corpus callosum); prosopagnosia (nondominant hemisphere).	
<b>Basilar artery</b>	Pons, medulla, lower midbrain.  Corticospinal and corticobulbar tracts.  Ocular cranial nerve nuclei, paramedian pontine reticular formation.	If RAS spared, consciousness is preserved.  Quadriplegia; loss of voluntary facial, mouth, and tongue movements.  Loss of horizontal, but not vertical, eye movements.	<b>Locked-in syndrome (locked in the basement).</b>
<b>Anterior inferior cerebellar artery</b>	Facial nucleus.  Vestibular nuclei. Spinothalamic tract, spinal trigeminal nucleus.  Sympathetic fibers. Middle and inferior cerebellar peduncles. Labyrinthine artery.	Paralysis of face (LMN lesion vs UMN lesion in cortical stroke), ↓ lacrimation, ↓ salivation, ↓ taste from anterior 2/3 of tongue.  Vomiting, vertigo, nystagmus ↓ pain and temperature sensation from contralateral body, ipsilateral face.  Ipsilateral Horner syndrome. Ipsilateral ataxia, dysmetria.  Ipsilateral sensorineural deafness, vertigo.	<b>Lateral pontine syndrome.</b> Facial nucleus effects are specific to AICA lesions.

**Effects of strokes (continued)**

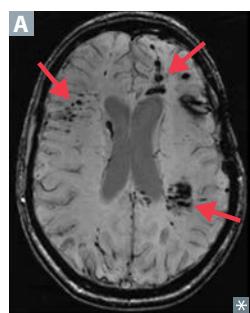
ARTERY	AREA OF LESION	SYMPTOMS	NOTES
<b>Posterior inferior cerebellar artery</b>	Nucleus ambiguus (CN IX, X, XI).  Vestibular nuclei.  Lateral spinothalamic tract, spinal trigeminal nucleus.  Sympathetic fibers.  Inferior cerebellar peduncle.	Dysphagia, hoarseness, ↓ gag reflex, hiccups.  Vomiting, vertigo, nystagmus ↓ pain and temperature sensation from contralateral body, ipsilateral face.  Ipsilateral Horner syndrome.  Ipsilateral ataxia, dysmetria.	Lateral medullary (Wallenberg) syndrome.  Nucleus ambiguus effects are specific to PICA lesions <b>D</b> . “Don’t pick a (PICA) horse (hoarseness) that can’t eat (dysphagia).”
<b>Anterior spinal artery</b>	Corticospinal tract.  Medial lemniscus.  Caudal medulla—hypoglossal nerve.	Contralateral paralysis—upper and lower limbs.  ↓ contralateral proprioception.  Ipsilateral hypoglossal dysfunction (tongue deviates ipsilaterally).	<b>Medial Medullary syndrome</b> —caused by infarct of paramedian branches of ASA and/or vertebral arteries. <b>Ants</b> love <b>M&amp;M’s</b> .

**Central poststroke pain syndrome**

Neuropathic pain due to thalamic lesions. Initial paresthesias followed in weeks to months by allodynia (ordinarily painless stimuli cause pain) and dysesthesia (altered sensation) on the contralateral side. Occurs in 10% of stroke patients.

**Diffuse axonal injury**

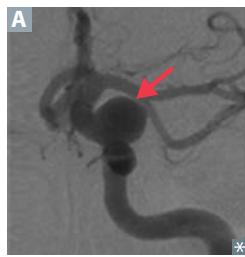
Traumatic shearing of white matter tracts during rapid acceleration and/or deceleration of the brain (eg, motor vehicle accident). Usually results in devastating neurologic injury, often causing coma or persistent vegetative state. MRI shows multiple lesions (punctate hemorrhages) involving white matter tracts **A**.



**Aphasia**

Aphasia—higher-order language deficit (inability to understand/produce/use language appropriately); caused by pathology in dominant cerebral hemisphere (usually left).  
Dysarthria—motor inability to produce speech (movement deficit).

TYPE	COMMENTS
<b>Broca (expressive)</b>	Broca area in inferior frontal gyrus of frontal lobe. Associated with defective language production. Patients appear frustrated, insight intact. <b>Broca</b> = <b>b</b> roken <b>b</b> oca ( <i>boca</i> = mouth in Spanish).
<b>Wernicke (receptive)</b>	Wernicke area in superior temporal gyrus of temporal lobe. Associated with impaired language comprehension. Patients do not have insight. <b>Wernicke</b> is a <b>w</b> ord <b>s</b> alad and makes no sense.
<b>Conduction</b>	Can be caused by damage to ar <b>C</b> uate fasciculus.
<b>Global</b>	Broca and Wernicke areas affected.

**Aneurysms****Saccular aneurysm**

Abnormal dilation of an artery due to weakening of vessel wall.

Also called berry aneurysm **A**. Occurs at bifurcations in the circle of Willis. Most common site is junction of ACom and ACA. Associated with ADPKD, Ehlers-Danlos syndrome. Other risk factors: advanced age, hypertension, tobacco smoking.

Usually clinically silent until rupture (most common complication) → subarachnoid hemorrhage (“worst headache of my life” or “thunderclap headache”) → focal neurologic deficits. Can also cause symptoms via direct compression of surrounding structures by growing aneurysm.

- ACom—compression → bitemporal hemianopia (compression of optic chiasm); visual acuity deficits; rupture → ischemia in ACA distribution → contralateral lower extremity hemiparesis, sensory deficits.
- MCA—rupture → ischemia in MCA distribution → contralateral upper extremity and lower facial hemiparesis, sensory deficits.
- PCom—compression → ipsilateral CN III palsy → mydriasis (“blown pupil”); may also see ptosis, “down and out” eye.

**Charcot-Bouchard microaneurysm**

Common, associated with chronic hypertension; affects small vessels (eg, lenticulostriate arteries in basal ganglia, thalamus) and can cause hemorrhagic intraparenchymal strokes. Not visible on angiography.

**Fever vs heat stroke**

	Fever	Heat stroke
<b>PATHOPHYSIOLOGY</b>	Cytokine activation during inflammation (eg, infection)	Inability of body to dissipate heat (eg, exertion)
<b>TEMPERATURE</b>	Usually $< 40^{\circ}\text{C}$ ( $104^{\circ}\text{F}$ )	Usually $> 40^{\circ}\text{C}$ ( $104^{\circ}\text{F}$ )
<b>COMPLICATIONS</b>	Febrile seizure (benign, usually self-limiting)	CNS dysfunction (eg, confusion), end-organ damage, acute respiratory distress syndrome, rhabdomyolysis
<b>MANAGEMENT</b>	Acetaminophen or ibuprofen for comfort (does not prevent future febrile seizures), antibiotic therapy if indicated	Rapid external cooling, rehydration and electrolyte correction

**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. Types:

- **Simple partial** (consciousness intact)—motor, sensory, autonomic, psychic
- **Complex partial** (impaired consciousness, automatisms)

**Generalized seizures**

Diffuse. Types:

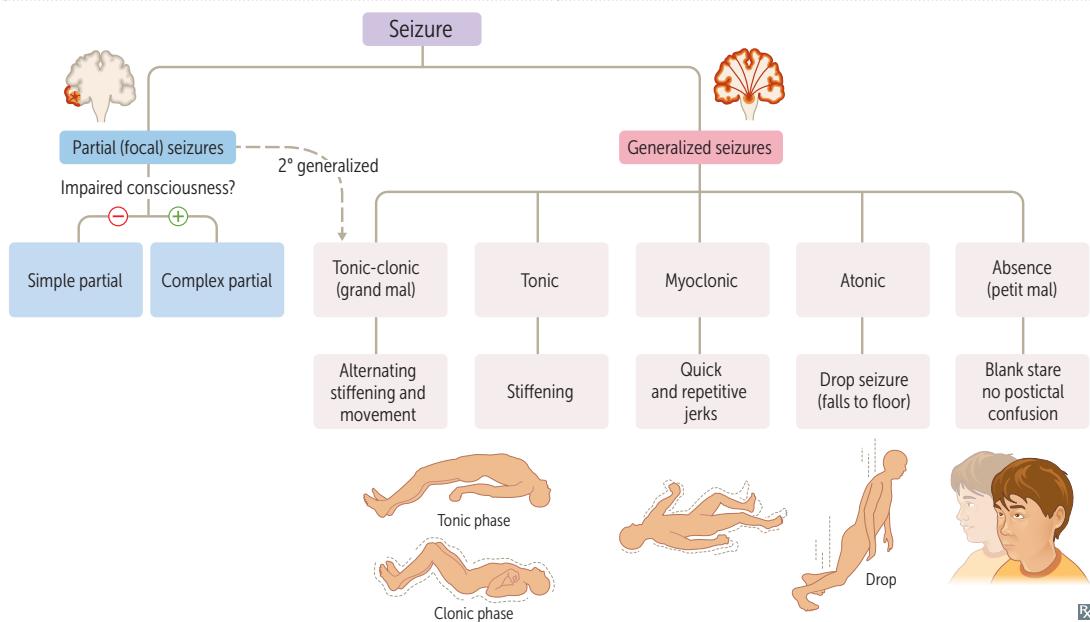
- **Absence** (petit mal)—3 Hz spike-and-wave discharges, short (usually 10 seconds) and frequent episodes of blank stare, no postictal confusion. Can be triggered by hyperventilation
- **Myoclonic**—quick, repetitive jerks
- **Tonic-clonic** (grand mal)—alternating stiffening and movement, postictal confusion, urinary incontinence, tongue biting
- **Tonic**—stiffening
- **Atonic**—“drop” seizures (falls to floor); commonly mistaken for fainting

**Epilepsy**—disorder of recurrent, unprovoked seizures (febrile seizures are not epilepsy).

**Status epilepticus**—continuous ( $\geq 5$  min) or recurring seizures that may result in brain injury.

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.

Primary headaches include cluster, migraine, and tension; migraine and tension headaches are more common in females. Secondary headaches include subarachnoid hemorrhage, meningitis, hydrocephalus, neoplasia, giant cell (temporal) arteritis.

CLASSIFICATION	LOCALIZATION	DURATION	DESCRIPTION	TREATMENT
<b>Cluster<sup>a</sup></b>	Unilateral	15 min–3 hr; repetitive	Excruciating periorbital pain (“suicide headache”) with autonomic symptoms (eg, lacrimation, rhinorrhea, conjunctival injection). May present with Horner syndrome. More common in males.	Acute: sumatriptan, 100% O <sub>2</sub> . Prophylaxis: verapamil.
<b>Migraine</b>	Unilateral	4–72 hr	Pulsating pain with nausea, photophobia, and/or phonophobia. May have “aura.” Due to irritation of CN V, meninges, or blood vessels (release of vasoactive neuropeptides [eg, substance P, calcitonin gene-related peptide]).	Acute: NSAIDs, triptans, dihydroergotamine, antiemetics (eg, prochlorperazine, metoclopramide). Prophylaxis: lifestyle changes (eg, sleep, exercise, diet), β-blockers, amitriptyline, topiramate, valproate, botulinum toxin, anti-CGRP monoclonal antibodies. <b>POUND</b> —Pulsatile, One-day duration, Unilateral, Nausea, Disabling
<b>Tension</b>	Bilateral	> 30 min (typically 4–6 hr); constant	Steady, “band-like” pain. No photophobia or phonophobia. No aura.	Acute: analgesics, NSAIDs, acetaminophen. Prophylaxis: TCAs (eg, amitriptyline), behavioral therapy.

<sup>a</sup>Compare with **trigeminal neuralgia**, which produces repetitive, unilateral, shooting/shock-like pain in the distribution of CN V. Triggered by chewing, talking, touching certain parts of the face. Lasts (typically) for seconds to minutes, but episodes often increase in intensity and frequency over time. First-line therapy: carbamazepine.

**Movement disorders**

DISORDER	PRESENTATION	CHARACTERISTIC LESION	NOTES
<b>Akathisia</b>	Restlessness and intense urge to move		Can be seen with neuroleptic use or as a side effect of Parkinson treatment
<b>Asterixis</b>	Extension of wrists causes “flapping” motion		Associated with hepatic encephalopathy, Wilson disease, and other metabolic derangements
<b>Athetosis</b>	Slow, snake-like, writhing movements; especially seen in the fingers	Basal ganglia	Seen in Huntington disease
<b>Chorea</b>	Sudden, jerky, purposeless movements	Basal ganglia	<i>Chorea</i> = dancing Seen in Huntington disease and in acute rheumatic fever (Sydenham chorea)
<b>Dystonia</b>	Sustained, involuntary muscle contractions		Writer’s cramp, blepharospasm, torticollis Treatment: botulinum toxin injection
<b>Essential tremor</b>	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), barbiturates (primidone)
<b>Intention tremor</b>	Slow, zigzag motion when pointing/extending toward a target	Cerebellar dysfunction	
<b>Resting tremor</b>	Uncontrolled movement of distal appendages (most noticeable in hands); tremor alleviated by intentional movement	Substantia nigra ( <b>Parkinson disease</b> )	Occurs at rest; “pill-rolling tremor” of Parkinson disease When you <b>park</b> your car, it is at <b>rest</b>
<b>Hemiballismus</b>	Sudden, wild flailing of one side of the body	Contralateral subthalamic nucleus (eg, lacunar stroke)	Pronounce “ <b>Half</b> -of-body is going <b>ballistic</b> ”
<b>Myoclonus</b>	Sudden, brief, uncontrolled muscle contraction		Jerks; hiccups; common in metabolic abnormalities (eg, renal and liver failure), Creutzfeldt-Jakob disease
<b>Restless legs syndrome</b>	Uncomfortable sensations in legs causing irresistible urge to move them; relieved by movement; worse at rest/nighttime		Associated with iron deficiency, CKD Treatment: dopamine agonists (pramipexole, ropinirole)

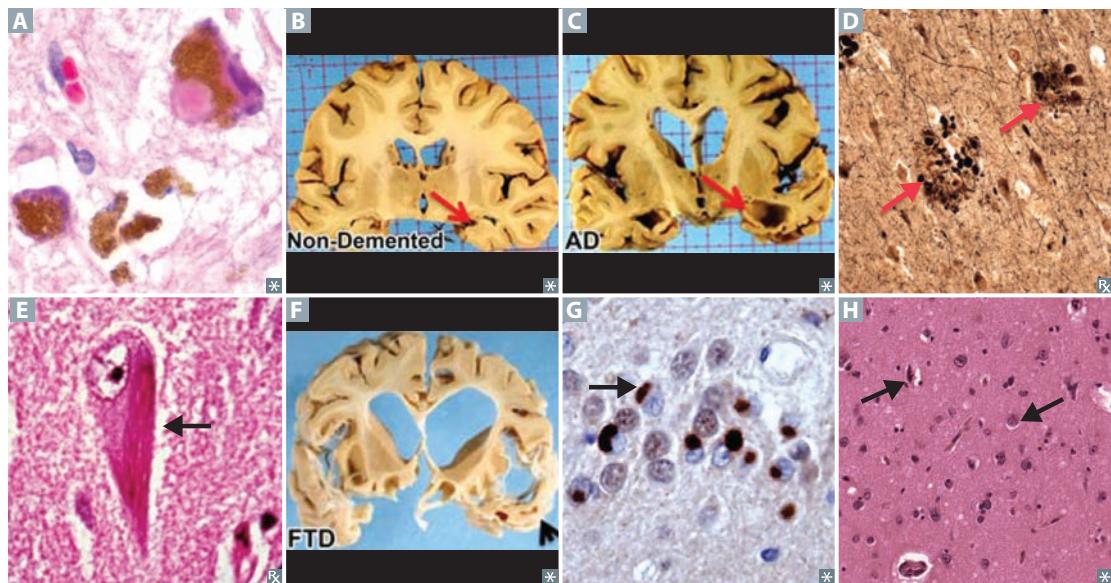
**Neurodegenerative disorders**

↓ in cognitive ability, memory, or function with intact consciousness.  
Must rule out depression as cause of dementia (called pseudodementia). Other reversible causes of dementia: hypothyroidism, vitamin B<sub>12</sub> deficiency, neurosyphilis, normal pressure hydrocephalus.

DISEASE	DESCRIPTION	HISTOLOGIC/GROSS FINDINGS
Parkinson disease	<p>Parkinson <b>TRAPSS</b> your body:</p> <ul style="list-style-type: none"> <li>Tremor (pill-rolling tremor at rest)</li> <li>Rigidity (Cogwheel)</li> <li>Akinesia (or bradykinesia)</li> <li>Postural instability</li> <li>Shuffling gait</li> <li>Small handwriting (micrographia)</li> </ul> <p>Dementia is usually a late finding. MPTP, a contaminant in illegal drugs, is metabolized to MPP+, which is toxic to substantia nigra.</p>	<p>Loss of dopaminergic neurons (ie, depigmentation) of substantia nigra pars compacta. Lewy bodies: composed of α-synuclein (intracellular eosinophilic inclusions <b>A</b>).</p>
Huntington disease	<p>Autosomal dominant trinucleotide (CAG)<sub>n</sub> repeat expansion in the <b>huntingtin (HTT)</b> gene on chromosome <b>4</b> (<b>4 letters</b>). Symptoms manifest between ages 20 and 50: chorea, athetosis, aggression, depression, dementia (sometimes initially mistaken for substance use).</p> <p>Anticipation results from expansion of <b>CAG</b> repeats. Caudate loses ACh and GABA.</p>	<p>Atrophy of caudate and putamen with ex vacuo ventriculomegaly. ↑ dopamine, ↓ GABA, ↓ ACh in brain. Neuronal death via NMDA-R binding and glutamate excitotoxicity.</p>
Alzheimer disease	<p>Most common cause of dementia in elderly. Down syndrome patients have ↑ risk of developing early-onset Alzheimer disease, as APP is located on chromosome 21.</p> <p>↓ ACh.</p> <p>Associated with the following altered proteins:</p> <ul style="list-style-type: none"> <li>▪ ApoE-2: ↓ risk of sporadic form</li> <li>▪ ApoE-4: ↑ risk of sporadic form</li> <li>▪ APP, presenilin-1, presenilin-2: familial forms (10%) with earlier onset</li> </ul>	<p>Widespread cortical atrophy (normal cortex <b>B</b>; cortex in Alzheimer disease <b>C</b>), especially hippocampus (arrows in <b>B</b> and <b>C</b>). Narrowing of gyri and widening of sulci.</p> <p>Senile plaques <b>D</b> in gray matter: extracellular β-amyloid core; may cause amyloid angiopathy → intracranial hemorrhage; Aβ (amyloid-β) synthesized by cleaving amyloid precursor protein (APP).</p> <p>Neurofibrillary tangles <b>E</b>: intracellular, hyperphosphorylated tau protein = insoluble cytoskeletal elements; number of tangles correlates with degree of dementia.</p> <p>Hirano bodies—intracellular eosinophilic proteinaceous rods in hippocampus.</p>
Frontotemporal dementia	<p>Formerly called Pick disease. Early changes in personality and behavior (behavioral variant), or aphasia (primary progressive aphasia). May have associated movement disorders.</p>	<p>Frontotemporal lobe degeneration <b>F</b>. Inclusions of hyperphosphorylated tau (round Pick bodies <b>G</b>) or ubiquitinated TDP-43.</p>

**Neurodegenerative disorders (continued)**

DISEASE	DESCRIPTION	HISTOLOGIC/GROSS FINDINGS
<b>Lewy body dementia</b>	Visual hallucinations (“haLewycinations”), dementia with fluctuating cognition/alertness, REM sleep behavior disorder, and parkinsonism. Called Lewy body dementia if cognitive and motor symptom onset < 1 year apart, otherwise considered dementia 2° to Parkinson disease.	Intracellular Lewy bodies <b>A</b> primarily in cortex.
<b>Vascular dementia</b>	Result of multiple arterial infarcts and/or chronic ischemia. Step-wise decline in cognitive ability with late-onset memory impairment. 2nd most common cause of dementia in elderly.	MRI or CT shows multiple cortical and/or subcortical infarcts.
<b>Creutzfeldt-Jakob disease</b>	Rapidly progressive (weeks to months) dementia with myoclonus (“startle myoclonus”) and ataxia. Associated with periodic sharp waves on EEG and ↑ 14-3-3 protein in CSF. May be transmitted by contaminated materials (eg, corneal transplant, neurosurgical equipment). Fatal.	Spongiform cortex (vacuolation without inflammation). Prions ( $\text{PrP}^{\text{C}} \rightarrow \text{PrP}^{\text{Sc}}$ sheet [ $\beta$ -pleated sheet resistant to proteases]) <b>H</b> .
<b>HIV-associated dementia</b>	Subcortical dysfunction associated with advanced HIV infection. Characterized by cognitive deficits, gait disturbance, irritability, depressed mood.	Diffuse gray matter and subcortical atrophy. Microglial nodules with multinucleated giant cells.



**Idiopathic intracranial hypertension**

Also called pseudotumor cerebri. ↑ ICP with no obvious findings on imaging. Risk factors include **female** sex, **Tetracyclines**, **Obesity**, vitamin **A** excess, **Danazol** (**female TOAD**). Associated with cerebral venous sinus stenosis. Findings: headache, tinnitus, diplopia (usually from CN VI palsy), no change in mental status. Impaired optic nerve axoplasmic flow → papilledema. Visual field testing shows enlarged blind spot and peripheral constriction. Lumbar puncture reveals ↑ opening pressure and provides temporary headache relief.

Treatment: weight loss, acetazolamide, invasive procedures for refractory cases (eg, CSF shunt placement, optic nerve sheath fenestration surgery for visual loss).

**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**

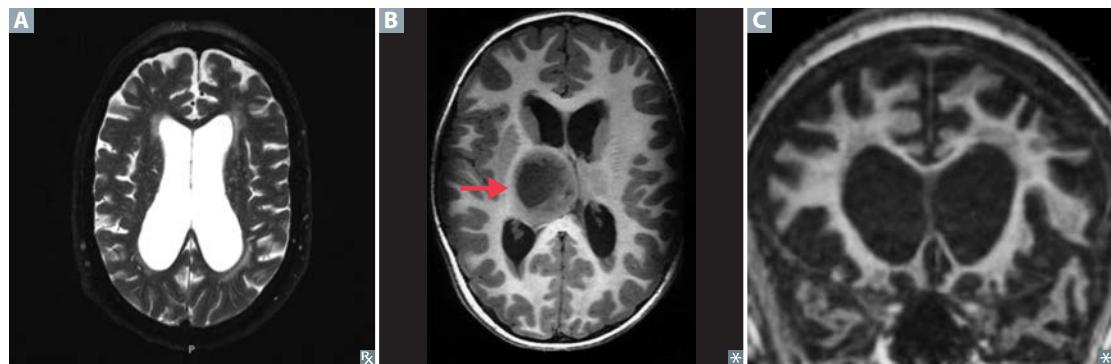
Affects the elderly; idiopathic; CSF pressure elevated only episodically; does not result in increased subarachnoid space volume. Expansion of ventricles **A** distorts the fibers of the corona radiata → triad of **urinary incontinence**, **gait apraxia** (magnetic gait), and **cognitive dysfunction**. “**Wet, wobbly, and wacky**.” Symptoms potentially reversible with CSF drainage via lumbar puncture or shunt placement.

**Noncommunicating (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, tumor **B**).

**Hydrocephalus mimics****Ex vacuo ventriculomegaly**

Appearance of ↑ CSF on imaging **C**, but is actually due to ↓ brain tissue and neuronal atrophy (eg, Alzheimer disease, advanced HIV, frontotemporal dementia, Huntington disease). ICP is normal; NPH triad is not seen.

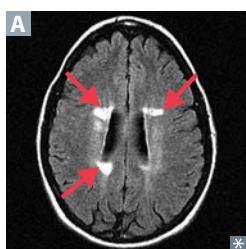


**Multiple sclerosis**

Autoimmune inflammation and demyelination of CNS (brain and spinal cord) with subsequent axonal damage. Can present with:

- Acute optic neuritis (painful unilateral visual loss associated with Marcus Gunn pupil)
- Brain stem/cerebellar syndromes (eg, diplopia, ataxia, scanning speech, intention tremor, nystagmus/INO [bilateral > unilateral])
- Pyramidal tract demyelination (eg, weakness, spasticity)
- Spinal cord syndromes (eg, electric shock-like sensation along cervical spine on neck flexion, neurogenic bladder, paraparesis, sensory manifestations affecting the trunk or one or more extremity)

Symptoms may exacerbate with increased body temperature (eg, hot bath, exercise). Relapsing and remitting is most common clinical course. Most often affects females in their 20s and 30s; more common in individuals who grew up farther from equator and with low serum vitamin D levels.

**FINDINGS**

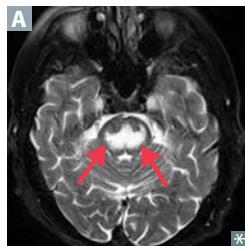
↑ IgG level and myelin basic protein in CSF. Oligoclonal bands are diagnostic. MRI is gold standard. Periventricular plaques **A** (areas of oligodendrocyte loss and reactive gliosis). Multiple white matter lesions disseminated in space and time.

**TREATMENT**

Stop relapses and halt/slow progression with disease-modifying therapies (eg,  $\beta$ -interferon, glatiramer, natalizumab). Treat acute flares with IV steroids. Symptomatic treatment for neurogenic bladder (catheterization, muscarinic antagonists), spasticity (baclofen, GABA<sub>B</sub> receptor agonists), pain (TCAs, anticonvulsants).

### Other demyelinating and dysmyelinating disorders

#### Osmotic demyelination syndrome



Also called central pontine myelinolysis. Massive axonal demyelination in pontine white matter **A** 2° to rapid osmotic changes, most commonly iatrogenic correction of hyponatremia but also rapid shifts of other osmolytes (eg, glucose). Acute paralysis, dysarthria, dysphagia, diplopia, loss of consciousness. Can cause “locked-in syndrome.”

Correcting serum Na<sup>+</sup> too fast:

- “From low to high, your pons will die” (osmotic demyelination syndrome)
- “From high to low, your brains will blow” (cerebral edema/herniation)

#### Acute inflammatory demyelinating polyneuropathy

Most common subtype of **Guillain-Barré syndrome**.

Autoimmune condition that destroys Schwann cells via inflammation and demyelination of motor fibers, sensory fibers, peripheral nerves (including CN III-XII). Likely facilitated by molecular mimicry and triggered by inoculations or stress. Despite association with infections (eg, *Campylobacter jejuni*, viruses [eg, Zika]), no definitive causal link to any pathogen.

Results in symmetric ascending muscle weakness/paralysis and depressed/absent DTRs beginning in lower extremities. Facial paralysis (usually bilateral) and respiratory failure are common. May see autonomic dysregulation (eg, cardiac irregularities, hypertension, hypotension) or sensory abnormalities. Most patients survive with good functional recovery.

↑ CSF protein with normal cell count (albuminocytologic dissociation).

Respiratory support is critical until recovery. Disease-modifying treatment: plasma exchange or IV immunoglobulins. No role for steroids.

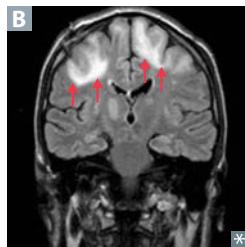
#### Acute disseminated (postinfectious) encephalomyelitis

Multifocal inflammation and demyelination after infection or vaccination. Presents with rapidly progressive multifocal neurologic symptoms, altered mental status.

#### Charcot-Marie-Tooth disease

Also called hereditary motor and sensory neuropathy. Group of progressive hereditary nerve disorders related to the defective production of proteins involved in the structure and function of peripheral nerves or the myelin sheath. Typically autosomal dominant and associated with foot deformities (eg, pes cavus, hammer toe), lower extremity weakness (eg, foot drop), and sensory deficits (**Can't Move Toes**). Most common type, CMT1A, is caused by PMP22 gene duplication.

#### Progressive multifocal leukoencephalopathy



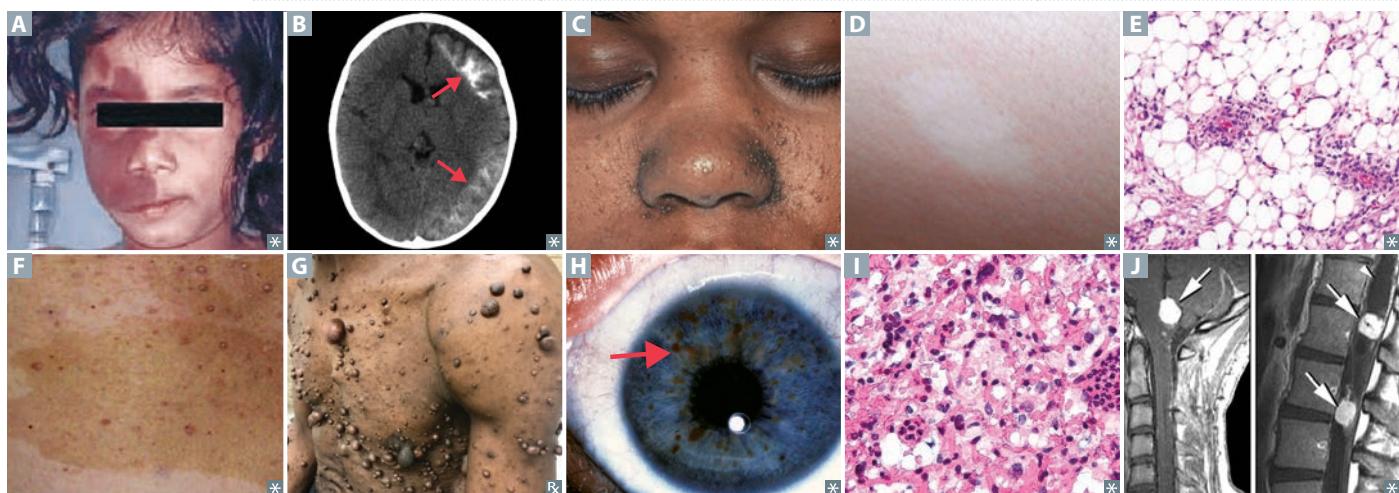
Demyelination of CNS **B** due to destruction of oligodendrocytes (2° to reactivation of latent JC virus infection). Associated with severe immunosuppression (eg, lymphomas and leukemias, AIDS, organ transplantation). Rapidly progressive, usually fatal. Predominantly involves parietal and occipital areas; visual symptoms are common. ↑ risk associated with natalizumab and rituximab.

#### Other disorders

Krabbe disease, metachromatic leukodystrophy, adrenoleukodystrophy.

**Neurocutaneous disorders**

DISORDER	GENETICS	PRESENTATION	NOTES
<b>Sturge-Weber syndrome</b>	Congenital nonhereditary anomaly of neural crest derivatives. Somatic mosaicism of an activating mutation in one copy of the GNAQ gene.	Capillary vascular malformation → port-wine stain <b>A</b> (nevus flammeus or non-neoplastic birthmark) in CN V <sub>1</sub> /V <sub>2</sub> distribution; ipsilateral leptomeningeal angioma with calcifications <b>B</b> → seizures/epilepsy; intellectual disability; episcleral hemangioma → ↑ IOP → early-onset glaucoma.	Also called encephalotrigeminal angiomatosis.
<b>Tuberous sclerosis</b>	AD, variable expression. Mutation in tumor suppressor genes TSC1 on chromosome 9 (hamartin), TSC2 on chromosome 16 (tuberin; pronounce “twoberin”).	Hamartomas in CNS and skin, angiomyomas <b>C</b> , mitral regurgitation, ash-leaf spots <b>D</b> , cardiac rhabdomyoma, intellectual disability, renal angiomyolipoma <b>E</b> , seizures, shagreen patches.	Autosomal dominant. ↑ incidence of subependymal giant cell astrocytomas and ungual fibromas.
<b>Neurofibromatosis type I</b>	AD, 100% penetrance. Mutation in NF1 tumor suppressor gene on chromosome 17 (encodes neurofibromin, a negative RAS regulator).	Café-au-lait spots <b>F</b> , Intellectual disability, Cutaneous neurofibromas <b>G</b> , Lisch nodules (pigmented iris hamartomas <b>H</b> ), Optic gliomas, Pheochromocytomas, Seizures/focal neurologic Signs (often from meningioma), bone lesions (eg, sphenoid dysplasia).	Also called von Recklinghausen disease. <b>17</b> letters in “von Recklinghausen.” <b>CICLOPSS</b> .
<b>Neurofibromatosis type II</b>	AD. Mutation in NF2 tumor suppressor gene (merlin) on chromosome 22.	Bilateral vestibular schwannomas, juvenile cataracts, meningiomas, ependymomas.	NF2 affects <b>2</b> ears, <b>2</b> eyes.
<b>von Hippel-Lindau disease</b>	AD. Deletion of VHL gene on chromosome 3p. pVHL ubiquitinates hypoxia-inducible factor 1α.	Hemangioblastomas (high vascularity with hyperchromatic nuclei <b>I</b> ) in retina, brain stem, cerebellum, spine <b>J</b> ; Angiomatosis; bilateral Renal cell carcinomas; Pheochromocytomas.	Numerous tumors, benign and malignant. <b>HARP</b> . <b>VHL</b> = <b>3</b> letters = chromosome <b>3</b> ; associated with RCC (also <b>3</b> letters).

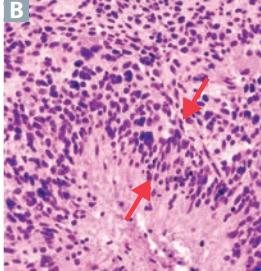


**Adult primary brain tumors**

TUMOR	DESCRIPTION	HISTOLOGY
<b>Glioblastoma</b>	Grade IV astrocytoma. Common, highly malignant 1° brain tumor with ~ 1-year median survival. Found in cerebral hemispheres. Can cross corpus callosum (“butterfly glioma” <b>A</b> ). Associated with EGFR amplification.	Astrocyte origin, GFAP $\oplus$ . “Pseudopalisading” pleomorphic tumor cells <b>B</b> border central areas of necrosis, hemorrhage, and/or microvascular proliferation.
<b>Oligodendrogloma</b>	Relatively rare, slow growing. Most often in frontal lobes <b>C</b> . Often calcified.	Oligodendrocyte origin. “Fried egg” cells—round nuclei with clear cytoplasm <b>D</b> . “Chicken-wire” capillary pattern.
<b>Meningioma</b>	Common, typically benign. Females > males. Most often occurs near surfaces of brain and in parasagittal region. Extra-axial (external to brain parenchyma) and may have a dural attachment (“tail” <b>E</b> ). Often asymptomatic; may present with seizures or focal neurologic signs. Resection and/or radiosurgery.	Arachnoid cell origin. Spindle cells concentrically arranged in a whorled pattern <b>F</b> ; psammoma bodies (laminated calcifications).
<b>Hemangioblastoma</b>	Most often cerebellar <b>G</b> . Associated with von Hippel-Lindau syndrome when found with retinal angiomas. Can produce erythropoietin $\rightarrow$ 2° polycythemia.	Blood vessel origin. Closely arranged, thin-walled capillaries with minimal intervening parenchyma <b>H</b> .



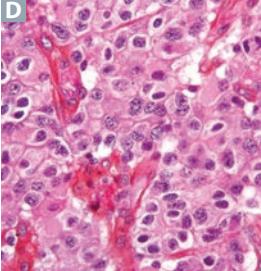
**A**



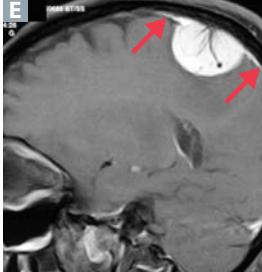
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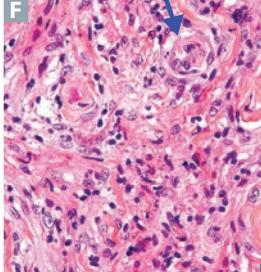
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**D**



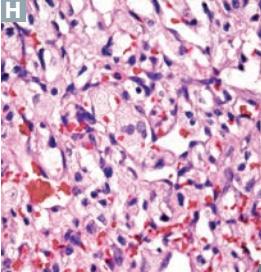
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**F**



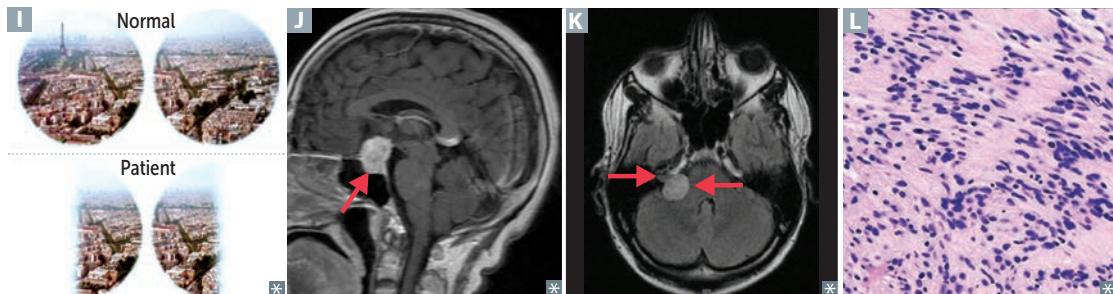
**G**



**H**

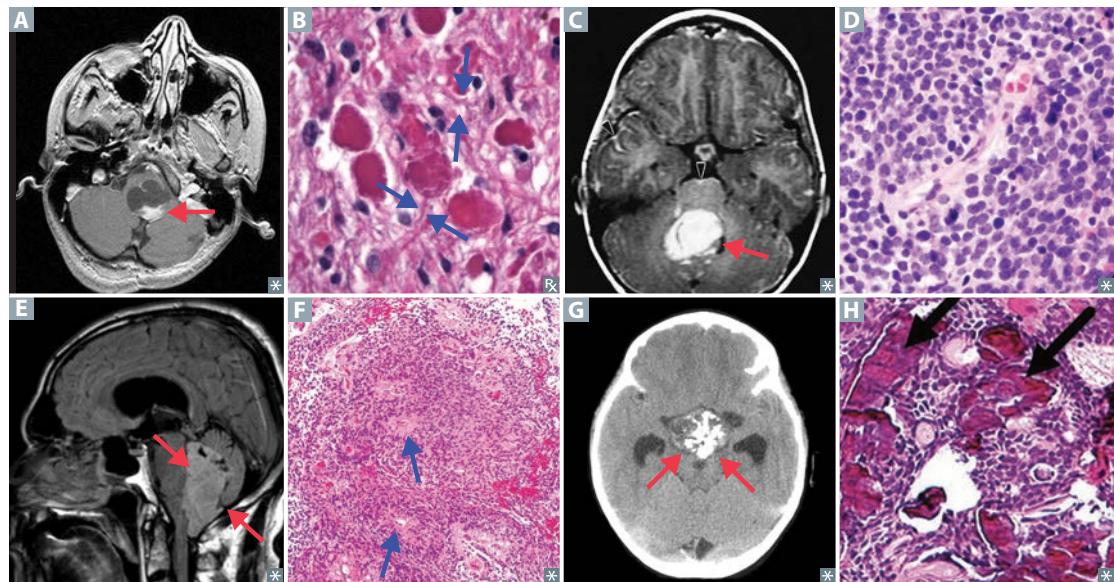
**Adult primary brain tumors (continued)**

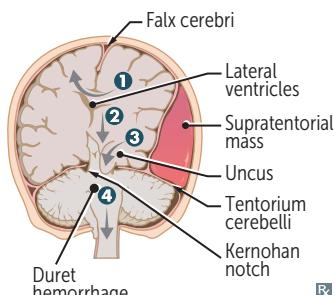
TUMOR	DESCRIPTION	HISTOLOGY
<b>Pituitary adenoma</b>	<p>May be nonfunctioning (silent) or hyperfunctioning (hormone-producing). Nonfunctional tumors present with mass effect (eg, bitemporal hemianopia [due to pressure on optic chiasm <b>I</b>]). Pituitary apoplexy → hyper- or hypopituitarism.</p> <p>Prolactinoma classically presents as galactorrhea, amenorrhea, ↓ bone density due to suppression of estrogen in females and as ↓ libido, infertility in males.</p> <p>Treatment: dopamine agonists (eg, bromocriptine, cabergoline), transsphenoidal resection.</p>	<p>Hyperplasia of only one type of endocrine cells found in pituitary. Most commonly from lactotrophs (prolactin) <b>J</b> → hyperprolactinemia. Less commonly, from somatotrophs (GH) → acromegaly, gigantism; corticotrophs (ACTH) → Cushing disease. Rarely, from thyrotrophs (TSH), gonadotrophs (FSH, LH).</p>
<b>Schwannoma</b>	<p>Classically at the cerebellopontine angle <b>K</b>, benign, involving CNs V, VII, and VIII, but can be along any peripheral nerve. Often localized to CN VIII in internal acoustic meatus → vestibular schwannoma (can present as hearing loss and tinnitus). Bilateral vestibular schwannomas found in NF-2.</p> <p>Resection or stereotactic radiosurgery.</p>	<p>Schwann cell origin, S-100 <math>\oplus</math>. Biphasic, dense, hypercellular areas containing spindle cells alternating with hypocellular, myxoid areas <b>L</b>.</p>



**Childhood primary brain tumors**

TUMOR	DESCRIPTION	HISTOLOGY
<b>Pilocytic astrocytoma</b>	Low-grade astrocytoma. Most common 1° brain tumor in childhood. Usually well circumscribed. In children, most often found in posterior fossa <b>A</b> (eg, cerebellum). May be supratentorial. Benign; good prognosis.	Astrocyte origin, GFAP $\oplus$ . Bipolar neoplastic cells with hair-like projections. Associated with microcysts and Rosenthal fibers (eosinophilic, corkscrew fibers <b>B</b> ). Cystic + solid (gross).
<b>Medulloblastoma</b>	Most common malignant brain tumor in childhood. Commonly involves cerebellum <b>C</b> . Can compress 4th ventricle, causing noncommunicating hydrocephalus → headaches, papilledema. Can involve the cerebellar vermis → truncal ataxia. Can send “drop metastases” to spinal cord.	Form of primitive neuroectodermal tumor (PNET). Homer-Wright rosettes, small blue cells <b>D</b> . Synaptophysin $\oplus$ .
<b>Ependymoma</b>	Most commonly found in 4th ventricle <b>E</b> . Can cause hydrocephalus. Poor prognosis.	Ependymal cell origin. Characteristic perivascular pseudorosettes <b>F</b> . Rod-shaped blepharoplasts (basal ciliary bodies) found near the nucleus.
<b>Craniopharyngioma</b>	Most common childhood supratentorial tumor. May be confused with pituitary adenoma (both cause bitemporal hemianopia). Associated with a high recurrence rate.	Derived from remnants of Rathke pouch (ectoderm). Calcification is common <b>G H</b> . Cholesterol crystals found in “motor oil”-like fluid within tumor.
<b>Pinealoma</b>	Tumor of pineal gland. Can cause Parinaud syndrome (compression of tectum → vertical gaze palsy); obstructive hydrocephalus (compression of cerebral aqueduct); precocious puberty in males (hCG production).	Similar to germ cell tumors (eg, testicular seminoma).



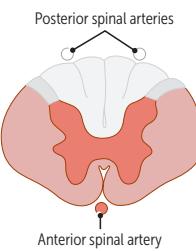
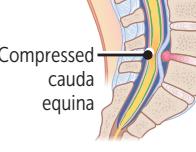
**Herniation syndromes**

- ①** Cingulate (subfalcine) herniation under falx cerebri  
Can compress anterior cerebral artery.
- ②** Central/downward transtentorial herniation  
Caudal displacement of brain stem → rupture of paramedian basilar artery branches → Duret hemorrhages. Usually fatal.
- ③** Uncal transtentorial herniation  
Uncus = medial temporal lobe. Early herniation → ipsilateral blown pupil (unilateral CN III compression), contralateral hemiparesis. Late herniation → coma, Kernohan phenomenon (misleading contralateral blown pupil and ipsilateral hemiparesis due to contralateral compression against Kernohan notch).
- ④** Cerebellar tonsillar herniation into the foramen magnum  
Coma and death result when these herniations compress the brain stem.

**Motor neuron signs**

SIGN	UMN LESION	LMN LESION	COMMENTS
Weakness	+	+	<b>Lower</b> motor neuron (LMN) = everything <b>lowered</b> (less muscle mass, ↓ muscle tone, ↓ reflexes, downgoing toes)
Atrophy	-	+	
Fasciculations	-	+	<b>Upper</b> motor neuron (UMN) = everything <b>up</b> (tone, DTRs, toes)
Reflexes	↑	↓	
Tone	↑	↓	Fasciculations = muscle twitching Positive Babinski is normal in infants
Babinski	+	-	
Spastic paresis	+	-	
Flaccid paralysis	-	+	
Clasp knife spasticity	+	-	

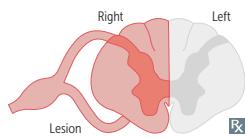
**Spinal lesions**

AREA AFFECTED	DISEASE	CHARACTERISTICS
	<b>Spinal muscular atrophy</b>	Congenital degeneration of anterior horns. LMN symptoms only, symmetric weakness. “Floppy baby” with marked hypotonia (flaccid paralysis) and tongue fasciculations. Autosomal recessive <i>SMN1</i> mutation → defective snRNP assembly. SMA type 1 is called <b>Werdnig-Hoffmann disease</b> .
	<b>Amyotrophic lateral sclerosis</b>	Also called <b>Lou Gehrig disease</b> . Combined UMN (corticobulbar/corticospinal) and LMN (medullary and spinal cord) degeneration. No sensory or bowel/bladder deficits.
		Can be caused by defect in superoxide dismutase 1. LMN deficits: flaccid limb weakness, fasciculations, atrophy, bulbar palsy (dysarthria, dysphagia, tongue atrophy). UMN deficits: spastic limb weakness, hyperreflexia, clonus, pseudobulbar palsy (dysarthria, dysphagia, emotional lability). Fatal (most often from respiratory failure). Treatment: “riLouzole”.
	<b>Complete occlusion of anterior spinal artery</b>	Spares dorsal columns and Lissauer tract; mid-thoracic ASA territory is watershed area, as artery of Adamkiewicz supplies ASA below T8. Can be caused by aortic aneurysm repair. Presents with UMN deficit below the lesion (corticospinal tract), LMN deficit at the level of the lesion (anterior horn), and loss of pain and temperature sensation below the lesion (spinothalamic tract).
	<b>Tabes dorsalis</b>	Caused by 3° syphilis. Results from degeneration/demyelination of dorsal columns and roots → progressive sensory ataxia (impaired proprioception → poor coordination). + Romberg sign and absent DTRs. Associated with Charcot joints, shooting pain, Argyll Robertson pupils.
	<b>Syringomyelia</b>	Syrinx expands and damages anterior white commissure of spinothalamic tract (2nd-order neurons) → bilateral symmetric loss of pain and temperature sensation in cape-like distribution. Seen with Chiari I malformation. Can affect other tracts.
	<b>Vitamin B<sub>12</sub> deficiency</b>	Subacute combined degeneration ( <b>SCD</b> )—demyelination of Spinocerebellar tracts, lateral Corticospinal tracts, and Dorsal columns. Ataxic gait, paresthesia, impaired position/vibration sense (+ Romberg sign), UMN symptoms.
	<b>Cauda equina syndrome</b>	Compression of spinal roots L2 and below, often due to intervertebral disc herniation or tumor. Radicular pain, absent knee and ankle reflexes, loss of bladder and anal sphincter control, saddle anesthesia.

**Poliomyelitis**

Caused by poliovirus (fecal-oral transmission). Replicates in lymphoid tissue of oropharynx and small intestine before spreading via bloodstream to CNS. Infection causes destruction of cells in anterior horn of spinal cord (LMN death).

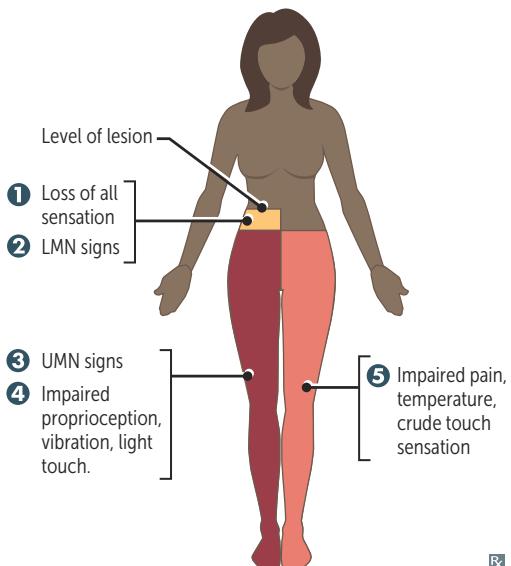
Signs of LMN lesion: asymmetric weakness (vs symmetric weakness in spinal muscular atrophy), hypotonia, flaccid paralysis, fasciculations, hyporeflexia, muscle atrophy. Respiratory muscle involvement leads to respiratory failure. Signs of infection: malaise, headache, fever, nausea, etc. CSF shows ↑ WBCs (lymphocytic pleocytosis) and slight ↑ of protein (with no change in CSF glucose). Virus recovered from stool or throat.

**Brown-Séquard syndrome**

Hemisection of spinal cord. Findings:

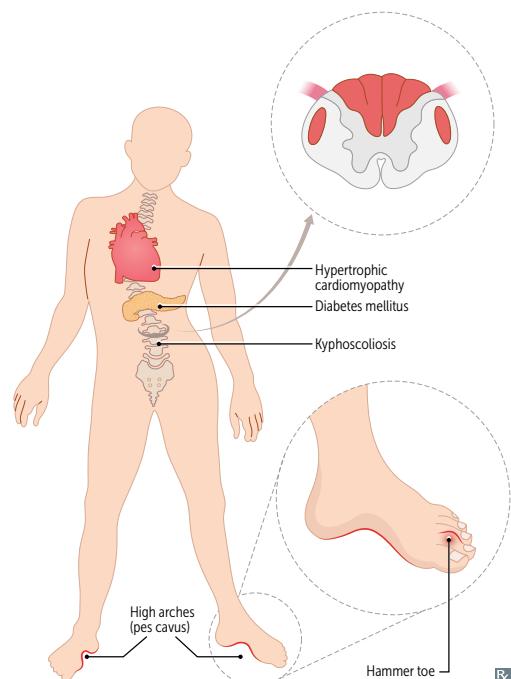
- ❶ Ipsilateral loss of all sensation **at** level of lesion
- ❷ Ipsilateral LMN signs (eg, flaccid paralysis) **at** level of lesion
- ❸ Ipsilateral UMN signs **below** level of lesion (due to corticospinal tract damage)
- ❹ Ipsilateral loss of proprioception, vibration, and light (2-point discrimination) touch **below** level of lesion (due to dorsal column damage)
- ❺ Contralateral loss of pain, temperature, and crude (non-discriminative) touch **below** level of lesion (due to spinothalamic tract damage)

If lesion occurs above T1, patient may present with ipsilateral Horner syndrome due to damage of oculosympathetic pathway.

**Friedreich ataxia**

Autosomal recessive trinucleotide repeat disorder (**GAA**)<sub>n</sub> on chromosome 9 in gene that encodes frataxin (iron-binding protein). Leads to impairment in mitochondrial functioning. Degeneration of lateral corticospinal tract (spastic paralysis), spinocerebellar tract (ataxia), dorsal columns (↓ vibratory sense, proprioception), and dorsal root ganglia (loss of DTRs). **Staggering** gait, frequent **falling**, nystagmus, dysarthria, pes cavus, hammer toes, **diabetes** mellitus, **hypertrophic cardiomyopathy** (cause of death). Presents in childhood with kyphoscoliosis **A**.

Friedreich is **fratastic** (**frataxin**): he's your favorite **frat** brother, always **staggering** and **falling** but has a **sweet, big heart**. Ataxic **GAAit**.



### Common cranial nerve lesions

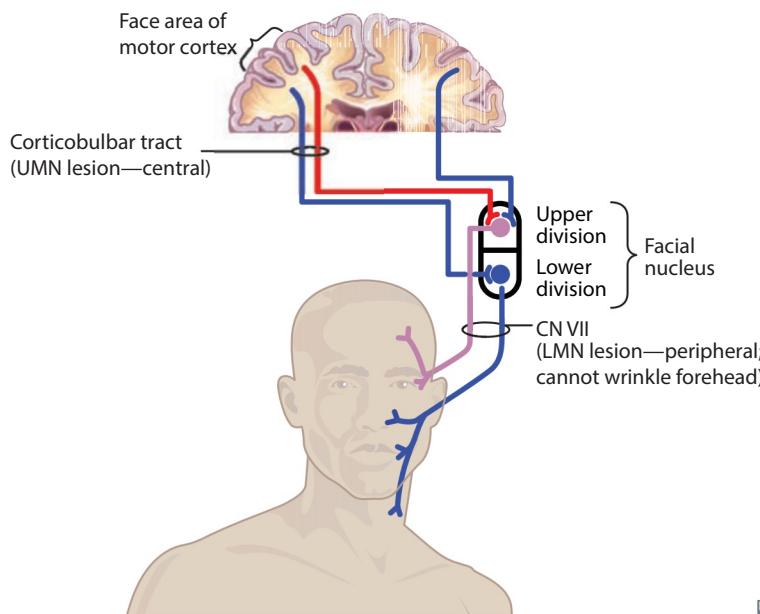
<b>CN V motor lesion</b>	Jaw deviates <b>toward</b> side of lesion due to unopposed force from the opposite pterygoid muscle.
<b>CN X lesion</b>	Uvula deviates <b>away</b> from side of lesion. Weak side collapses and uvula points away.
<b>CN XI lesion</b>	Weakness turning head to contralateral side of lesion (SCM). Shoulder droop on side of lesion (trapezius).
<b>CN XII lesion</b>	The left SCM contracts to help turn the head to the right. LMN lesion. Tongue deviates <b>toward</b> side of lesion (“lick your wounds”) due to weakened tongue muscles on affected side.

### Facial nerve lesions

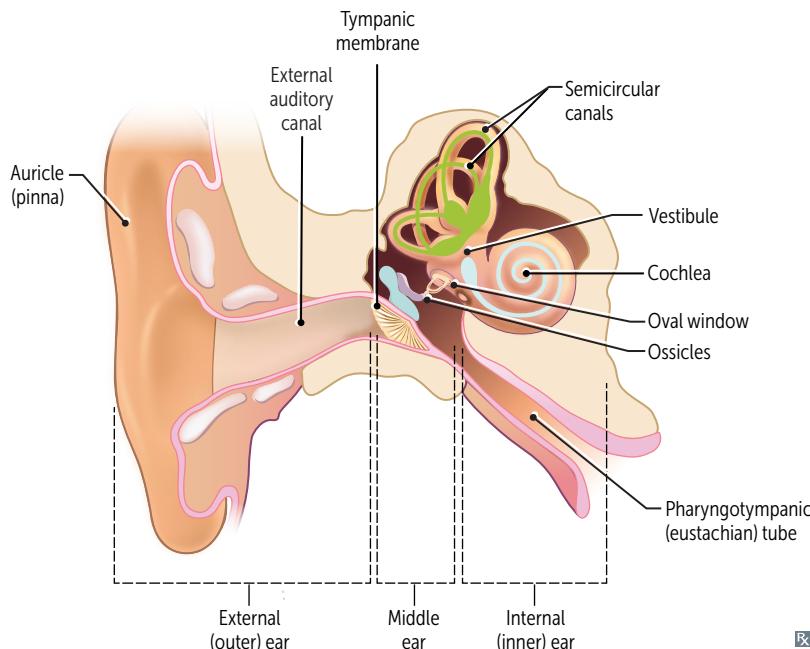


**Bell palsy** is the most common cause of peripheral facial palsy **A**. Usually develops after HSV reactivation. Treatment: corticosteroids +/- acyclovir. Most patients gradually recover function, but aberrant regeneration can occur. Other causes of peripheral facial palsy include Lyme disease, herpes zoster (Ramsay Hunt syndrome), sarcoidosis, tumors (eg, parotid gland), diabetes mellitus.

	Upper motor neuron lesion	Lower motor neuron lesion
<b>LESION LOCATION</b>	Motor cortex, connection from motor cortex to facial nucleus in pons	Facial nucleus, anywhere along CN VII
<b>AFFECTED SIDE</b>	Contralateral	Ipsilateral
<b>MUSCLES INVOLVED</b>	Lower muscles of facial expression	Upper and lower muscles of facial expression
<b>FOREHEAD INVOLVED?</b>	Spared, due to bilateral UMN innervation	Affected
<b>OTHER SYMPTOMS</b>	Variable; depends on size of lesion	Incomplete eye closure (dry eyes, corneal ulceration), hyperacusis, loss of taste sensation to anterior tongue



## ▶ NEUROLOGY—OTOLGY

**Auditory anatomy and physiology****Outer ear**

Visible portion of ear (pinna), includes auditory canal and tympanic membrane. Transfers sound waves via vibration of tympanic membrane.

**Middle ear**

Air-filled space with three bones called the ossicles (malleus, incus, stapes). Ossicles conduct and amplify sound from tympanic membrane to inner ear.

**Inner ear**

Snail-shaped, fluid-filled cochlea. Contains basilar membrane that vibrates  $2^\circ$  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).

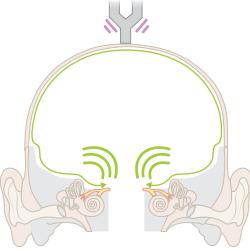
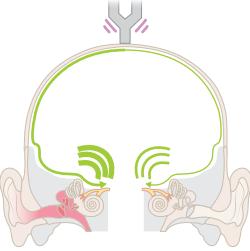
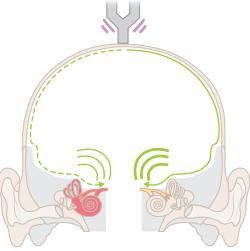
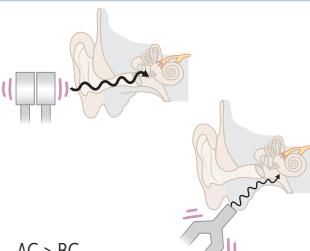
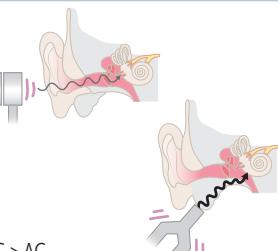
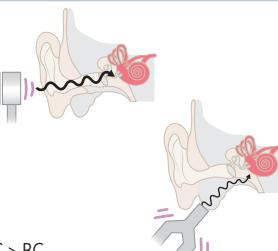
**Types of hearing loss****Noise-induced hearing loss**

Damage to stereociliated cells in organ of Corti. Loss of high-frequency hearing first. Sudden extremely loud noises can produce hearing loss due to tympanic membrane rupture.

**Presbycusis**

**Aging**-related progressive bilateral/symmetric sensorineural hearing loss (often of higher frequencies) due to destruction of hair cells at the cochlear base (preserved low-frequency hearing at apex).

**Diagnosing hearing loss**

	Normal	Conductive	Sensorineural
<b>Weber test</b> Tuning fork on vertex of skull			
	No localization	Localizes to affected ear ↓ transmission of background noise	Localizes to unaffected ear ↓ transmission of all sound
<b>Rinne test</b> Tuning fork in front of ear (air conduction, AC), Tuning fork on mastoid process (bone conduction, BC)			
	AC > BC	BC > AC	AC > BC

**Cholesteatoma**

Overgrowth of desquamated keratin debris within the middle ear space (**A**, arrows). Can be congenital or acquired (eg, 2° to recurrent/chronic otitis media). May erode ossicles, mastoid air cells → conductive hearing loss. Often presents with painless otorrhea.

**Vertigo**

Sensation of spinning while actually stationary. Subtype of “dizziness,” but distinct from “lightheadedness.” Peripheral vertigo more common than central vertigo.

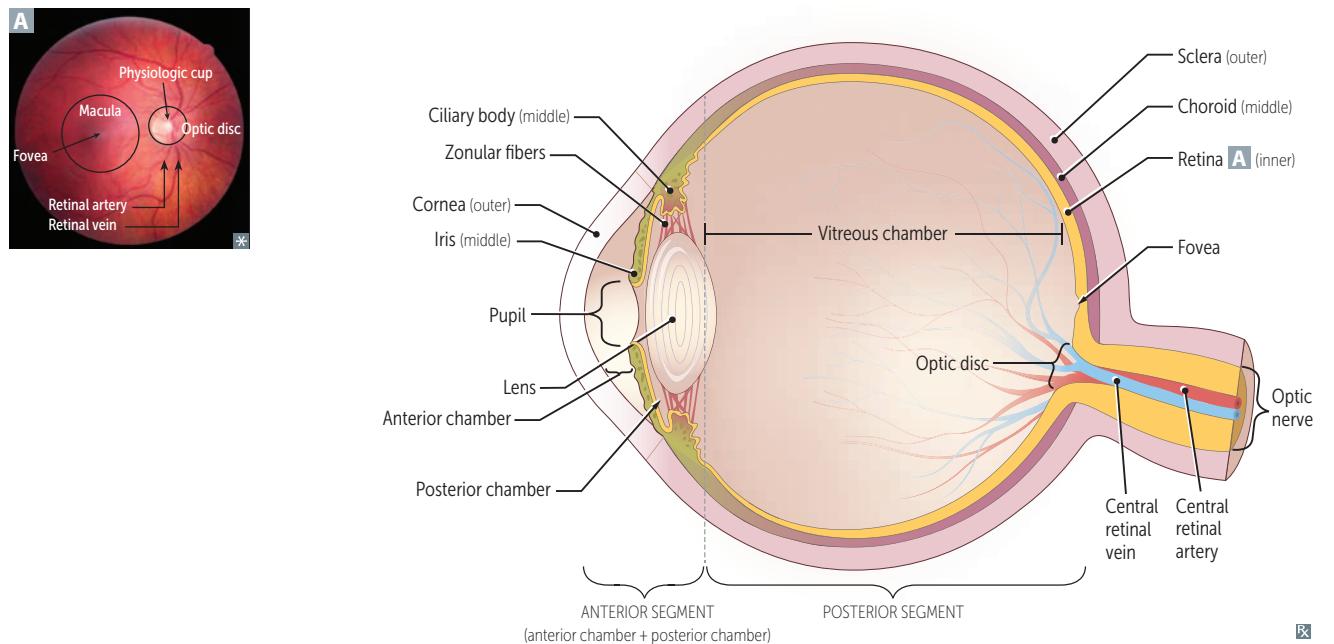
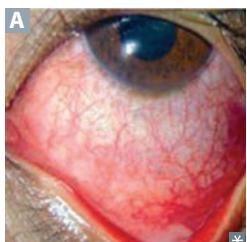
**Peripheral vertigo**

Due to inner ear pathologies such as semicircular canal debris (benign paroxysmal positional vertigo, BPPV), vestibular nerve infection, **Ménière disease**—triad of sensorineural hearing loss, vertigo, tinnitus; endolymphatic hydrops → ↑ endolymph within the inner ear. Treatment: antihistamines, anticholinergics, antiemetics (symptomatic relief); low-salt diet +/- diuretics (Ménière disease); Epley maneuver (BPPV).

**Central vertigo**

Brain stem or cerebellar lesion (eg, stroke affecting vestibular nuclei, demyelinating disease, or posterior fossa tumor). Findings: directional or purely vertical nystagmus, skew deviation (vertical misalignment of the eyes), diplopia, dysmetria. Focal neurologic findings.

## ► NEUROLOGY—OPHTHALMOLOGY

**Normal eye anatomy****Conjunctivitis**

Inflammation of the conjunctiva → red eye **A**.

Allergic—itchy eyes, bilateral.

Bacterial—pus; treat with antibiotics.

Viral—most common, often adenovirus; sparse mucous discharge, swollen preauricular node, ↑ lacrimation; self-resolving.

**Refractive errors**

Common cause of impaired vision, correctable with glasses.

**Hyperopia**

Also called “farsightedness.” Eye too short for refractive power of cornea and lens → light focused behind retina. Correct with convex (converging) lenses.

**Myopia**

Also called “nearsightedness.” Eye too long for refractive power of cornea and lens → light focused in front of retina. Correct with concave (diverging) lens.

**Astigmatism**

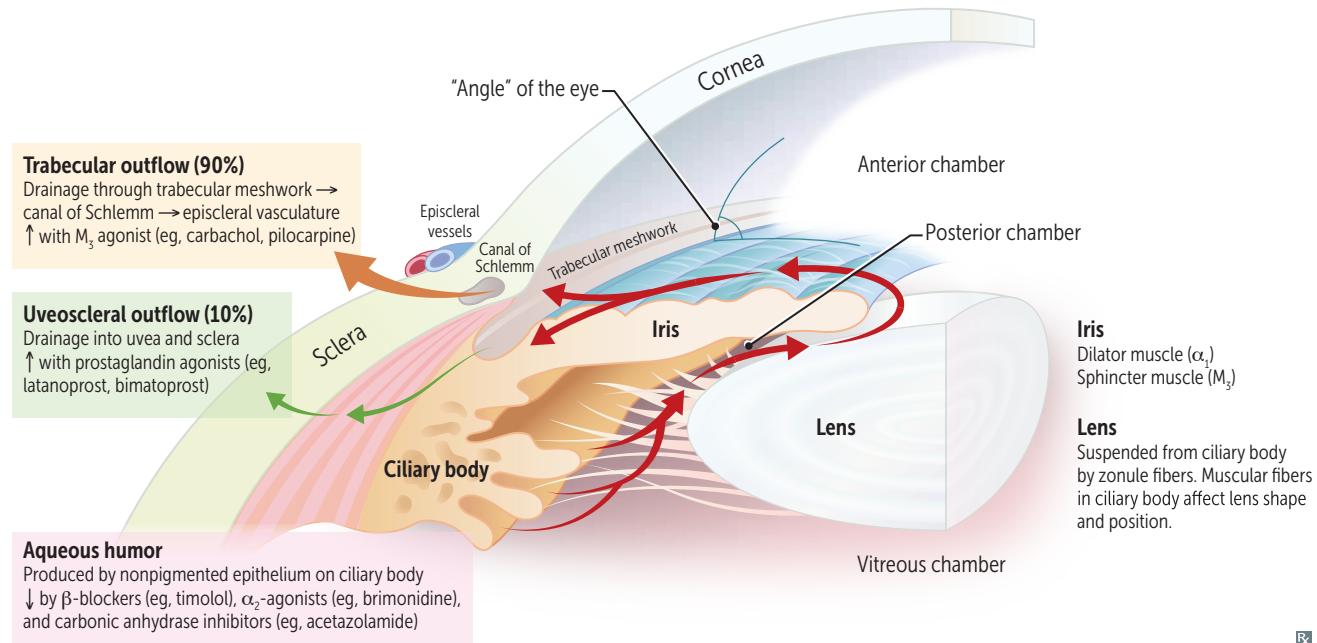
Abnormal curvature of cornea → different refractive power at different axes. Correct with cylindrical lens.

**Presbyopia**

Aging-related impaired accommodation (focusing on near objects), primarily due to ↓ lens elasticity, changes in lens curvature, ↓ strength of the ciliary muscle. Patients often need “reading glasses” (magnifiers).

**Cataract**

Painless, often bilateral, opacification of lens **A**. Can result in glare and ↓ vision, especially at night, and loss of the red reflex. Acquired risk factors: ↑ age, tobacco smoking, alcohol overuse, excessive sunlight, prolonged corticosteroid use, diabetes mellitus, trauma, infection. Congenital risk factors: classic galactosemia, galactokinase deficiency, trisomies (13, 18, 21), TORCH infections (eg, rubella), Marfan syndrome, Alport syndrome, myotonic dystrophy, neurofibromatosis 2.

**Aqueous humor pathway**

**Glaucoma**

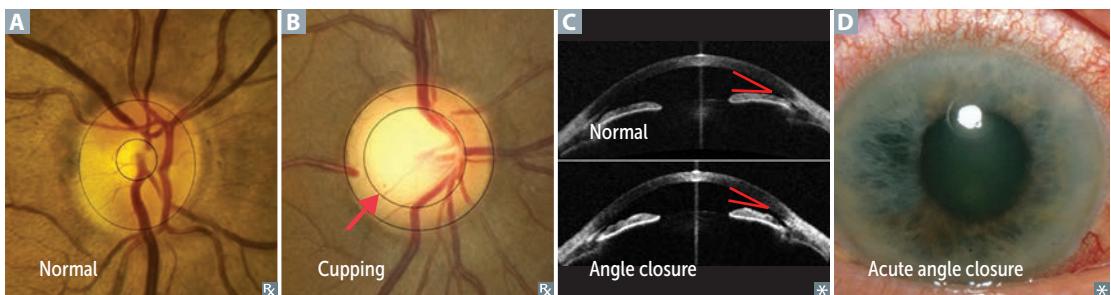
Optic disc atrophy with characteristic cupping (normal **A** versus thinning of outer rim of optic nerve head **B**), usually with elevated intraocular pressure (IOP) and progressive peripheral visual field loss if untreated. Treatment is through pharmacologic or surgical lowering of IOP.

**Open-angle glaucoma**

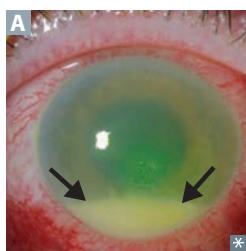
↑ incidence in older people, Black people, and patients with family history of condition. Painless, more common in US.  
Primary—cause unclear.  
Secondary—blocked trabecular meshwork from WBCs (eg, uveitis), RBCs (eg, vitreous hemorrhage), retinal elements (eg, retinal detachment).

**Closed- or narrow-angle glaucoma**

Primary—enlargement or anterior movement of lens against central iris (pupil margin)  
→ obstruction of normal aqueous flow through pupil → fluid builds up behind iris, pushing peripheral iris against cornea **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, frontal headache, fixed and mid-dilated pupil, nausea and vomiting. Mydriatic agents contraindicated. Hurts in a hurry with halos, a headache, and a “half-dilated” pupil.

**Uveitis**

Inflammation of uvea; specific name based on location within affected eye. Anterior uveitis: iritis; posterior uveitis: choroiditis and/or retinitis. May have hypopyon (accumulation of pus in anterior chamber **A**) or conjunctival redness. Associated with systemic inflammatory disorders (eg, sarcoidosis, rheumatoid arthritis, juvenile idiopathic arthritis, HLA-B27-associated conditions).



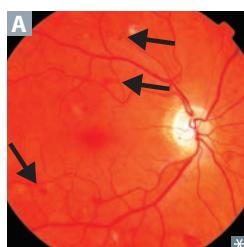
### Age-related macular degeneration



Degeneration of macula (central area of retina). Causes distortion of straight lines (metamorphopsia) and eventual loss of central vision (scotomas).

- Dry (nonexudative, > 80%)—deposition of yellowish extracellular material (“drusen”) in between Bruch membrane and retinal pigment epithelium **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, bevacizumab, ranibizumab).

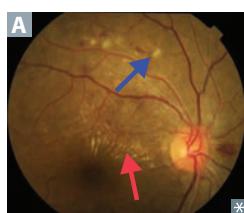
### Diabetic retinopathy



Retinal damage due to chronic hyperglycemia. Two types:

- Nonproliferative—damaged capillaries leak blood → lipids and fluid seep into retina → hemorrhages (arrows in **A**) and macular edema. Treatment: blood sugar control.
- Proliferative—chronic hypoxia results in new blood vessel formation with resultant traction on retina → retinal detachment. Treatment: anti-VEGF injections, peripheral retinal photocoagulation, surgery.

### Hypertensive retinopathy

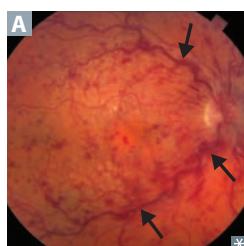


Chronic uncontrolled hypertension → endothelial disruption → fibrinoid necrosis → retinal damage.

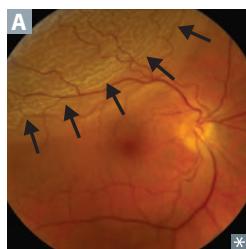
Flame-shaped retinal hemorrhages, arteriovenous nicking, microaneurysms, macular star (exudate, red arrow in **A**), cotton-wool spots (blue arrow in **A**). Presence of papilledema requires immediate lowering of BP.

Associated with ↑ risk of stroke, CAD, kidney disease.

### Retinal vein occlusion

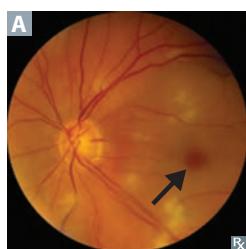


Blockage of central or branch retinal vein due to compression from nearby arterial atherosclerosis. Retinal hemorrhage and venous engorgement (“blood and thunder appearance”; arrows in **A**), edema in affected area.

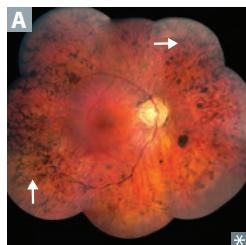
**Retinal detachment**

Separation of neurosensory layer of retina (photoreceptor layer with rods and cones) from outermost pigmented epithelium (normally shields excess light, supports retina) → degeneration of photoreceptors → vision loss. May be 2° to retinal breaks, diabetic traction, inflammatory effusions. Visualized on fundoscopy as crinkling of retinal tissue **A** and changes in vessel direction.

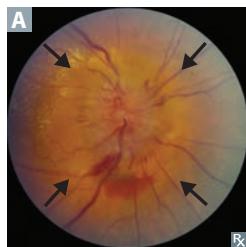
Breaks more common in patients with high myopia and/or history of head trauma. Often preceded by posterior vitreous detachment (“flashes” and “floaters”) and eventual monocular loss of vision like a “curtain drawn down.” Surgical emergency.

**Central retinal artery occlusion**

Acute, painless monocular vision loss. Retina cloudy with attenuated vessels and “cherry-red” spot at fovea (center of macula) **A**. Evaluate for embolic source (eg, carotid artery atherosclerosis, cardiac vegetations, patent foramen ovale).

**Retinitis pigmentosa**

Inherited progressive dystrophy of retinal pigmented epithelium and photoreceptors. May be associated with abetalipoproteinemia. Early findings: nyctalopia (night blindness), peripheral vision loss. Fundoscopy may show triad of optic disc pallor, retinal vessel attenuation, and retinal pigmentation with bone spicule-shaped deposits **A**.

**Papilledema**

Optic disc swelling (usually bilateral) due to ↑ ICP (eg, 2° to mass effect). Enlarged blind spot and elevated optic disc with blurred margins **A**.

**Leukocoria**

Loss (whitening) of the red reflex. Important causes in children include retinoblastoma **A**, congenital cataract.

### Pupillary control

#### Miosis

Constriction, parasympathetic:

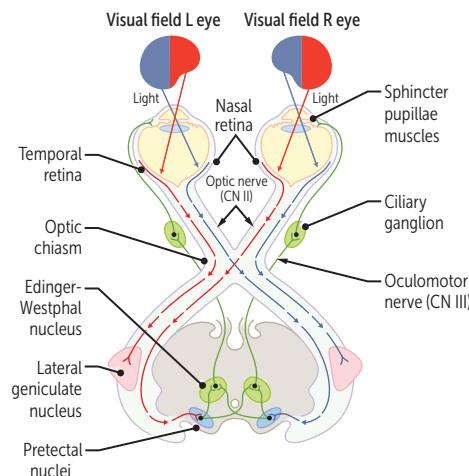
- 1st neuron: Edinger-Westphal nucleus to ciliary ganglion via CN III
- 2nd neuron: short ciliary nerves to sphincter pupillae muscles

**Short** ciliary nerves **shorten** the pupil diameter.

#### Pupillary light reflex

Light in either retina sends a signal via CN II to pretectal nuclei (dashed lines in image) in midbrain that activates bilateral Edinger-Westphal nuclei; pupils constrict bilaterally (direct and consensual reflex).

Result: illumination of 1 eye results in bilateral pupillary constriction.



#### Mydriasis

Dilation, sympathetic:

- 1st neuron: hypothalamus to ciliospinal center of Budge (C8-T2)
- 2nd neuron: exit at T1 to superior cervical ganglion (travels along cervical sympathetic chain near lung apex, subclavian vessels)
- 3rd neuron: plexus along internal carotid, through cavernous sinus; enters orbit as long ciliary nerve to pupillary dilator muscles. Sympathetic fibers also innervate smooth muscle of eyelids (minor retractors) and sweat glands of forehead and face.

**Long** ciliary nerves make the pupil diameter **longer**.

**Marcus Gunn pupil**

Also called relative afferent pupillary defect (RAPD). When the light shines into a normal eye, constriction of the ipsilateral (direct reflex) and contralateral eye (consensual reflex) is observed. When the light is then swung to the affected eye, both pupils dilate instead of constrict due to impaired conduction of light signal along the injured optic nerve. Associated with optic neuritis (eg, multiple sclerosis), optic neuropathies (eg, giant cell arteritis).

**Horner syndrome**

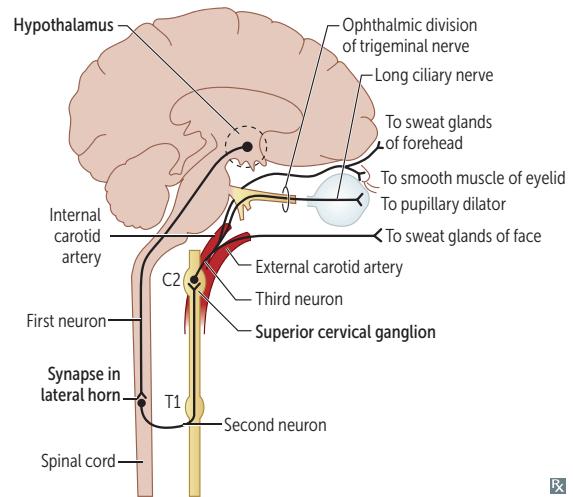
Sympathetic denervation of face →:

- **Ptosis** (slight drooping of eyelid: superior tarsal muscle)
- **Anhidrosis** (absence of sweating) and flushing of affected side of face
- **Miosis** (pupil constriction)

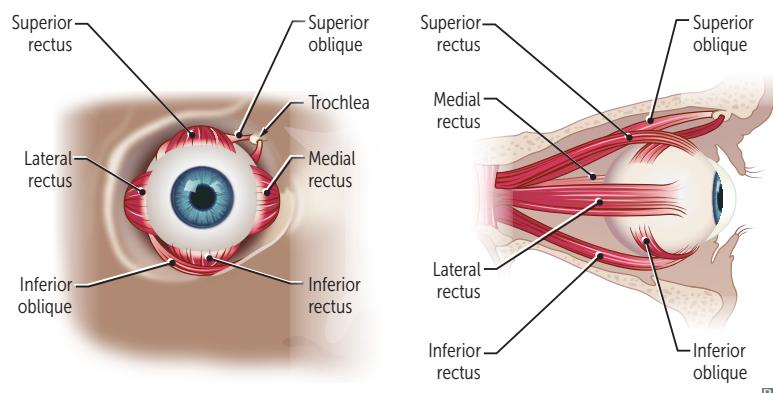
Associated with lesions along the sympathetic chain:

- 1st neuron: pontine hemorrhage, lateral medullary syndrome, spinal cord lesion above T1 (eg, Brown-Séquard syndrome, late-stage syringomyelia)
- 2nd neuron: stellate ganglion compression by Pancoast tumor
- 3rd neuron: carotid dissection (painful); anhidrosis is usually absent

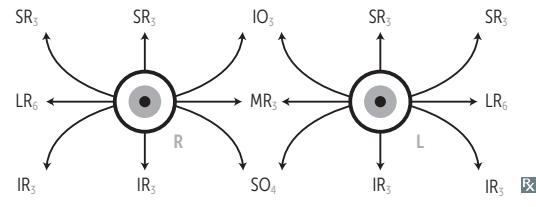
**PAM is horny (Horner).**



Rx

**Ocular motility**

CN **VI** innervates the **Lateral Rectus**.  
 CN **IV** innervates the **Superior Oblique**.  
 CN **III** innervates the **Rest**.  
 The “chemical formula”  **$LR_6 SO_4 R_3$** .



**Obliques go Opposite** (left SO and IO tested with patient looking right)

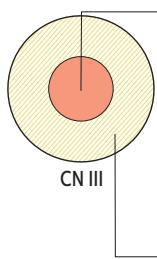
**IOU: IO** tested looking **Up**

**Blowout fracture**—orbital floor fracture; usually caused by direct trauma to eyeball or intraorbital rim. ↑ risk of IR muscle **A** and/or orbital fat entrapment. May lead to infraorbital nerve injury

**CN III, IV, VI palsies****CN III damage**

CN III has both motor (central) and parasympathetic (peripheral) components. Common causes include:

- Ischemia → pupil sparing (motor fibers affected more than parasympathetic fibers)
- Uncal herniation → coma
- PCom aneurysm → sudden-onset headache
- Cavernous sinus thrombosis → proptosis, involvement of CNs IV, V<sub>1</sub>/V<sub>2</sub>, VI
- Midbrain stroke → contralateral hemiplegia



- Motor output to extraocular 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.
- Parasympathetic output—fibers on the periphery are first affected by compression (eg, PCom aneurysm, uncal herniation). Signs: diminished or absent pupillary light reflex, “blown pupil” often with “down-and-out” gaze **A**.

**Motor = middle (central)**

**Parasympathetic = peripheral**

**CN IV damage**

Pupil is higher in the affected eye **B**. Characteristic head tilt to contralateral/unaffected side to compensate for lack of intorsion in affected eye.

Can't see the **floor** with CN **IV** damage (eg, difficulty going down stairs, reading).

**CN VI damage**

Affected eye unable to abduct **C** and is displaced medially in primary position of gaze.

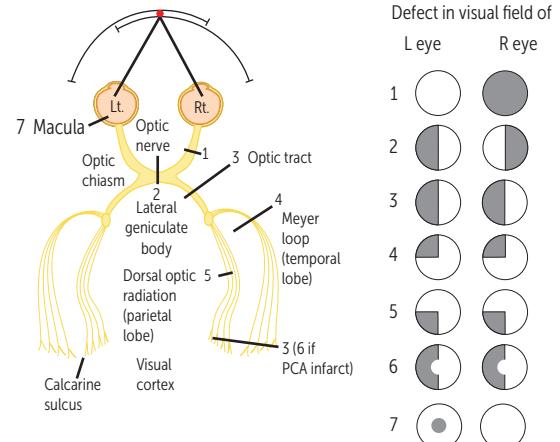


**Visual field defects**

1. Right anopia (monocular vision loss)
2. Bitemporal hemianopia  
(pituitary lesion, chiasm)
3. Left homonymous hemianopia
4. Left upper quadrantanopia  
(right temporal lesion, MCA)
5. Left lower quadrantanopia  
(right parietal lesion, MCA)
6. Left hemianopia with macular sparing  
(right occipital lesion, PCA)
7. Central scotoma (eg, macular degeneration)

Meyer loop—lower retina; loops around inferior horn of lateral ventricle.

Dorsal optic radiation—superior retina; takes shortest path via internal capsule.



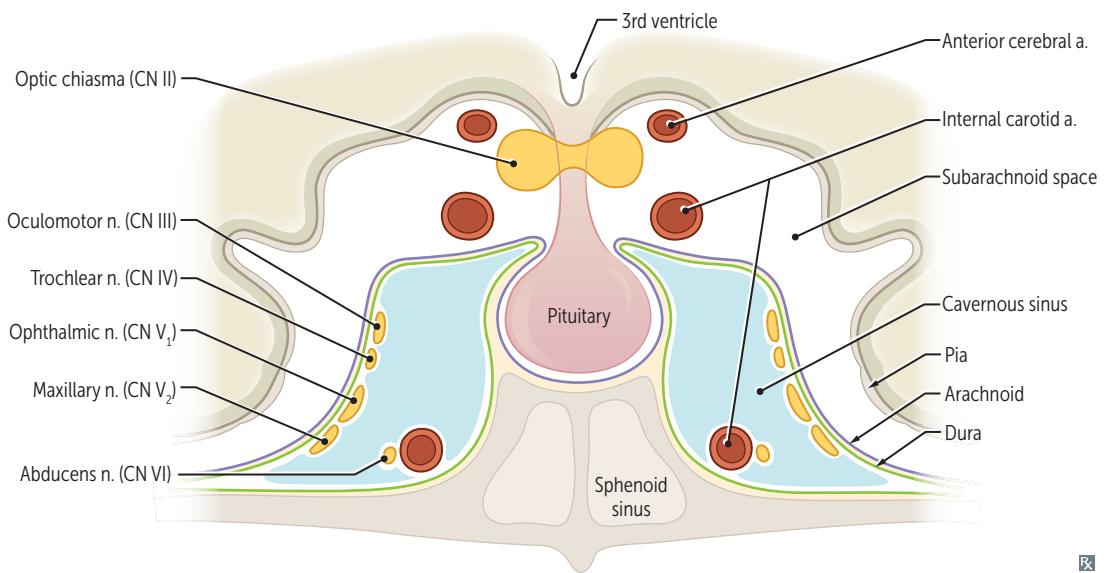
Note: When an image hits 1° visual cortex, it is upside down and left-right reversed.

**Cavernous sinus**

Collection of venous sinuses on either side of pituitary. Blood from eye and superficial cortex → cavernous sinus → internal jugular vein.

CNs III, IV, V<sub>1</sub>, V<sub>2</sub>, and VI plus postganglionic sympathetic pupillary fibers en route to orbit all pass through cavernous sinus. Cavernous portion of internal carotid artery is also here.

**Cavernous sinus syndrome**—presents with variable ophthalmoplegia (eg, CN III and CN VI), ↓ 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.

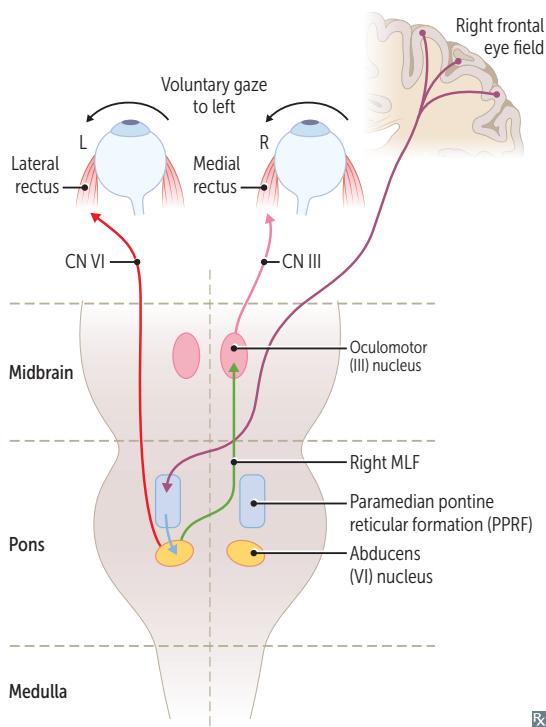


### Internuclear ophthalmoplegia

Medial longitudinal fasciculus (MLF): pair of tracts that interconnect CN VI and CN III nuclei. Coordinates both eyes to move in same horizontal direction. Highly myelinated (must communicate quickly so eyes move at same time). Lesions may be unilateral or bilateral (latter classically seen in multiple sclerosis, stroke).

Lesion in MLF = internuclear ophthalmoplegia (INO), a conjugate horizontal gaze palsy.

Lack of communication such that when CN VI nucleus activates ipsilateral lateral rectus, contralateral CN III nucleus does not stimulate medial rectus to contract. Abducting eye displays nystagmus (CN VI overfires to stimulate CN III). Convergence normal.

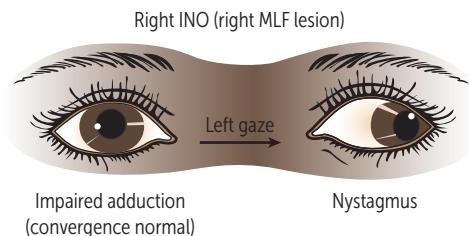


### MLF in MS.

When looking left, the left nucleus of CN VI fires, which contracts the left lateral rectus and stimulates the contralateral (right) nucleus of CN III via the right MLF to contract the right medial rectus.

Directional term (eg, right INO, left INO) refers to the eye that is unable to adduct.

**INO** = Ipsilateral adduction failure, **Nystagmus Opposite.**



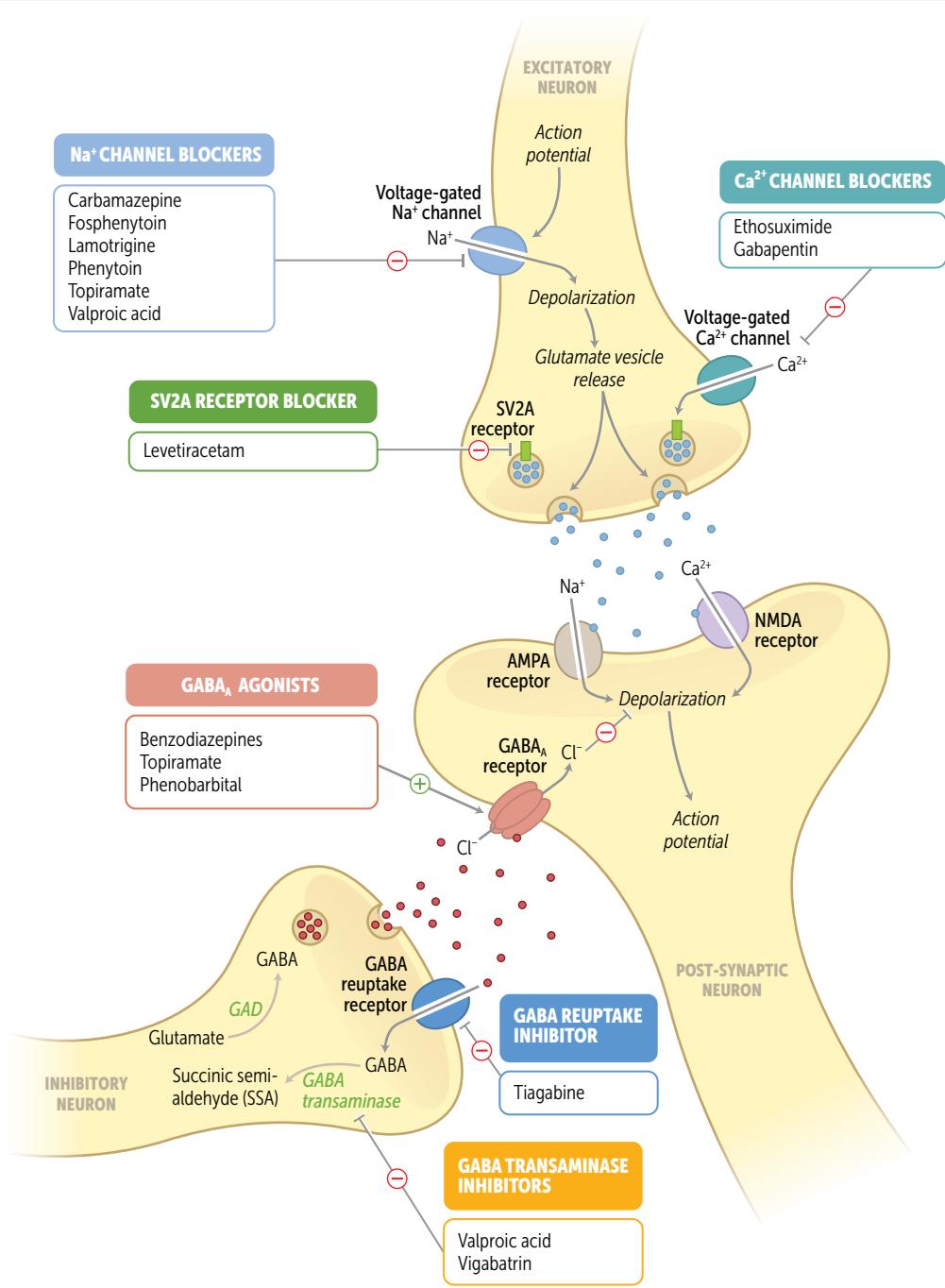
## ► NEUROLOGY—PHARMACOLOGY

## Epilepsy therapy

	PARTIAL (FOCAL) TONIC-CLONIC ABSENCE	1° GENERALIZED TONIC-CLONIC ABSENCE	STATUS EPILEPTICUS	MECHANISM	SIDE EFFECTS	NOTES
Benzodiazepines			** ✓	↑ GABA <sub>A</sub> action	Sedation, tolerance, dependence, respiratory depression	Also for eclampsia seizures (1st line is MgSO <sub>4</sub> )
Carbamazepine	*	✓		Blocks Na <sup>+</sup> channels	Diplopia, ataxia, blood dyscrasias (agranulocytosis, aplastic anemia), liver toxicity, teratogenesis (cleft lip/palate, spina bifida), induction of cytochrome P-450, SIADH, SJS	1st line for trigeminal neuralgia
Ethosuximide		*	✓	Blocks thalamic T-type Ca <sup>2+</sup> channels	<b>EFGHIJ</b> —Ethosuximide causes <b>Fatigue</b> , <b>GI</b> distress, <b>Headache</b> , <b>Itching</b> (and urticaria), <b>SJS</b>	Sucks to have <b>silent</b> (absence) <b>seizures</b>
Gabapentin	✓			Primarily inhibits high-voltage-activated Ca <sup>2+</sup> channels; designed as GABA analog	Sedation, ataxia	Also used for peripheral neuropathy, postherpetic neuralgia
Lamotrigine	✓	✓	✓	Blocks voltage-gated Na <sup>+</sup> channels, inhibits the release of glutamate	SJS (must be titrated slowly), hemophagocytic lymphohistiocytosis (black box warning)	
Levetiracetam	✓	✓		SV2A receptor blocker; may modulate GABA and glutamate release, inhibit voltage-gated Ca <sup>2+</sup> channels	Neuropsychiatric symptoms (eg, personality change), fatigue, drowsiness, headache	
Phenobarbital	✓	✓	✓	↑ GABA <sub>A</sub> action	Sedation, tolerance, dependence, induction of cytochrome P-450, cardiorespiratory depression	1st line in <b>neonates</b> (“phenobabytal”)
Phenytoin, fosphenytoin	✓		*** ✓	Blocks Na <sup>+</sup> channels; zero-order kinetics	<b>PHENYTOIN</b> : cytochrome P-450 induction, <b>Pseudolymphoma</b> , <b>Hirsutism</b> , <b>Enlarged gums</b> , <b>Nystagmus</b> , <b>Yellow-brown skin</b> , <b>Teratogenicity</b> (fetal hydantoin syndrome), <b>Osteopenia</b> , <b>Inhibited folate absorption</b> , <b>Neuropathy</b> . Rare: SJS, DRESS syndrome, drug-induced lupus. Toxicity leads to diplopia, ataxia, sedation.	
Topiramate	✓	✓		Blocks Na <sup>+</sup> channels, ↑ GABA action	Sedation, slow cognition, kidney stones, skinny (weight loss), sight threatened (glaucoma), speech (word-finding) difficulties	Also used for migraine prophylaxis
Valproic acid	✓	*	✓	↑ Na <sup>+</sup> channel inactivation, ↑ GABA concentration by inhibiting GABA transaminase	<b>VALPROATE</b> : Vomiting, <b>Alopecia</b> , <b>Liver damage</b> (hepatotoxic), <b>Pancreatitis</b> , <b>P-450 inhibition</b> , <b>Rash</b> , <b>Obesity</b> (weight gain), <b>Tremor</b> , <b>Teratogenesis</b> (neural tube defects). <b>Epigastric pain</b> (GI distress).	Also used for myoclonic seizures, bipolar disorder, migraine prophylaxis
Vigabatrin	✓			↑ GABA. Irreversible GABA transaminase inhibitor	Permanent visual loss (black box warning)	Vision loss with <b>GABA transaminase inhibitor</b>

\* = Common use, \*\* = 1st line for acute, \*\*\* = 1st line for recurrent seizure prophylaxis.

<sup>†</sup> Includes partial simple/complex and 2° generalized seizures.

**Epilepsy therapy (continued)**

Rx

**Barbiturates**

Phenobarbital, pentobarbital, thiopental, secobarbital.

**MECHANISM**

Facilitate GABA<sub>A</sub> action by ↑ duration of Cl<sup>-</sup> channel opening, thus ↓ neuron firing (barbiturates ↑ duration).

**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).

Contraindicated in porphyria.

**Benzodiazepines**

Diazepam, lorazepam, triazolam, temazepam, oxazepam, midazolam, chlordiazepoxide, alprazolam.

**MECHANISM**

Facilitate GABA<sub>A</sub> action by ↑ frequency of Cl<sup>-</sup> channel opening (“frenzodiazepines” ↑ frequency). ↓ REM sleep. Most have long half-lives and active metabolites (exceptions [ATOM]: Alprazolam, Triazolam, Oxazepam, and Midazolam are short acting → higher addictive potential).

**CLINICAL USE**

Anxiety, panic disorder, spasticity, status epilepticus (lorazepam, diazepam, midazolam), eclampsia, detoxification (eg, alcohol withdrawal/DTs; long-acting chlordiazepoxide and diazepam are preferred), night terrors, sleepwalking, general anesthetic (amnesia, muscle relaxation), hypnotic (insomnia). Lorazepam, Oxazepam, and Temazepam can be used for those with liver disease who drink a LOT due to minimal first-pass metabolism.

**ADVERSE EFFECTS**

Dependence, additive CNS depression effects with alcohol and barbiturates (all bind the GABA<sub>A</sub> receptor). Less risk of respiratory depression and coma than with barbiturates. Treat overdose with flumazenil (competitive antagonist at GABA benzodiazepine receptor). Can precipitate seizures by causing acute benzodiazepine withdrawal.

**Insomnia therapy**

AGENT	MECHANISM	ADVERSE EFFECTS	NOTES
<b>Nonbenzodiazepine hypnotics</b>	Examples: Zolpidem, Zaleplon, esZopiclone Act via the BZ <sub>1</sub> subtype of GABA receptor	Ataxia, headaches, confusion Cause only modest day-after psychomotor depression and few amnestic effects (vs older sedative-hypnotics)	These <b>ZZZs</b> put you to sleep Short duration due to rapid metabolism by liver enzymes; effects reversed by flumazenil ↓ dependency risk and ↓ sleep cycle disturbance (vs benzodiazepine hypnotics)
<b>Suvorexant</b>	<b>Orexin</b> (hypocretin) receptor antagonist	CNS depression (somnolence), headache, abnormal sleep-related activities	Contraindications: narcolepsy, combination with strong CYP3A4 inhibitors Not recommended in patients with liver disease Limited risk of dependency
<b>Ramelteon</b>	Melatonin receptor agonist: binds MT1 and MT2 in suprachiasmatic nucleus	Dizziness, nausea, fatigue, headache	No known risk of dependency

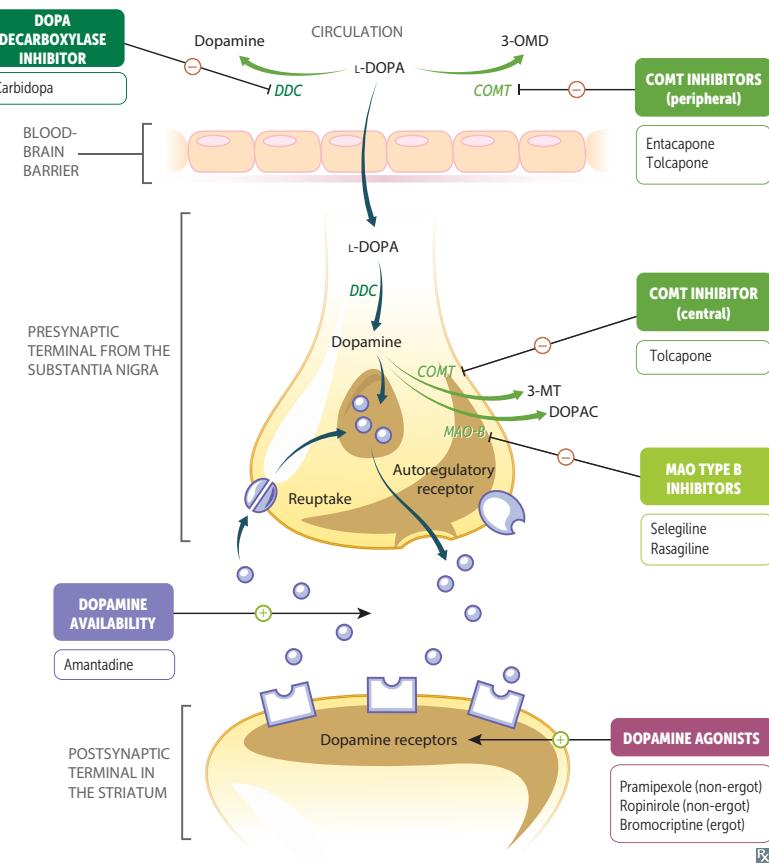
**Triptans****Sumatriptan**

MECHANISM	5-HT <sub>IB/ID</sub> agonists. Inhibit trigeminal nerve activation, prevent vasoactive peptide release, induce vasoconstriction.	A sumo wrestler <b>trips</b> and falls on their <b>head</b> .
CLINICAL USE	Acute migraine, cluster <b>headache</b> attacks.	
ADVERSE EFFECTS	Coronary vasospasm (contraindicated in patients with CAD or vasospastic angina), mild paresthesia, serotonin syndrome (in combination with other 5-HT agonists).	

### Parkinson disease therapy

The most effective treatments are non-ergot dopamine agonists which are usually started in younger patients, and Levodopa (with carbidopa) which is usually started in older patients. Deep brain stimulation of the STN or GPi may be helpful in advanced disease.

STRATEGY	AGENTS
<b>Dopamine agonists</b>	Non-ergot (preferred)—pramipexole, ropinirole; toxicity includes nausea, impulse control disorder (eg, gambling), postural hypotension, hallucinations, confusion. Ergot—bromocriptine rarely used due to toxicity.
<b>↑ dopamine availability</b>	Amantadine ( $\uparrow$ dopamine release and $\downarrow$ dopamine reuptake); toxicity = peripheral edema, livedo reticularis, ataxia.
<b>↑ L-DOPA availability</b>	Agents prevent peripheral (pre-BBB) L-DOPA degradation $\rightarrow$ $\uparrow$ L-DOPA entering CNS $\rightarrow$ $\uparrow$ central L-DOPA available for conversion to dopamine. <ul style="list-style-type: none"> <li>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).</li> <li>Entacapone and tolcapone prevent peripheral L-DOPA degradation to 3-O-methyldopa (3-OMD) by inhibiting COMT. Used in conjunction with levodopa.</li> </ul>
<b>Prevent dopamine breakdown</b>	Agents act centrally (post-BBB) to inhibit breakdown of dopamine. <ul style="list-style-type: none"> <li>Selegiline, rasagiline—block conversion of dopamine into DOPAC by selectively inhibiting MAO-B.</li> <li>Tolcapone—crosses BBB and blocks conversion of dopamine to 3-methoxytyramine (3-MT) in the brain by inhibiting central COMT.</li> </ul>
<b>Curb excess cholinergic activity</b>	Benztropine, trihexyphenidyl (Antimuscarinic; improves tremor and rigidity but has little effect on bradykinesia in Parkinson disease). <b>Tri Park</b> ing my Mercedes-Benz.



**Carbidopa/levodopa**

MECHANISM	↑ dopamine in brain. Unlike dopamine, L-DOPA can cross blood-brain barrier and is converted by dopa decarboxylase in the CNS to dopamine. Carbidopa, a peripheral DOPA decarboxylase inhibitor, is given with L-DOPA to ↑ bioavailability of L-DOPA in the brain and to limit peripheral side effects.
CLINICAL USE	Parkinson disease.
ADVERSE EFFECTS	Nausea, hallucinations, postural hypotension. With progressive disease, L-DOPA can lead to “on-off” phenomenon with improved mobility during “on” periods, then impaired motor function during “off” periods when patient responds poorly to L-DOPA or medication wears off.

**Selegiline, rasagiline**

MECHANISM	Selectively inhibit MAO-B (metabolize dopamine) → ↑ dopamine availability. <b>Selegiline</b> selectively inhibits MAO-B and is more commonly found in the Brain than in the periphery.
CLINICAL USE	Adjunctive agent to L-DOPA in treatment of Parkinson disease.
ADVERSE EFFECTS	May enhance adverse effects of L-DOPA.

**Neurodegenerative disease therapy**

DISEASE	AGENT	MECHANISM	NOTES
<b>Alzheimer disease</b>	Donepezil, rivastigmine, galantamine	AChE inhibitor	1st-line treatment Adverse effects: nausea, dizziness, insomnia. Contraindicated in patients with cardiac conduction abnormalities. <b>Dona Riva</b> dances at the <b>gala</b>
	Memantine	NMDA receptor antagonist; helps prevent excitotoxicity (mediated by Ca <sup>2+</sup> )	Used for moderate to advanced dementia Adverse effects: dizziness, confusion, hallucinations
<b>Amyotrophic lateral sclerosis</b>	Riluzole	↓ neuron glutamate excitotoxicity	↑ survival Treat <b>Lou</b> Gehrig disease with <b>riLouzole</b>
<b>Huntington disease</b>	Tetrabenazine	Inhibit vesicular monoamine transporter (VMAT) → ↓ dopamine vesicle packaging and release	May be used for Huntington chorea and tardive dyskinesia

**Anesthetics—general principles**

CNS drugs must be lipid soluble (cross the blood-brain barrier) or be actively transported.

Drugs with ↓ solubility in blood = rapid induction and recovery times.

Drugs with ↑ solubility in lipids = ↑ potency.

**MAC** = Minimum Alveolar Concentration (of inhaled anesthetic) required to prevent 50% of subjects from moving in response to noxious stimulus (eg, skin incision). Potency = 1/MAC.

Examples: nitrous oxide ( $N_2O$ ) has ↓ blood and lipid solubility, and thus fast induction and low potency. Halothane has ↑ lipid and blood solubility, and thus high potency and slow induction.

**Inhaled anesthetics**

Desflurane, halothane, enflurane, isoflurane, sevoflurane, methoxyflurane,  $N_2O$ .

## MECHANISM

Mechanism unknown.

## EFFECTS

Myocardial depression, respiratory depression, postoperative nausea/vomiting, ↑ cerebral blood flow and ICP, ↓ cerebral metabolic demand.

## ADVERSE EFFECTS

Hepatotoxicity (halothane), nephrotoxicity (methoxyflurane), proconvulsant (enflurane, epileptogenic), expansion of trapped gas in a body cavity ( $N_2O$ ).

**Malignant hyperthermia**—rare, life-threatening condition in which inhaled anesthetics or succinylcholine induce severe muscle contractions and hyperthermia. Susceptibility is often inherited as autosomal dominant with variable penetrance. Mutations in ryanodine receptor (*RYR1*) cause ↑  $Ca^{2+}$  release from sarcoplasmic reticulum.

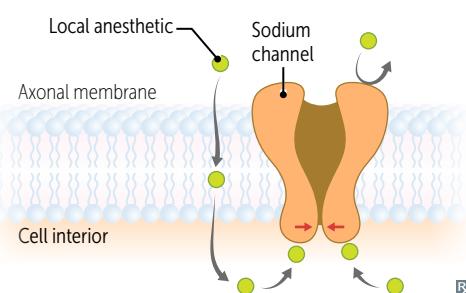
Treatment: dantrolene (a ryanodine receptor antagonist).

**Intravenous anesthetics**

AGENT	MECHANISM	ANESTHESIA USE	NOTES
<b>Thiopental</b>	Facilitates GABA <sub>A</sub> (barbiturate)	Anesthesia induction, short surgical procedures	↓ cerebral blood flow. High lipid solubility Effect terminated by rapid redistribution into tissue, fat
<b>Midazolam</b>	Facilitates GABA <sub>A</sub> (benzodiazepine)	Procedural sedation (eg, endoscopy), anesthesia induction	May cause severe postoperative respiratory depression, ↓ BP, anterograde amnesia
<b>Propofol</b>	Potentiates GABA <sub>A</sub>	Rapid anesthesia induction, short procedures, ICU sedation	May cause respiratory depression, ↓ BP
<b>Ketamine</b>	NMDA receptor antagonist	Dissociative anesthesia Sympathomimetic	↑ cerebral blood flow Emergence reaction possible with disorientation, hallucination, vivid dreams

**Local anesthetics**

Esters—procaine, tetracaine, benzocaine, chloroprocaine.  
 Amides—**lidocaine**, mepivacaine, bupivacaine, ropivacaine, prilocaine (amides have **2 i's** in name).

**MECHANISM**

Block neurotransmission via binding to voltage-gated  $\text{Na}^+$  channels on inner portion of the channel along nerve fibers. Most effective in rapidly firing neurons.  $3^\circ$  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 block duration of action by ↓ systemic absorption.  
 In infected (acidic) tissue, alkaline anesthetics are charged and cannot penetrate membrane effectively → need more anesthetic.  
 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, prilocaine).

**Neuromuscular blocking drugs**

Muscle paralysis in surgery or mechanical ventilation. Selective for Nm nicotinic receptors at neuromuscular junction but not autonomic Nn receptors.

**Depolarizing neuromuscular blocking drugs**

Succinylcholine—strong ACh receptor agonist; produces sustained depolarization and prevents muscle contraction.

Reversal of blockade:

- Phase I (prolonged depolarization)—no antidote. Block potentiated by cholinesterase inhibitors.
- Phase II (repolarized but blocked; ACh receptors are available, but desensitized)—may be reversed with cholinesterase inhibitors.

Complications include hypercalcemia, hyperkalemia, malignant hyperthermia. ↑ risk of prolonged muscle paralysis in patients with pseudocholinesterase deficiency.

**Nondepolarizing neuromuscular blocking drugs**

Atracurium, cisatracurium, pancuronium, rocuronium, tubocurarine, vecuronium—competitive ACh antagonist.

Reversal of blockade—sugammadex or cholinesterase inhibitors (eg, neostigmine, edrophonium).

Anticholinergics (eg, atropine, glycopyrrolate) are given with cholinesterase inhibitors to prevent muscarinic effects (eg, bradycardia).

**Spasmolytics, antispasmodics**

DRUG	MECHANISM	CLINICAL USE	NOTES
<b>Baclofen</b>	GABA <sub>B</sub> receptor agonist in spinal cord	Muscle spasticity, dystonia, multiple sclerosis	Acts on the <b>back</b> (spinal cord)
<b>Cyclobenzaprine</b>	Acts within CNS, mainly at the brain stem	Muscle spasticity	Centrally acting Structurally related to TCAs May cause anticholinergic side effects, sedation
<b>Dantrolene</b>	Prevents release of Ca <sup>2+</sup> from sarcoplasmic reticulum of skeletal muscle by inhibiting the ryanodine receptor	Malignant hyperthermia (toxicity of inhaled anesthetics and succinylcholine) and neuroleptic malignant syndrome (toxicity of antipsychotic drugs)	Acts <b>directly</b> on muscle
<b>Tizanidine</b>	α <sub>2</sub> agonist, acts centrally	Muscle spasticity, multiple sclerosis, ALS, cerebral palsy	

**Opioid analgesics**

MECHANISM	Act as agonists at opioid receptors ( $\mu$ = $\beta$ -endorphin, $\delta$ = enkephalin, $\kappa$ = dynorphin) to modulate synaptic transmission—close presynaptic Ca <sup>2+</sup> channels, open postsynaptic K <sup>+</sup> channels → ↓ synaptic transmission. Inhibit release of ACh, norepinephrine, 5-HT, glutamate, substance P.
EFFICACY	Full agonist: morphine, heroin, meperidine (long acting), methadone, codeine (prodrug; activated by CYP2D6), fentanyl. Partial agonist: buprenorphine. Mixed agonist/antagonist: nalbuphine, pentazocine, butorphanol. Antagonist: naloxone, naltrexone, methylnaltrexone.
CLINICAL USE	Moderate to severe or refractory pain, diarrhea (loperamide, diphenoxylate), acute pulmonary edema, maintenance programs for opiate use disorder (methadone, buprenorphine + naloxone), neonatal abstinence syndrome (methadone, morphine).
ADVERSE EFFECTS	Nausea, vomiting, pruritus (histamine release), opiate use disorder, respiratory depression, constipation, sphincter of Oddi spasm, miosis (except meperidine → mydriasis), additive CNS depression with other drugs. Tolerance does not develop to miosis and constipation. Treat toxicity with naloxone (competitive opioid receptor antagonist) and prevent relapse with naltrexone once detoxified.

**Mixed agonist and antagonist opioid analgesics**

DRUG	MECHANISM	CLINICAL USE	NOTES
<b>Pentazocine</b>	$\kappa$ -opioid receptor agonist and $\mu$ -opioid receptor weak antagonist or partial agonist.	Analgesia for moderate to severe pain.	Can cause opioid withdrawal symptoms if patient is also taking full opioid agonist (due to competition for opioid receptors).
<b>Butorphanol</b>	$\kappa$ -opioid receptor agonist and $\mu$ -opioid receptor partial agonist.	Severe pain (eg, migraine, labor).	Causes less respiratory depression than full opioid agonists. Use with full opioid agonist can precipitate withdrawal. Not easily reversed with naloxone.

**Tramadol**

MECHANISM	Very weak opioid agonist; also inhibits the reuptake of norepinephrine and serotonin.	Tramadol is a slight opioid agonist, and a serotonin and norepinephrine reuptake inhibitor. It is used for stubborn pain, but can lower seizure threshold, and may cause serotonin syndrome.
CLINICAL USE	Chronic pain.	
ADVERSE EFFECTS	Similar to opioids; decreases seizure threshold; serotonin syndrome.	

<b>Glaucoma therapy</b>	$\downarrow$ IOP via $\downarrow$ amount of aqueous humor (inhibit synthesis/secretion or $\uparrow$ drainage). <b>BAD</b> humor may not be politically correct.		
DRUG CLASS	EXAMPLES	MECHANISM	ADVERSE EFFECTS
$\beta$ -blockers	Timolol, betaxolol, carteolol	$\downarrow$ aqueous humor synthesis	No pupillary or vision changes
$\alpha$ -agonists	Epinephrine ( $\alpha_1$ ), apraclonidine, brimonidine ( $\alpha_2$ )	$\downarrow$ aqueous humor synthesis via vasoconstriction (epinephrine) $\downarrow$ aqueous humor synthesis (apraclonidine, brimonidine)	Mydriasis ( $\alpha_1$ ); do not use in closed-angle glaucoma Blurry vision, ocular hyperemia, foreign body sensation, ocular allergic reactions, ocular pruritus
Diuretics	Acetazolamide	$\downarrow$ aqueous humor synthesis via inhibition of carbonic anhydrase	No pupillary or vision changes
Prostaglandins	Bimatoprost, latanoprost (PGF <sub>2<math>\alpha</math></sub> )	$\uparrow$ outflow of aqueous humor via $\downarrow$ resistance of flow through uveoscleral pathway	Darkens color of iris (browning), eyelash growth
Cholinomimetics (M <sub>3</sub> )	Direct: pilocarpine, carbachol Indirect: physostigmine, echothiophate	$\uparrow$ outflow of aqueous humor via contraction of ciliary muscle and opening of trabecular meshwork  Use pilocarpine in acute angle closure glaucoma—very effective at opening meshwork into canal of Schlemm	Miosis (contraction of pupillary sphincter muscles) and cyclospasm (contraction of ciliary muscle)

▶ NOTES

# HIGH-YIELD PRINCIPLES IN

# Psychiatry

*“Words of comfort, skillfully administered, are the oldest therapy known to man.”*

—Louis Nizer

*“Even a happy life cannot be without a measure of darkness, and the word happy would lose its meaning if it were not balanced by sadness.”*

—Carl G. Jung

*“The sorrow which has no vent in tears may make other organs weep.”*

—Henry Maudsley

*“I have schizophrenia. I am not schizophrenia. I am not my mental illness. My illness is a part of me.”*

—Jonathan Harnisch

This chapter encompasses overlapping areas in psychiatry, psychology, sociology, and psychopharmacology. High-yield topics include schizophrenia, mood disorders, eating disorders, personality disorders, somatic symptom disorders, substance use disorders, and antipsychotic agents. Know the DSM-5 criteria for diagnosing common psychiatric disorders.

► Psychology 576

► Pathology 579

► Pharmacology 596

## ► 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 elicits **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 elicits **voluntary** responses.

**Reinforcement**

Target behavior (response) is followed by desired reward (positive reinforcement) or removal of aversive stimulus (negative reinforcement).

Skinner operant conditioning quadrants:

**Increase behavior      Decrease behavior**

Add a stimulus	Positive reinforcement	Positive punishment
	Negative reinforcement	Negative punishment
Remove a stimulus		

**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**

Physician projects feelings about formative or other important persons onto patient (eg, patient reminds physician of younger sibling).

**Ego defenses**

Thoughts and behaviors (voluntary or involuntary) used to resolve conflict and prevent undesirable feelings (eg, anxiety, depression).

IMMATURE DEFENSES	DESCRIPTION	EXAMPLE
<b>Acting out</b>	Subconsciously coping with stressors or emotional conflict using actions rather than reflections or feelings.	A patient skips therapy appointments after deep discomfort from dealing with his past.
<b>Denial</b>	Avoiding the awareness of some painful reality.	A patient with cancer plans a full-time work schedule despite being warned of significant fatigue during chemotherapy.
<b>Displacement</b>	Redirection of emotions or impulses to a neutral person or object (vs projection).	After being reprimanded by her principal, a frustrated teacher returns home and criticizes her wife's cooking instead of confronting the principal directly.
<b>Dissociation</b>	Temporary, drastic change in personality, memory, consciousness, or motor behavior to avoid emotional stress. Patient has incomplete or no memory of traumatic event.	A survivor of sexual abuse sees the abuser and suddenly becomes numb and detached.

**Ego defenses (continued)**

IMMATURE DEFENSES	DESCRIPTION	EXAMPLE
<b>Fixation</b>	Partially remaining at a more childish level of development (vs regression).	A surgeon throws a tantrum in the operating room because the last case ran very late.
<b>Idealization</b>	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.
<b>Identification</b>	Largely unconscious assumption of the characteristics, qualities, or traits of another person or group.	A resident starts putting her stethoscope in her pocket like her favorite attending, instead of wearing it around her neck like before.
<b>Intellectualization</b>	Using facts and logic to emotionally distance oneself from a stressful situation.	A patient diagnosed with cancer discusses the pathophysiology of the disease.
<b>Isolation (of affect)</b>	Separating feelings from ideas and events.	Describing murder in graphic detail with no emotional response.
<b>Passive aggression</b>	Demonstrating hostile feelings in a nonconfrontational manner; showing indirect opposition.	A disgruntled employee is repeatedly late to work, but won't admit it is a way to get back at the manager.
<b>Projection</b>	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.
<b>Rationalization</b>	Asserting plausible explanations for events that actually occurred for other reasons, usually to avoid self-blame.	An employee who was recently fired claims that the job was not important anyway.
<b>Reaction formation</b>	Replacing a warded-off idea or feeling with an emphasis on its opposite (vs sublimation).	A stepfather treats a child he resents with excessive nurturing and overprotection.
<b>Regression</b>	Involuntarily turning back the maturational clock to behaviors previously demonstrated under stress (vs fixation).	A previously toilet-trained child begins bedwetting again following the birth of a sibling.
<b>Repression</b>	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.
<b>Splitting</b>	Believing that people are either all good or all bad at different times due to intolerance of ambiguity. Common in borderline personality disorder.	A patient says that all the nurses are cold and insensitive, but the physicians are warm and friendly.
MATURE DEFENSES		
<b>Sublimation</b>	Replacing an unacceptable wish with a course of action that is similar to the wish but socially acceptable (vs reaction formation).	A teenager's aggression toward her parents because of their high expectations is channeled into excelling in sports.
<b>Altruism</b>	Alleviating negative feelings via unsolicited generosity, which provides gratification (vs reaction formation).	A mafia boss makes a large donation to charity.
<b>Suppression</b>	Intentionally withholding an idea or feeling from conscious awareness (vs repression); temporary.	An athlete focuses on other tasks to prevent worrying about an important upcoming match.
<b>Humor</b>	Lightheartedly expressing uncomfortable feelings to shift the internal focus away from the distress.	A nervous medical student jokes about the boards.
<b>Mature adults wear a SASH.</b>		

**Grief**

The five stages of grief per the Kübler-Ross model are denial, anger, bargaining, depression, and acceptance (may occur in any order). Other common grief symptoms include shock, guilt, sadness, anxiety, yearning, and somatic symptoms that usually occur in waves. Auditory or visual hallucinations can occur in the context of normal bereavement (eg, hearing the deceased speaking). Duration varies widely. Persistent complex bereavement disorder is diagnosed if severe grief interferes with functioning for > 12 months.

**Normal infant and child development**

AGE	MOTOR	SOCIAL	VERBAL/COGNITIVE
Infant	Parents	Start	Observing,
0–12 mo	<b>P</b> rimitive reflexes disappear— Moro (by 3 mo), rooting (by 4 mo), palmar (by 6 mo), Babinski (by 12 mo) <b>P</b> osture—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) <b>P</b> icks—passes toys hand to hand (by 6 mo), <b>P</b> incer grasp (by 10 mo) <b>P</b> oints to objects (by 12 mo)	<b>S</b> ocial smile (by 2 mo) <b>S</b> tranger anxiety (by 6 mo) <b>S</b> eparation anxiety (by 9 mo)	<b>O</b> rients—first to voice (by 4 mo), then to name and gestures (by 9 mo) <b>O</b> bject permanence (by 9 mo) <b>O</b> ratory—says “mama” and “dada” (by 10 mo)
Toddler	Child	Rearing	Working,
12–36 mo	<b>C</b> ruises, takes first steps (by 12 mo) <b>C</b> limbs stairs (by 18 mo) <b>C</b> ubes stacked (number) = age (yr) × 3 <b>C</b> utlery—feeds self with fork and spoon (by 20 mo) <b>K</b> icks ball (by 24 mo)	<b>R</b> ecreation—parallel play (by 24–36 mo) <b>R</b> approchement—moves away from and returns to parent (by 24 mo) <b>R</b> ealization—core gender identity formed (by 36 mo)	<b>W</b> ords—uses 50–200 words (by 2 yr), uses 300+ words (by 3 yr)
Preschool	Don't	Forget, they're still	Learning!
3–5 yr	<b>D</b> rive—tricycle (3 wheels at 3 yr) <b>D</b> rawings—copies line or circle, stick figure (by 4 yr) <b>D</b> exterity—hops on one foot by 4 yr (“4 on one foot”), uses buttons or zippers, grooms self (by 5 yr)	<b>F</b> reedom—comfortably spends part of day away from parent (by 3 yr) <b>F</b> riends—cooperative play, has imaginary friends (by 4 yr)	<b>L</b> anguage—understands 1000 (3 zeros) words (by 3 yr), uses complete sentences and prepositions (by 4 yr) <b>L</b> egends—can tell detailed stories (by 4 yr)

## ► PSYCHIATRY—PATHOLOGY

**Infant deprivation effects**

Long-term deprivation of affection results in:

- Failure to thrive
- Poor language/socialization skills
- Lack of basic trust
- Reactive attachment disorder (infant withdrawn/unresponsive to comfort)
- Disinhibited social engagement (child indiscriminately attaches to strangers)

Deprivation for > 6 months can lead to irreversible changes.  
Severe deprivation can result in infant death.

**Child abuse**

	<b>Physical abuse</b>	<b>Sexual abuse</b>	<b>Emotional abuse</b>
SIGNS	<p>Nonaccidental trauma (eg, fractures, bruises, burns). Injuries often in different stages of healing or in patterns resembling possible implements of injury.</p> <p>Includes abusive head trauma (shaken baby syndrome), characterized by subdural hematomas or retinal hemorrhages.</p> <p>Caregivers may delay seeking medical attention for the child or provide explanations inconsistent with the child's developmental stage or pattern of injury.</p>	<p>STIs, UTIs, and genital, anal, or oral trauma. Most often, there are no physical signs; sexual abuse should not be excluded from a differential diagnosis in the absence of physical trauma.</p> <p>Children often exhibit sexual knowledge or behavior incongruent with their age.</p>	<p>Babies or young children may lack a bond with the caregiver but are overly affectionate with less familiar adults. They may be aggressive toward children and animals or unusually anxious.</p> <p>Older children are often emotionally labile and prone to angry outbursts. They may distance themselves from caregivers and other children. They can experience vague somatic symptoms for which a medical cause cannot be found.</p>
EPIDEMIOLOGY	40% of deaths related to child abuse or neglect occur in children < 1 year old.	Peak incidence 9–12 years old.	~80% of young adult victims of child emotional abuse meet the criteria for ≥ 1 psychiatric illness by age 21.

**Child neglect**

Failure to provide a child with adequate food, shelter, supervision, education, and/or affection. Most common form of child maltreatment. Signs: 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 (vs factitious disorder imposed on another). Usually follows a serious illness or life-threatening event. Can result in missed school or overuse of medical services.

**Childhood and early-onset disorders**

<b>Attention-deficit hyperactivity disorder</b>	Onset before age 12. $\geq 6$ months of limited attention span and/or poor impulse control. Characterized by hyperactivity, impulsivity, and/or inattention in $\geq 2$ settings (eg, school, home, places of worship). Normal intelligence, but commonly coexists with difficulties in school. Often persists into adulthood. Commonly coexists with oppositional defiant disorder. Treatment: stimulants (eg, methylphenidate) +/- behavioral therapy; alternatives include atomoxetine and $\alpha_2$ -agonists (eg, clonidine, guanfacine).
<b>Autism spectrum disorder</b>	Onset in early childhood. Social and communication deficits, repetitive/ritualized behaviors, restricted interests. May be accompanied by intellectual disability and/or above average abilities in specific skills (eg, music). More common in males. Associated with $\uparrow$ head and/or brain size.
<b>Conduct disorder</b>	Repetitive, pervasive behavior violating societal norms or the basic rights of others (eg, aggression toward people and animals, destruction of property, theft). After age 18, often reclassified as antisocial personality disorder. Treatment: psychotherapy (eg, cognitive behavioral therapy [CBT]).
<b>Disruptive mood dysregulation disorder</b>	Onset before age 10. Severe, recurrent temper outbursts out of proportion to situation. Child is constantly angry and irritable between outbursts. Treatment: CBT, stimulants, antipsychotics.
<b>Intellectual disability</b>	Global cognitive deficits (vs specific learning disorder) that affect reasoning, memory, abstract thinking, judgment, language, learning. Adaptive functioning is impaired, leading to major difficulties with education, employment, communication, socialization, independence. Treatment: psychotherapy, occupational therapy, special education.
<b>Intermittent explosive disorder</b>	Onset after age 6. Recurrent verbal or physical outbursts representing a failure to control aggressive impulses. Outbursts are out of proportion to provocation and may lead to legal, financial, or social consequences. Episodes are not premeditated and last $< 30$ minutes. Treatment: psychotherapy, SSRIs.
<b>Oppositional defiant disorder</b>	Pattern of anger and irritability with argumentative, vindictive, and defiant behavior toward authority figures lasting $\geq 6$ months. Treatment: psychotherapy (eg, CBT).
<b>Selective mutism</b>	Onset before age 5. Anxiety disorder lasting $\geq 1$ month involving refraining from speech in certain situations despite speaking in other, usually more comfortable situations. Development (eg, speech and language) not typically impaired. Interferes with social, academic, and occupational tasks. Commonly coexists with social anxiety disorder. Treatment: behavioral, family, and play therapy; SSRIs.
<b>Separation anxiety disorder</b>	Overwhelming fear of separation from home or attachment figure lasting $\geq 4$ weeks. Can be normal behavior up to age 3–4. May lead to factitious physical complaints to avoid school. Treatment: CBT, play therapy, family therapy.
<b>Specific learning disorder</b>	Onset during school-age years. Inability to acquire or use information from a specific subject (eg, math, reading, writing) near age-expected proficiency for $\geq 6$ months despite focused intervention. General functioning and intelligence are normal (vs intellectual disability). Treatment: academic support, counseling, extracurricular activities.
<b>Tourette syndrome</b>	Onset before age 18. Sudden, recurrent, nonrhythmic, stereotyped motor and vocal tics that persist for $> 1$ year. Coprolalia (involuntary obscene speech) found in some patients. Associated with OCD and ADHD. Treatment: psychoeducation, behavioral therapy. For intractable and distressing tics: tetrabenazine, antipsychotics, $\alpha_2$ -agonists.

**Orientation**

Patients' ability to know the date and time, where they are, and who they are (order of loss: time → place → person). Common causes of loss of orientation: alcohol, drugs, fluid/electrolyte imbalance, head trauma, hypoglycemia, infection, nutritional deficiencies, hypoxia.

**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) and disorientation caused by vitamin B<sub>1</sub> deficiency. Associated with disruption and destruction of the limbic system, especially mammillary bodies and anterior thalamus. Seen in chronic alcohol use as a late neuropsychiatric manifestation of Wernicke encephalopathy. Confabulations are characteristic.

**Dissociative disorders****Depersonalization/  
derealization  
disorder**

Persistent feelings of detachment or estrangement from one's own body, thoughts, perceptions, and actions (depersonalization) or one's environment (derealization). Intact reality testing (vs psychosis).

**Dissociative amnesia**

Inability to recall important personal information, usually following severe trauma or stress. May be accompanied by **dissociative fugue** (abrupt, unexpected travelling away from home).

**Dissociative identity  
disorder**

Formerly called multiple personality disorder. Presence of ≥ 2 distinct identities or personality states, typically with distinct memories and patterns of behavior. More common in females. Associated with history of sexual abuse, PTSD, depression, substance use, borderline personality disorder, somatic symptom disorders.

**Delirium**

"Waxing and waning" level of consciousness with acute onset, ↓ attention span, ↓ level of arousal. Characterized by disorganized thinking, hallucinations (often visual), misperceptions (eg, illusions), disturbance in sleep-wake cycle, cognitive dysfunction, agitation. Reversible.

Usually 2° to other identifiable illness (eg, CNS disease, infection, trauma, substance use/withdrawal, metabolic/electrolyte disturbances, hemorrhage, urinary/fecal retention), or medications (eg, anticholinergics), especially in the elderly.

Most common presentation of altered mental status in inpatient setting, especially in the ICU or during prolonged hospital stays.

**Delirium** = changes in **sensorium**.

EEG may show diffuse background rhythm slowing.

Treatment: identification and management of underlying condition. Orientation protocols (eg, keeping a clock or calendar nearby), ↓ sleep disturbances, and ↑ cognitive stimulation to manage symptoms.

Antipsychotics (eg, haloperidol) as needed. Avoid unnecessary restraints and drugs that may worsen delirium (eg, anticholinergics, benzodiazepines, opioids).

**Psychosis**

Distorted perception of reality characterized by delusions, hallucinations, and/or disorganized thought/speech. Can occur in patients with medical illness, psychiatric illness, or both.

**Delusions**

False, fixed, idiosyncratic beliefs that persist despite evidence to the contrary and are not typical of a patient's culture or religion (eg, a patient who believes that others are reading his thoughts). Types include erotomanic, grandiose, jealous, persecutory, somatic, mixed, and unspecified.

**Disorganized thought**

Speech may be incoherent ("word salad"), tangential, or derailed ("loose associations").

**Hallucinations**

Perceptions in the absence of external stimuli (eg, seeing a light that is not actually present).

Contrast with misperceptions (eg, illusions) of real external stimuli. Types include:

- Auditory—more commonly due to psychiatric illness (eg, schizophrenia) than medical illness.
- Visual—more commonly due to medical illness (eg, drug intoxication, delirium) than psychiatric illness.
- Tactile—common in alcohol withdrawal and stimulant use (eg, "cocaine crawlies," a type of delusional parasitosis).
- Olfactory—often occur as an aura of temporal lobe epilepsy (eg, burning rubber) and in brain tumors.
- Gustatory—rare, but seen in epilepsy.
- Hypnagogic—occurs while **going** to sleep. Sometimes seen in narcolepsy.
- Hypnopompic—occurs while waking from sleep ("get **pumped** up in the morning"). Sometimes seen in narcolepsy.

Contrast with illusions, which are misperceptions of real external stimuli (eg, mistaking a shadow for a black cat).

**Mood disorder**

Characterized by an abnormal range of moods or internal emotional states and loss of control over them. Severity of moods causes distress and impairment in social and occupational functioning. Includes major depressive, bipolar, dysthymic, and cyclothymic disorders. Episodic superimposed psychotic features (delusions, hallucinations, disorganized speech/behavior) may be present.

## Schizophrenia spectrum disorders

### Schizophrenia

Chronic illness causing profound functional impairment. Symptom categories include:

- Positive—excessive or distorted functioning (eg, hallucinations, delusions, unusual thought processes, disorganized speech, bizarre behavior)
- Negative—diminished functioning (eg, flat or blunted affect, apathy, anhedonia, alogia, social withdrawal)
- Cognitive—reduced ability to understand or make plans, diminished working memory, inattention

Diagnosis requires ≥ 2 of the following active symptoms, including ≥ 1 from symptoms #1–3:

1. Delusions
2. Hallucinations, often auditory
3. Disorganized speech
4. Disorganized or catatonic behavior
5. Negative symptoms

Symptom onset ≥ 6 months prior to diagnosis; requires ≥ 1 month of active symptoms over the past 6 months.

**Brief psychotic disorder**—≥ 1 positive symptom(s) lasting < 1 month, usually stress-related.

**Schizophreniform disorder**—≥ 2 symptoms lasting 1–6 months.

Associated with altered dopaminergic activity, ↑ serotonergic activity, and ↓ dendritic branching. Ventriculomegaly on brain imaging. Lifetime prevalence—1.5% (males > females). Presents earlier in males (late teens to early 20s) than in females (late 20s to early 30s). ↑ suicide risk.

Heavy cannabis use in adolescence is associated with ↑ incidence and worsened course of psychotic, mood, and anxiety disorders. Treatment: atypical antipsychotics (eg, risperidone) are first line.

Negative symptoms often persist after treatment, despite resolution of positive symptoms.

### Schizoaffective disorder

Shares symptoms with both schizophrenia and mood disorders (major depressive or bipolar disorder). To differentiate from a mood disorder with psychotic features, patient must have > 2 weeks of psychotic symptoms without a manic or depressive episode.

### Delusional disorder

≥ 1 delusion(s) lasting > 1 month, but without a mood disorder or other psychotic symptoms. Daily functioning, including socialization, may be impacted by the pathological, fixed belief but is otherwise unaffected. Can be shared by individuals in close relationships (folie à deux).

### Schizotypal personality disorder

Cluster A personality disorder that also falls on the schizophrenia spectrum. May include brief psychotic episodes (eg, delusions) that are less frequent and severe than in schizophrenia.

### Manic episode

Distinct period of abnormally and persistently elevated, expansive, or irritable mood and ↑ activity or energy lasting ≥ 1 week. Diagnosis requires hospitalization or marked functional impairment with ≥ 3 of the following (manics **DIG FAST**):

- **D**istractibility
- **I**mpulsivity/**I**ndiscretion—seeks pleasure without regard to consequences (hedonistic)
- **G**randiosity—inflated self-esteem
- **F**light of ideas—racing thoughts
- ↑ goal-directed **A**ctivity/psychomotor **A**gitation
- ↓ need for **S**leep
- **T**alkativeness or pressured speech

**Hypomanic episode**

Similar to a manic episode except mood disturbance is not severe enough to cause marked impairment in social and/or occupational functioning or to necessitate hospitalization. Abnormally ↑ activity or energy usually present. No psychotic features. Lasts ≥ 4 consecutive days.

**Bipolar disorder**

**Bipolar I**—≥ 1 manic episode +/- a hypomanic or depressive episode (may be separated by any length of time).

**Bipolar II**—a hypomanic and a depressive episode (no history of manic episodes).

Patient's mood and functioning usually normalize between episodes. Use of antidepressants can destabilize mood. High suicide risk. Treatment: mood stabilizers (eg, lithium, valproic acid, carbamazepine, lamotrigine), atypical antipsychotics.

**Cyclothymic disorder**—milder form of bipolar disorder fluctuating between mild depressive and hypomanic symptoms. Must last ≥ 2 years with symptoms present at least half of the time, with any remission lasting ≤ 2 months.

**Major depressive disorder**

Recurrent episodes lasting ≥ 2 weeks characterized by ≥ 5 of 9 diagnostic symptoms including depressed mood or anhedonia (or irritability in children). **SIG E CAPS:**

- **S**leep disturbances
- ↓ **I**nterest in pleasurable activities (anhedonia)
- **G**uilt or feelings of worthlessness
- ↓ **E**nergy
- ↓ **C**oncentration
- **A**ppetite/weight changes
- **P**sychomotor retardation or agitation
- **S**uicidal ideation

Screen for previous manic or hypomanic episodes to rule out bipolar disorder.

Treatment: CBT and SSRIs are first line; alternatives include SNRIs, mirtazapine, bupropion, electroconvulsive therapy (ECT), ketamine.

Responses to a significant loss (eg, bereavement, natural disaster, disability) may resemble a depressive episode. Diagnosis of MDD is made if criteria are met.

**MDD with psychotic features**

MDD + hallucinations or delusions. Psychotic features are typically mood congruent (eg, depressive themes of inadequacy, guilt, punishment, nihilism, disease, or death) and occur only in the context of major depressive episode (vs schizoaffective disorder). Treatment: antidepressant with atypical antipsychotic, ECT.

**Persistent depressive disorder**

Also called dysthymia. Often milder than MDD; ≥ 2 depressive symptoms lasting ≥ 2 years (≥ 1 year in children), with any remission lasting ≤ 2 months.

**MDD with seasonal pattern**

Formerly called seasonal affective disorder. Major depressive episodes occurring only during a particular season (usually winter) in ≥ 2 consecutive years and in most years across a lifetime. Atypical symptoms common. Treatment: standard MDD therapies + light therapy.

**Depression with atypical features**

Characterized by mood reactivity (transient improvement in response to a positive event), hypersomnia, hyperphagia, leaden paralysis (heavy feeling in arms and legs), long-standing interpersonal rejection sensitivity. Most common subtype of depression. Treatment: CBT and SSRIs are first line. MAO inhibitors (MAOIs) are effective but not first line because of their risk profile.

<b>Peripartum mood disturbances</b>	Onset during pregnancy or within 4 weeks of delivery. ↑ risk with history of mood disorders.	
<b>Postpartum blues</b>	50–85% incidence rate. Characterized by depressed affect, tearfulness, and fatigue starting 2–3 days after delivery. Usually resolves within 2 weeks. Treatment: supportive. Follow up to assess for possible MDD with peripartum onset.	
<b>MDD with peripartum onset</b>	10–15% incidence rate. Formerly called postpartum depression. Meets MDD criteria with onset no later than 1 year after delivery. Treatment: CBT and SSRIs are first line.	
<b>Postpartum psychosis</b>	0.1–0.2% incidence rate. Characterized by mood-congruent delusions, hallucinations, and thoughts of harming the baby or self. Risk factors include first pregnancy, family history, bipolar disorder, psychotic disorder, recent medication change. Treatment: hospitalization and initiation of atypical antipsychotic; if insufficient, ECT may be used.	
<b>Electroconvulsive therapy</b>	Rapid-acting method to treat refractory depression, depression with psychotic symptoms, catatonia, and acute suicidality. Induces tonic-clonic seizure under anesthesia and neuromuscular blockade. Adverse effects include disorientation, headache, partial anterograde/retrograde amnesia usually resolving in 6 months. No absolute contraindications. Safe in pregnant and elderly individuals.	
<b>Risk factors for suicide completion</b>	<b>S</b> ex (male) <b>A</b> ge (young adult or elderly) <b>D</b> epression <b>P</b> revious attempt (highest risk factor) <b>E</b> thanol or drug use <b>R</b> ational thinking loss (psychosis) <b>S</b> ickness (medical illness) <b>O</b> rganized plan <b>N</b> o spouse or other social support <b>S</b> tated future intent	<b>SAD PERSONS</b> are more likely to complete suicide. Most common method in US is firearms; access to guns ↑ risk of suicide completion. Women try more often; men complete more often. Other risk factors include recent psychiatric hospitalization and family history of completed suicide. Protective factors include effective care for comorbidities; medical, familial, or community connectedness; cultural/religious beliefs encouraging self-preservation; and strong problem-solving skills.
<b>Anxiety disorders</b>	Inappropriate experiences of fear/worry and their physical manifestations incongruent with the magnitude of the stressors. Symptoms are not attributable to another psychiatric disorder, medical condition (eg, hyperthyroidism), or substance use. Includes panic disorder, phobias, generalized anxiety disorder, and selective mutism.	

**Panic disorder**

Recurrent panic attacks involving intense fear and discomfort +/– a known trigger. Attacks typically peak in 10 minutes with ≥ 4 of the following: palpitations, paresthesias, depersonalization or derealization, abdominal pain, nausea, intense fear of dying, intense fear of losing control, lightheadedness, chest pain, chills, choking, sweating, shaking, shortness of breath. Strong genetic component. ↑ risk of suicide.

Diagnosis requires attack followed by ≥ 1 month of ≥ 1 of the following:

- Persistent concern of additional attacks
- Worrying about consequences of attack
- Behavioral change related to attacks

Symptoms are systemic manifestations of fear.

Treatment: CBT, SSRIs, and venlafaxine are first line. Benzodiazepines occasionally used in acute setting.

**Phobias**

Severe, persistent (≥ 6 months) fear or anxiety due to presence or anticipation of a specific object or situation. Person often recognizes fear is excessive. Treatment: CBT with exposure therapy.

**Social anxiety disorder**—exaggerated fear of embarrassment in social situations (eg, public speaking, using public restrooms). Treatment: CBT, SSRIs, venlafaxine. For performance type (eg, anxiety restricted to public speaking), use β-blockers or benzodiazepines as needed.

**Agoraphobia**—irrational fear/anxiety while facing or anticipating ≥ 2 specific situations (eg, open/closed spaces, lines, crowds, public transport). If severe, patients may refuse to leave their homes. Associated with panic disorder. Treatment: CBT, SSRIs.

**Generalized anxiety disorder**

Excessive anxiety and worry about different aspects of daily life (eg, work, school, children) for most days of ≥ 6 months. Associated with ≥ 3 of the following for adults (≥ 1 for kids): restlessness, irritability, sleep disturbance, fatigue, muscle tension, difficulty concentrating. Treatment: CBT, SSRIs, SNRIs are first line. Buspirone, TCAs, benzodiazepines are second line.

**Obsessive-compulsive disorders**

Obsessions (recurring intrusive thoughts, feelings, or sensations) that cause severe distress, relieved in part by compulsions (performance of repetitive, often time-consuming actions). Ego-dystonic: behavior inconsistent with one's beliefs and attitudes (vs obsessive-compulsive personality disorder, ego-syntonic). Associated with Tourette syndrome. Treatment: CBT and SSRIs; clomipramine and venlafaxine are second line.

**Body dysmorphic disorder**—preoccupation with minor or imagined defects in appearance. Causes significant emotional distress and repetitive appearance-related behaviors (eg, mirror checking, excessive grooming). Common in eating disorders. Treatment: CBT.

**Trichotillomania**

Compulsively pulling out one's hair. Causes significant distress and persists despite attempts to stop. Presents with areas of thinning hair or baldness on any area of the body, most commonly the scalp.

**A.** Remaining hair shafts are of different lengths (vs alopecia). Incidence highest in childhood but spans all ages. Treatment: psychotherapy.

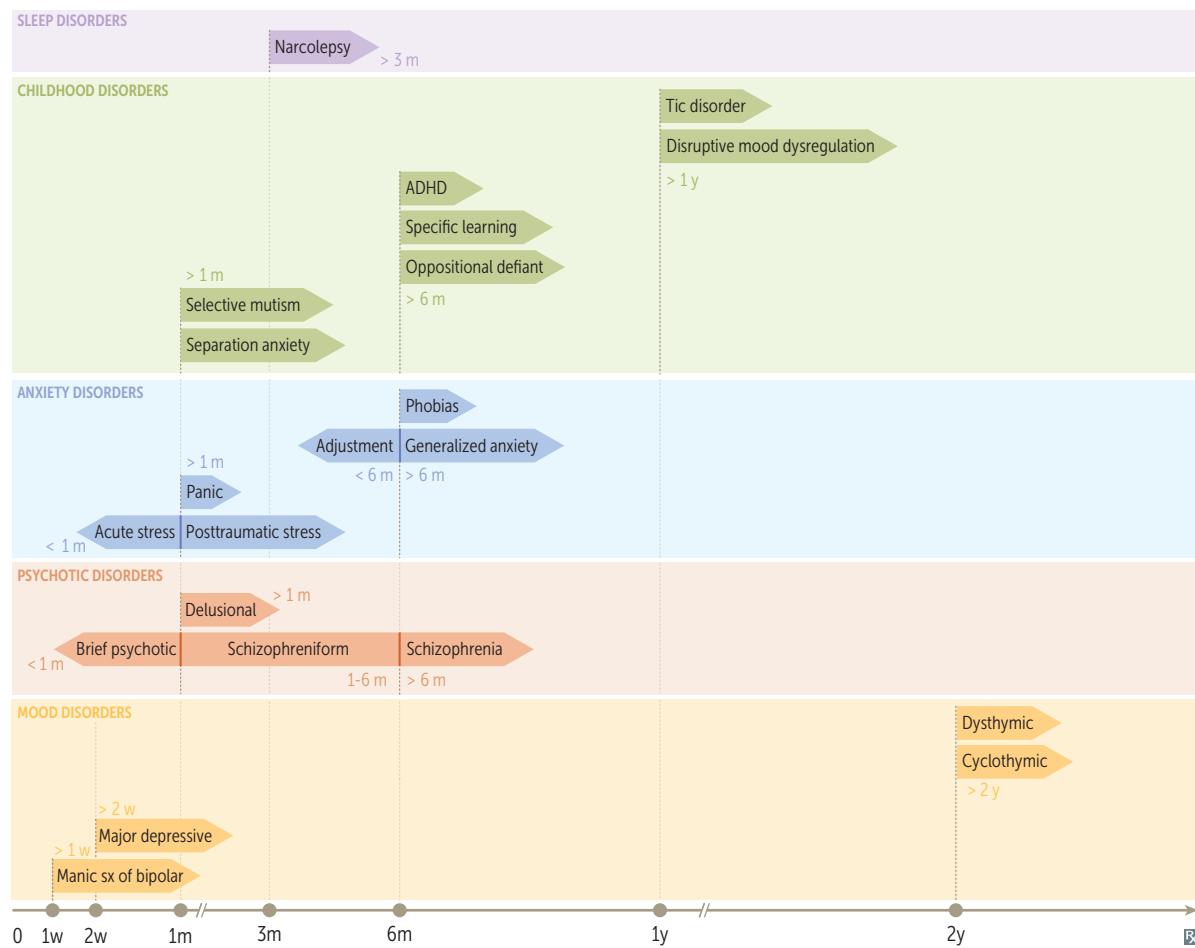
## Trauma and stress-related disorders

**Adjustment disorder** Emotional or behavioral symptoms (eg, anxiety, outbursts) that occur within 3 months of an identifiable psychosocial stressor (eg, divorce, illness) lasting < 6 months once the stressor has ended. Symptoms do not meet criteria for another psychiatric illness. If symptoms persist > 6 months after stressor ends, reevaluate for other explanations (eg, MDD, GAD). Treatment: CBT is first line; antidepressants and anxiolytics may be considered.

**Post-traumatic stress disorder** Experiencing, or discovering that a loved one has experienced, a life-threatening situation (eg, serious injury, rape, witnessing death) → persistent Hyperarousal, Avoidance of associated stimuli, intrusive Re-experiencing of the event (eg, nightmares, flashbacks), changes in cognition or mood (eg, fear, horror, Distress) (having PTSD is HARD). Disturbance lasts > 1 month with significant distress or impaired functioning. Treatment: CBT, SSRIs, and venlafaxine are first line. Prazosin can reduce nightmares.

**Acute stress disorder**—lasts between 3 days and 1 month. Treatment: CBT; pharmacotherapy is usually not indicated.

## Diagnostic criteria by symptom duration



**Personality**

<b>Personality trait</b>	An enduring, repetitive pattern of perceiving, relating to, and thinking about the environment and oneself.	
<b>Personality disorder</b>	Inflexible, maladaptive, and rigidly pervasive pattern of behavior causing subjective distress and/or impaired functioning; person is usually not aware of problem (ego-syntonic). Usually presents by early adulthood. Three clusters: <b>A, B, C</b> ; remember as <b>weird, wild, and worried</b> , respectively, based on symptoms.	
<b>Cluster A personality disorders</b>	Odd or eccentric; inability to develop meaningful social relationships. No psychosis; genetic association with schizophrenia.	Cluster <b>A</b> : accusatory, aloof, awkward. " <b>Weird</b> ."
<b>Paranoid</b>	Pervasive distrust (accusatory), suspiciousness, hypervigilance, and a profoundly cynical view of the world.	
<b>Schizoid</b>	Prefers social withdrawal and solitary activities (vs avoidant), limited emotional expression, indifferent to others' opinions ( <b>Aloof</b> ).	
<b>Schizotypal</b>	Eccentric appearance, odd beliefs or magical thinking, interpersonal <b>Awkwardness</b> .	Included on the schizophrenia spectrum. Pronounce <b>schizo-type-al</b> : <b>odd-type</b> thoughts.
<b>Cluster B personality disorders</b>	Dramatic, emotional, or erratic; genetic association with mood disorders and substance use.	Cluster <b>B</b> : <b>bad, borderline, flamboyant</b> , must be the <b>best</b> . " <b>Wild</b> ."
<b>Antisocial</b>	Disregard for the rights of others with lack of remorse. Involves criminality, impulsivity, hostility, and manipulation. Males > females. Must be ≥ 18 years old with evidence of conduct disorder onset before age 15. Diagnosis is conduct disorder if < 18 years old.	Antisocial = <b>sociopath</b> . <b>Bad</b> .
<b>Borderline</b>	Unstable mood and interpersonal relationships, fear of abandonment, impulsivity, self-mutilation, suicidality, sense of emotional emptiness. Females > males. Splitting is a major defense mechanism.	Treatment: dialectical behavior therapy. <b>Borderline</b> .
<b>Histrionic</b>	Attention-seeking, dramatic speech and emotional expression, shallow and labile emotions, sexually provocative. May use physical appearance to draw attention.	<b>Flamboyant</b> .
<b>Narcissistic</b>	Grandiosity, sense of entitlement; lacks empathy and requires excessive admiration; often demands the "best" and reacts to criticism with rage and/or defensiveness. Fragile self-esteem. Often envious of others.	Must be the <b>best</b> .

<b>Cluster C personality disorders</b>	Anxious or fearful; genetic association with anxiety disorders.	Cluster C: cowardly, obsessive-compulsive, clingy. “ <b>Worried</b> .”
<b>Avoidant</b>	Hypersensitive to rejection and criticism, socially inhibited, timid, feelings of inadequacy, desires relationships with others (vs schizoid).	Cowardly.
<b>Obsessive-compulsive</b>	Preoccupation with order, perfectionism, and control; ego-syntonic: behavior consistent with one's own beliefs and attitudes (vs OCD).	
<b>Dependent</b>	Excessive need for support, low self-confidence. Patients often get stuck in abusive relationships.	Submissive and <b>clingy</b> .
<b>Malingering</b>	Symptoms are intentional, motivation is intentional. Patient consciously fakes, profoundly exaggerates, or claims to have a disorder in order to attain a specific $2^{\circ}$ (external) gain (eg, avoiding work, obtaining compensation). Poor compliance with treatment or follow-up of diagnostic tests. Complaints cease after gain (vs factitious disorder).	
<b>Factitious disorders</b>	Symptoms are intentional, motivation is unconscious. Patient consciously creates physical and/or psychological symptoms in order to assume “sick role” and to get medical attention and sympathy ( $1^{\circ}$ [internal] gain).	
<b>Factitious disorder imposed on self</b>	Formerly called Munchausen syndrome. Chronic factitious disorder with predominantly physical signs and symptoms. Characterized by a history of multiple hospital admissions and willingness to undergo invasive procedures. More common in women and healthcare workers.	
<b>Factitious disorder imposed on another</b>	Formerly called Munchausen syndrome by proxy. Illness in a child or elderly patient is caused or fabricated by the caregiver. Motivation is to assume a sick role by proxy. Form of child/elder abuse.	
<b>Somatic symptom and related disorders</b>	Symptoms are unconscious, motivation is unconscious. Category of disorders characterized by physical symptoms causing significant distress and impairment. Symptoms not intentionally produced or feigned.	
<b>Somatic symptom disorder</b>	$\geq 1$ bodily complaints (eg, abdominal pain, fatigue) lasting months to years. Associated with excessive, persistent thoughts and anxiety about symptoms. May co-occur with medical illness. Treatment: regular office visits with the same physician in combination with psychotherapy.	
<b>Conversion disorder</b>	Also called functional neurologic symptom disorder. Unexplained loss of sensory or motor function (eg, paralysis, blindness, mutism), often following an acute stressor; patient may be aware of but indifferent toward symptoms (“la belle indifférence”); more common in females, adolescents, and young adults.	
<b>Illness anxiety disorder</b>	Preoccupation with acquiring or having a serious illness, often despite medical evaluation and reassurance; minimal to no somatic symptoms.	

**Malingering vs factitious disorder vs somatic symptom disorders**

	<b>Malingering</b>	<b>Factitious disorder</b>	<b>Somatic symptom disorders</b>
<b>SYMPTOMS</b>	Intentional	Intentional	Unconscious
<b>MOTIVATION</b>	Intentional	Unconscious	Unconscious

**Eating disorders****Anorexia nervosa**

Most common in young women.

Intense fear of weight gain, overvaluation of thinness, and body image distortion leading to calorie restriction and severe weight loss resulting in inappropriately low body weight ( $BMI < 18.5 \text{ kg/m}^2$  for adults). May present with hypothyroidism, amenorrhea, osteoporosis, lanugo.

**Binge-eating/purgng type**—recurring purging behaviors (eg, laxative or diuretic abuse, self-induced vomiting) or binge eating over the last 3 months.

**Restricting type**—primary disordered behaviors include dieting, fasting, and/or over-exercising. No recurring purging behaviors or binge eating over the last 3 months.

**Refeeding syndrome**—often occurs in significantly malnourished patients with sudden ↑ calorie intake → ↑ insulin → ↓  $\text{PO}_4^{3-}$ , ↓  $\text{K}^+$ , ↓  $\text{Mg}^{2+}$  → cardiac complications, rhabdomyolysis, seizures.

Treatment: nutritional rehabilitation, psychotherapy, olanzapine.

**Bulimia nervosa**

Recurring episodes of binge eating with compensatory purging behaviors at least weekly over the last 3 months. BMI often normal or slightly overweight (vs anorexia). Associated with parotid gland hypertrophy (may see ↑ serum amylase), enamel erosion, Mallory-Weiss syndrome, electrolyte disturbances (eg, ↓  $\text{K}^+$ , ↓  $\text{Cl}^-$ ), metabolic alkalosis, dorsal hand calluses from induced vomiting (Russell sign).

Treatment: psychotherapy, nutritional rehabilitation, antidepressants (eg, SSRIs). Bupropion is contraindicated due to seizure risk.

**Binge-eating disorder**

Recurring episodes of binge eating without purging behaviors at least weekly over the last 3 months. ↑ diabetes risk. Most common eating disorder in adults.

Treatment: psychotherapy (first line); SSRIs; lisdexamfetamine.

**Pica**

Recurring episodes of eating non-food substances (eg, ice, dirt, hair, paint chips) over ≥ 1 month that are not culturally or developmentally recognized as normal. May provide temporary emotional relief. Common in children and during pregnancy. Associated with malnutrition, iron deficiency anemia, developmental disabilities, emotional trauma.

Treatment: psychotherapy and nutritional rehabilitation (first line); SSRIs (second line).

**Gender dysphoria**

Significant incongruence between one's experienced gender and the gender assigned at birth, lasting > 6 months and leading to persistent distress. Individuals may self-identify as another gender, pursue gender-affirming surgery, and/or live as another gender. Gender nonconformity itself is not a mental disorder. Gender identity develops at age ~3 years.

**Transgender**—desiring and often making lifestyle changes to live as a different gender. Medical interventions (eg, hormone therapy, gender-affirming surgery) may be utilized during the transition to enable the individual's appearance to match their gender identity.

**Sexual dysfunction**

Includes sexual desire disorders (hypoactive sexual desire or sexual aversion), sexual arousal disorders (erectile dysfunction), orgasmic disorders (anorgasmia, premature ejaculation), sexual pain disorders (dyspareunia, vaginismus).

Differential diagnosis includes (**PENIS**):

- Psychological (if nighttime erections still occur)
- Endocrine (eg, diabetes, low testosterone)
- Neurogenic (eg, postoperative, spinal cord injury)
- Insufficient blood flow (eg, atherosclerosis)
- Substances (eg, antihypertensives, antidepressants, ethanol)

**Sleep terror disorder**

Periods of inconsolable terror with screaming in the middle of the night. Most common in children. Occurs during slow-wave深深 (stage N3) non-REM sleep with no memory of the arousal episode, as opposed to nightmares that occur during **REM** sleep (**remembering** a scary dream). Triggers include emotional stress, fever, and lack of sleep. Usually self limited.

**Enuresis**

Nighttime urinary incontinence ≥ 2 times/week for ≥ 3 months in person > 5 years old. First-line treatment: behavioral modification (eg, scheduled voids, nighttime fluid restriction) and positive reinforcement. For refractory cases: bedwetting alarm, oral desmopressin (ADH analog; preferred over imipramine due to fewer side effects).

**Narcolepsy**

Excessive daytime sleepiness (despite awakening well-rested) with recurrent episodes of rapid-onset, overwhelming sleepiness ≥ 3 times/week for the last 3 months. Due to ↓ orexin (hypocretin) production in lateral hypothalamus and dysregulated sleep-wake cycles. Associated with:

- Hypnagogic (just before **going** to sleep) or hypnopompic (just before awakening; get **pumped** up in the morning) hallucinations.
- Nocturnal and narcoleptic sleep episodes that start with REM sleep (sleep paralysis).
- Cataplexy (loss of all muscle tone following strong emotional stimulus, such as laughter).

Treatment: good sleep hygiene (scheduled naps, regular sleep schedule), daytime stimulants (eg, amphetamines, modafinil) and/or nighttime sodium oxybate (GHB).

**Substance use disorder**

Maladaptive pattern of substance use involving ≥ 2 of the following in the past year:

- Tolerance
- Withdrawal
- Intense, distracting cravings
- Using more, or longer, than intended
- Persistent desire but inability to cut down
- Time-consuming substance acquisition, use, or recovery
- Impaired functioning at work, school, or home
- Social or interpersonal conflicts
- Reduced recreational activities
- > 1 episode of use involving danger (eg, unsafe sex, driving while impaired)
- Continued use despite awareness of harm

**Gambling disorder**

Persistent, recurrent, problematic gambling. May include preoccupation with gambling, compulsion to increase size of bet, unsuccessful attempts to decrease gambling, gambling to escape stressors, attempting to recoup losses with more gambling, lying to family or therapists to conceal extent. Treatment: psychotherapy.

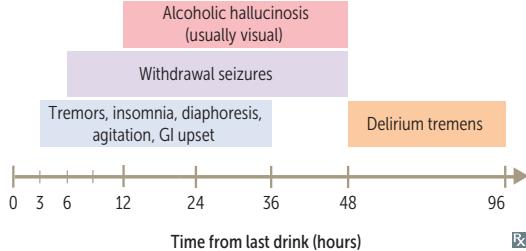
**Transtheoretical model of change**

STAGE	FEATURES	MOTIVATIONAL STRATEGIES
<b>Precontemplation</b>	Denies problem and its consequences.	Encourage introspection. Use patient's personal priorities in explaining risks. Affirm your availability to the patient.
<b>Contemplation</b>	Acknowledges problem but is ambivalent or unwilling to change.	Discuss pros of changing and cons of maintaining current behavior. Suggest means to support behavior changes.
<b>Preparation/ determination</b>	Committed to and planning for behavior change.	Encourage initial changes, promote expectations for positive results, provide resources to assist in planning.
<b>Action/willpower</b>	Executes a plan and demonstrates a change in behavior.	Assist with strategies for self-efficacy, contingency management, and coping with situations that trigger old behaviors.
<b>Maintenance</b>	New behaviors become sustained, integrate into personal identity and lifestyle.	Reinforce developing habits. Evaluate and mitigate relapse risk. Praise progress.
<b>Relapse</b>	Regression to prior behavior (does not always occur).	Varies based on degree of regression. Encourage return to changes. Provide reassurance that change remains possible.

**Psychiatric emergencies**

	CAUSE	MANIFESTATION	TREATMENT
<b>Serotonin syndrome</b>	Any drug that ↑ 5-HT. Psychiatric drugs: MAOIs, SSRIs, SNRIs, TCAs, vilazodone, vortioxetine, buspirone  Nonpsychiatric drugs: tramadol, ondansetron, triptans, linezolid, MDMA, dextromethorphan, meperidine, St. John's wort	<b>3 A's:</b> ↑ activity (neuromuscular; eg, clonus, hyperreflexia, hypertonia, tremor, seizure), autonomic instability (eg, hyperthermia, diaphoresis, diarrhea), altered mental status	Cyproheptadine (5-HT <sub>2</sub> receptor antagonist) Prevention: avoid simultaneous serotonergic drugs, and allow a washout period between them
<b>Hypertensive crisis</b>	Eating tyramine-rich foods (eg, aged cheeses, cured meats, wine, chocolate) while taking MAOIs	Hypertensive crisis (tyramine displaces other neurotransmitters [eg, NE] in the synaptic cleft → ↑ sympathetic stimulation)	Phentolamine
<b>Neuroleptic malignant syndrome</b>	Antipsychotics (typical > atypical) + genetic predisposition	<b>Malignant FEVER:</b> Myoglobinuria, Fever, Encephalopathy, Vitals unstable, ↑ Enzymes (eg, CK), muscle Rrigidity ("lead pipe")	Dantrolene, dopaminergics (eg, bromocriptine, amantadine), benzodiazepines; discontinue causative agent
<b>Delirium tremens</b>	Alcohol withdrawal; occurs 2–4 days after last drink Classically seen in hospital setting when inpatient cannot drink	Altered mental status, hallucinations, autonomic hyperactivity, anxiety, seizures, tremors, psychomotor agitation, insomnia, nausea	Longer-acting benzodiazepines
<b>Acute dystonia</b>	Typical antipsychotics, anticonvulsants (eg, carbamazepine), metoclopramide	Sudden onset of muscle spasms, stiffness, and/or oculogyric crisis occurring hours to days after medication use; can lead to laryngospasm requiring intubation	Benztropine or diphenhydramine
<b>Lithium toxicity</b>	↑ lithium dosage, ↓ renal elimination (eg, acute kidney injury), medications affecting clearance (eg, ACE inhibitors, thiazide diuretics, NSAIDs). Narrow therapeutic window.	Nausea, vomiting, slurred speech, hyperreflexia, seizures, ataxia, nephrogenic diabetes insipidus	Discontinue lithium, hydrate aggressively with isotonic sodium chloride, consider hemodialysis
<b>Tricyclic antidepressant toxicity</b>	TCA overdose	Respiratory depression, hyperpyrexia, prolonged QT <b>Tricyclic's:</b> convulsions, coma, cardiotoxicity (arrhythmia due to Na <sup>+</sup> channel inhibition)	Supportive treatment, monitor ECG, NaHCO <sub>3</sub> (prevents arrhythmia), activated charcoal

### Psychoactive drug intoxication and withdrawal

DRUG	INTOXICATION	WITHDRAWAL
<b>Depressants</b>	Nonspecific: mood elevation, ↓ anxiety, sedation, behavioral disinhibition, respiratory depression.	Nonspecific: anxiety, tremor, seizures, insomnia.
<b>Alcohol</b>	Emotional lability, slurred speech, ataxia, coma, blackouts. Serum $\gamma$ -glutamyltransferase (GGT)—sensitive indicator of alcohol use. AST value is $2\times$ ALT value (“ToAST 2 ALcohol”). Treatment: supportive (eg, fluids, antiemetics).	 <p>Time from last drink (hours)</p> <p>Alcoholic hallucinosis (usually visual)</p> <p>Withdrawal seizures</p> <p>Tremors, insomnia, diaphoresis, agitation, GI upset</p> <p>Delirium tremens</p>
<b>Barbiturates</b>	Low safety margin, marked respiratory depression. Treatment: symptom management (eg, assist respiration, ↑ BP).	Treatment: longer-acting benzodiazepines. Delirium, life-threatening cardiovascular collapse.
<b>Benzodiazepines</b>	Greater safety margin. Ataxia, minor respiratory depression. Treatment: flumazenil (benzodiazepine receptor antagonist, but rarely used as it can precipitate seizures).	Seizures, sleep disturbance, depression.
<b>Opioids</b>	Euphoria, respiratory and CNS depression, ↓ gag reflex, pupillary constriction (pinpoint pupils), seizures, ↓ GI motility. Most common cause of drug overdose death. Treatment: naloxone.	Sweating, dilated pupils, piloerection (“cold turkey”), rhinorrhea, lacrimation, yawning, nausea, stomach cramps, diarrhea (“flu-like” symptoms). Treatment: symptom management, methadone, buprenorphine.
<b>Inhalants</b>	Disinhibition, euphoria, slurred speech, disturbed gait, disorientation, drowsiness. Effects often have rapid onset and resolution. Perinasal/perioral rash with repeated use.	Irritability, dysphoria, sleep disturbance, headache.
<b>Stimulants</b>	Nonspecific: mood elevation, ↓ appetite, psychomotor agitation, insomnia, cardiac arrhythmias, tachycardia, anxiety.	Nonspecific: post-use “crash,” including depression, lethargy, ↑ appetite, sleep disturbance, vivid nightmares.
<b>Amphetamines</b>	Euphoria, grandiosity, pupillary dilation, prolonged wakefulness, hyperalertness, hypertension, paranoia, fever, fractured teeth. Skin excoriations with methamphetamine use. Severe: cardiac arrest, seizures. Treatment: benzodiazepines for agitation and seizures.	
<b>Caffeine</b>	Palpitation, agitation, tremor, insomnia.	Headache, difficulty concentrating, flu-like symptoms.

**Psychoactive drug intoxication and withdrawal (continued)**

DRUG	INTOXICATION	WITHDRAWAL
<b>Cocaine</b>	Impaired judgment, pupillary dilation, diaphoresis, hallucinations (including tactile), paranoia, angina, sudden cardiac death. Chronic use may lead to perforated nasal septum due to vasoconstriction and resulting ischemic necrosis. Treatment: benzodiazepines; use of $\beta$ -blockers or mixed $\alpha$ -/ $\beta$ -blockers (eg, labetalol) for hypertension and tachycardia is controversial as first-line therapy.	Restlessness, hunger, severe depression, sleep disturbance.
<b>Nicotine</b>	Restlessness.	Irritability, anxiety, restlessness, ↓ concentration, ↑ appetite/weight. Treatment: nicotine patch, gum, or lozenges; bupropion/varenicline.
<b>Hallucinogens</b>		
<b>Lysergic acid diethylamide</b>	Perceptual distortion (visual, auditory), depersonalization, anxiety, paranoia, psychosis, flashbacks (usually nondisturbing), mydriasis.	
<b>Cannabis/cannabinoids</b>	Euphoria, anxiety, paranoid delusions, perception of slowed time, impaired judgment, social withdrawal, ↑ appetite, dry mouth, conjunctival injection, hallucinations.	Irritability, anxiety, depression, insomnia, restlessness, ↓ appetite.
<b>MDMA</b>	Also known as ecstasy. Euphoria, hallucinations, disinhibition, hyperactivity, ↑ thirst, bruxism, distorted sensory and time perception, mydriasis. Life-threatening effects include hypertension, tachycardia, hyperthermia, hyponatremia, serotonin syndrome.	Depression, fatigue, change in appetite, difficulty concentrating, anxiety.
<b>Phencyclidine</b>	Violence, nystagmus, impulsivity, psychomotor agitation, miosis, tachycardia, hypertension, analgesia, psychosis, delirium, seizures.	
<b>Alcohol use disorder</b>		
	Diagnosed using criteria for substance use disorder. Complications: vitamin B <sub>1</sub> (thiamine) deficiency, alcoholic cirrhosis, hepatitis, pancreatitis, peripheral neuropathy, testicular atrophy. Treatment: naltrexone (reduces cravings), acamprosate, disulfiram (to condition the patient to abstain from alcohol use). Support groups such as Alcoholics Anonymous are helpful in sustaining abstinence and supporting patient and family.	
<b>Wernicke-Korsakoff syndrome</b>	Results from vitamin B <sub>1</sub> deficiency. Symptoms can be precipitated by administering dextrose before vitamin B <sub>1</sub> . Triad of confusion, ophthalmoplegia, ataxia ( <b>Wernicke encephalopathy</b> ). May progress to irreversible memory loss, confabulation, personality change ( <b>Korsakoff syndrome</b> ). Treatment: IV vitamin B <sub>1</sub> (before dextrose).	

## ► PSYCHIATRY—PHARMACOLOGY

**Psychotherapy**

<b>Behavioral therapy</b>	Teaches patients how to identify and change maladaptive behaviors or reactions to stimuli (eg, systematic desensitization for specific phobia).
<b>Cognitive behavioral therapy</b>	Teaches patients to recognize distortions in their thought processes, develop constructive coping skills, and ↓ maladaptive coping behaviors → greater emotional control and tolerance of distress (eg, recognizing triggers for alcohol consumption).
<b>Dialectical behavioral therapy</b>	Designed for use in borderline personality disorder, but can be used in other psychiatric conditions as well (eg, depression).
<b>Interpersonal therapy</b>	Focused on improving interpersonal relationships and communication skills.
<b>Motivational interviewing</b>	Enhances intrinsic motivation to change by exploring and resolving ambivalence. Used in substance use disorder and weight loss.
<b>Supportive therapy</b>	Utilizes empathy to help individuals during a time of hardship to maintain optimism or hope.

**Preferred medications for selected psychiatric conditions**

PSYCHIATRIC CONDITION	PREFERRED DRUGS
ADHD	Stimulants (methylphenidate, amphetamines)
Alcohol withdrawal	Benzodiazepines (eg, chlordiazepoxide, lorazepam, diazepam)
Bipolar disorder	Carbamazepine, atypical antipsychotics, lithium, lamotrigine, valproate. Character <b>a</b> little less variable
Bulimia nervosa	SSRIs
Depression	SSRIs
Generalized anxiety disorder	SSRIs, SNRIs
Obsessive-compulsive disorder	SSRIs, venlafaxine, clomipramine
Panic disorder	SSRIs, venlafaxine, benzodiazepines
PTSD	SSRIs, venlafaxine, prazosin (for nightmares)
Schizophrenia	Atypical antipsychotics
Social anxiety disorder	SSRIs, venlafaxine
Tourette syndrome	Performance only: β-blockers, benzodiazepines
	Antipsychotics (eg, fluphenazine, risperidone), tetrabenazine

**Central nervous system stimulants**

MECHANISM	↑ catecholamines in the synaptic cleft, especially norepinephrine and dopamine.
CLINICAL USE	ADHD, narcolepsy, binge-eating disorder.
ADVERSE EFFECTS	Nervousness, agitation, anxiety, insomnia, anorexia, tachycardia, hypertension, weight loss, tics, bruxism.

**Antipsychotics**

Typical (1st-generation) antipsychotics—haloperidol, pimozide, trifluoperazine, fluphenazine, thioridazine, chlorpromazine.

Atypical (2nd-generation) antipsychotics—aripiprazole, asenapine, clozapine, olanzapine, quetiapine, iloperidone, paliperidone, risperidone, lurasidone, ziprasidone.

**MECHANISM**

Block dopamine D<sub>2</sub> receptor ( $\uparrow$  cAMP). Atypical antipsychotics also block serotonin 5-HT<sub>2</sub> receptor. Aripiprazole is a D<sub>2</sub> partial agonist.

**CLINICAL USE**

Schizophrenia (typical antipsychotics primarily treat positive symptoms; atypical antipsychotics treat both positive and negative symptoms), disorders with concomitant psychosis (eg, bipolar disorder), Tourette syndrome, OCD, Huntington disease. Clozapine is used for treatment-resistant psychotic disorders or those with persistent suicidality.

**ADVERSE EFFECTS**

Antihistaminic (sedation), anti- $\alpha_1$ -adrenergic (orthostatic hypotension), antimuscarinic (dry mouth, constipation) (anti-HAM). Use with caution in dementia.

Metabolic: weight gain, hyperglycemia, dyslipidemia. Highest risk with clozapine and olanzapine (obesity).

Endocrine: hyperprolactinemia  $\rightarrow$  galactorrhea, oligomenorrhea, gynecomastia.

Cardiac: QT prolongation.

Neurologic: neuroleptic malignant syndrome.

Ophthalmologic: chlorpromazine—corneal deposits; thioridazine—retinal deposits.

Clozapine—agranulocytosis (monitor WBCs closely), seizures (dose related), myocarditis.

**Extrapyramidal symptoms—ADAPT:**

- Hours to days: Acute Dystonia (muscle spasm, stiffness, oculogyric crisis). Treatment: benztropine, diphenhydramine.
- Days to months:
  - Akathisia (restlessness). Treatment:  $\beta$ -blockers, benztropine, benzodiazepines.
  - Parkinsonism (bradykinesia). Treatment: benztropine, amantadine.
- Months to years: Tardive dyskinesia (chorea, especially orofacial). Treatment: benzodiazepines, botulinum toxin injections, valbenazine, deutetrabenazine.

**NOTES**

Lipid soluble  $\rightarrow$  stored in body fat  $\rightarrow$  slow to be removed from body.

Typical antipsychotics have greater affinity for D<sub>2</sub> receptor than atypical antipsychotics  $\rightarrow$   $\uparrow$  risk for hyperprolactinemia, extrapyramidal symptoms, neuroleptic malignant syndrome.

**High**-potency typical antipsychotics: haloperidol, trifluoperazine, pimozide, fluphenazine (Hal tries pie to fly high)—more neurologic side effects (eg, extrapyramidal symptoms).

**Low**-potency typical antipsychotics: chlorpromazine, thioridazine (cheating thieves are low)—more antihistaminic, anti- $\alpha_1$ -adrenergic, antimuscarinic effects.

**Lithium**

## MECHANISM

Not established; possibly related to inhibition of phosphoinositide cascade.

## CLINICAL USE

Mood stabilizer for bipolar disorder; treats acute manic episodes and prevents relapse.

## ADVERSE EFFECTS

Tremor, hypothyroidism, hyperthyroidism, polyuria (causes nephrogenic diabetes insipidus), teratogenesis (causes Ebstein anomaly). Narrow therapeutic window requires close monitoring of serum levels. Almost exclusively excreted by kidneys; most is reabsorbed at PCT via  $\text{Na}^+$  channels. Thiazides, NSAIDs, and other drugs affecting clearance are implicated in lithium toxicity.

**LiTHIUM:**

Low Thyroid (hypothyroidism)

Heart (Ebstein anomaly)

Insipidus (nephrogenic diabetes insipidus)

Unwanted Movements (tremor)

**Buspirone**

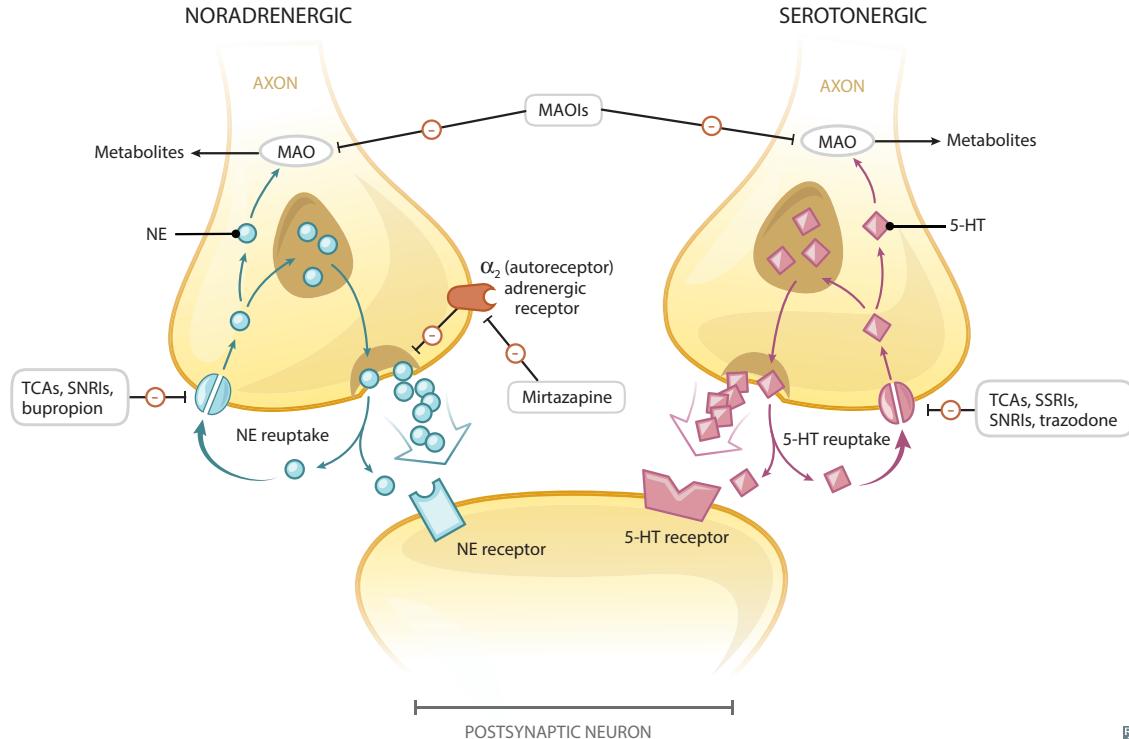
## MECHANISM

Partial 5-HT<sub>1A</sub> receptor agonist.

## CLINICAL USE

Generalized anxiety disorder. Does not cause sedation, addiction, or tolerance. Begins to take effect after 1–2 weeks. Does not interact with alcohol (vs barbiturates, benzodiazepines).

I get anxious if the bus doesn't arrive at one, so I take buspirone.

**Antidepressants**

**Selective serotonin****reuptake inhibitors**

Fluoxetine, fluvoxamine, paroxetine, sertraline, escitalopram, citalopram.

MECHANISM	Inhibit 5-HT reuptake.	It normally takes 4–8 weeks for antidepressants to show appreciable effect.
CLINICAL USE	Depression, generalized anxiety disorder, panic disorder, OCD, bulimia, binge-eating disorder, social anxiety disorder, PTSD, premature ejaculation, premenstrual dysphoric disorder.	
ADVERSE EFFECTS	Fewer than TCAs. Serotonin syndrome, GI distress, SIADH, sexual dysfunction (anorgasmia, ↓ libido), mania precipitation if underlying bipolar disorder.	

**Serotonin-****norepinephrine****reuptake inhibitors**

Venlafaxine, desvenlafaxine, duloxetine, levomilnacipran, milnacipran.

MECHANISM	Inhibit 5-HT and NE reuptake.	Depression, generalized anxiety disorder, diabetic neuropathy. Venlafaxine is also indicated for social anxiety disorder, panic disorder, PTSD, OCD. Duloxetine and milnacipran are also indicated for fibromyalgia.
CLINICAL USE		
ADVERSE EFFECTS	↑ BP, stimulant effects, sedation, nausea.	

**Tricyclic****antidepressants**

Amitriptyline, nortriptyline, imipramine, desipramine, clomipramine, doxepin, amoxapine.

MECHANISM	TCAs inhibit 5-HT and NE reuptake.	Sedation, $\alpha_1$ -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. <b>Tri-CyClic's:</b> Convulsions, Coma, Cardiotoxicity (arrhythmia due to $\text{Na}^+$ channel inhibition); also respiratory depression, hyperpyrexia. Confusion and hallucinations are more common in the elderly due to anticholinergic side effects (2° amines [eg, nortriptyline] better tolerated). Treatment: $\text{NaHCO}_3$ to prevent arrhythmia.
CLINICAL USE	MDD, peripheral neuropathy, chronic neuropathic pain, migraine prophylaxis, OCD (clomipramine), nocturnal enuresis (imipramine).	
ADVERSE EFFECTS	Sedation, $\alpha_1$ -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. <b>Tri-CyClic's:</b> Convulsions, Coma, Cardiotoxicity (arrhythmia due to $\text{Na}^+$ channel inhibition); also respiratory depression, hyperpyrexia. Confusion and hallucinations are more common in the elderly due to anticholinergic side effects (2° amines [eg, nortriptyline] better tolerated). Treatment: $\text{NaHCO}_3$ 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).	Atypical depression, anxiety. Parkinson disease (selegiline). CNS stimulation; hypertensive crisis, most notably with ingestion of tyramine. Contraindicated with SSRIs, TCAs, St. John's wort, meperidine, dextromethorphan, pseudoephedrine, linezolid (to avoid precipitating serotonin syndrome). Wait 2 weeks after stopping MAOIs before starting serotonergic drugs or stopping dietary restrictions.
CLINICAL USE	Atypical depression, anxiety. Parkinson disease (selegiline).	
ADVERSE EFFECTS	CNS stimulation; hypertensive crisis, most notably with ingestion of tyramine. Contraindicated with SSRIs, TCAs, St. John's wort, meperidine, dextromethorphan, pseudoephedrine, linezolid (to avoid precipitating serotonin syndrome). Wait 2 weeks after stopping MAOIs before starting serotonergic drugs or stopping dietary restrictions.	

**Atypical antidepressants**

<b>Bupropion</b>	Inhibits NE and DA reuptake. Also used for smoking cessation. Toxicity: stimulant effects (tachycardia, insomnia), headache, seizures in patients with bulimia and anorexia nervosa. ↓ risk of sexual side effects and weight gain compared to other antidepressants.
<b>Mirtazapine</b>	$\alpha_2$ -antagonist (↑ release of NE and 5-HT), potent 5-HT <sub>2</sub> and 5-HT <sub>3</sub> receptor antagonist, and H <sub>1</sub> antagonist. Toxicity: sedation (which may be desirable in depressed patients with insomnia), ↑ appetite, weight gain (which may be desirable in underweight patients), dry mouth.
<b>Trazodone</b>	Primarily blocks 5-HT <sub>2</sub> , $\alpha_1$ -adrenergic, and H <sub>1</sub> receptors; also weakly inhibits 5-HT reuptake. Used primarily for insomnia, as high doses are needed for antidepressant effects. Toxicity: sedation, nausea, priapism, postural hypotension. Think traZZZobone due to sedative and male-specific side effects.
<b>Varenicline</b>	Nicotinic ACh receptor partial agonist. Used for smoking cessation. Toxicity: sleep disturbance. Varenicline helps nicotine cravings decline.
<b>Vilazodone</b>	Inhibits 5-HT reuptake; 5-HT <sub>1A</sub> receptor partial agonist. Used for MDD. Toxicity: headache, diarrhea, nausea, anticholinergic effects. May cause serotonin syndrome if taken with other serotonergic agents.
<b>Vortioxetine</b>	Inhibits 5-HT reuptake; 5-HT <sub>1A</sub> receptor agonist and 5-HT <sub>3</sub> receptor antagonist. Used for MDD. Toxicity: nausea, sexual dysfunction, sleep disturbances, anticholinergic effects. May cause serotonin syndrome if taken with other serotonergic agents.

**Opioid detoxification and relapse prevention**

<b>Methadone</b>	Long-acting oral opiate used for heroin detoxification or long-term maintenance therapy.
<b>Buprenorphine</b>	Sublingual form (partial agonist) used to prevent relapse. Can precipitate withdrawal symptoms when combined with full agonist.
<b>Naloxone</b>	Short-acting opioid antagonist given IM, IV, or as a nasal spray to treat acute opioid overdose, particularly to reverse respiratory and CNS depression.
<b>Naltrexone</b>	Long-acting oral opioid antagonist used after detoxification to prevent relapse. May help alcohol and nicotine cessation, weight loss. Use naltrexone for the long trex back to sobriety.

# 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

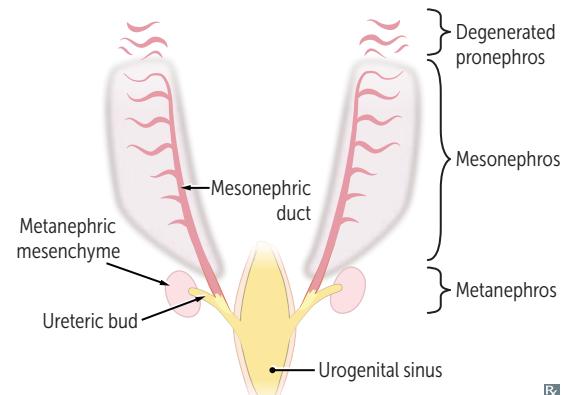
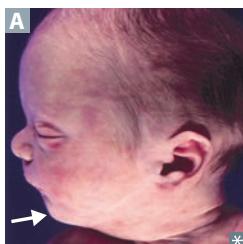
► Embryology	602
► Anatomy	604
► Physiology	605
► Pathology	618
► Pharmacology	630

Being able to understand and apply renal physiology will be critical for the exam. Important topics include electrolyte disorders, acid-base derangements, glomerular disorders (including histopathology), acute and chronic kidney disease, urine casts, diuretics, ACE inhibitors, and AT II receptor blockers. Renal anomalies associated with various congenital defects are also high-yield associations to think about when evaluating pediatric vignettes.

## ► RENAL—EMBRYOLOGY

**Kidney embryology**

- Pronephros—week 3 of development; then degenerates.
- Mesonephros—week 4 of development; functions as interim kidney for 1st trimester; persists in the male genital system as Wolffian duct, forming ductus deferens and epididymis.
- Metanephros—permanent; first appears in week 5 of development; nephrogenesis is normally completed by week 36 of gestation.
- Ureteric bud (metanephric diverticulum)—derived from caudal end of mesonephric duct; gives rise to ureter, pelvises, calyces, collecting ducts; fully canalized by week 10 of development
  - Metanephric mesenchyme (ie, metanephric blastema)—ureteric bud interacts with this tissue; interaction induces differentiation and formation of glomerulus through to distal convoluted tubule (DCT)
  - Aberrant interaction between these 2 tissues may result in several congenital malformations of the kidney (eg, renal agenesis, multicystic dysplastic kidney)
- Ureteropelvic junction—last to canalize  
→ congenital obstruction. Can be unilateral or bilateral. Most common pathologic cause of prenatal hydronephrosis. Detected by prenatal ultrasound.

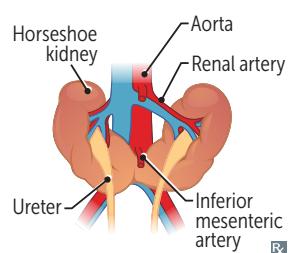
**Potter sequence**

- 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).  
Caused by chronic placental insufficiency or reduced renal output, including ARPKD, obstructive uropathy (eg, posterior urethral valves), bilateral renal agenesis.

Babies who can't "Pee" in utero develop Potter sequence.

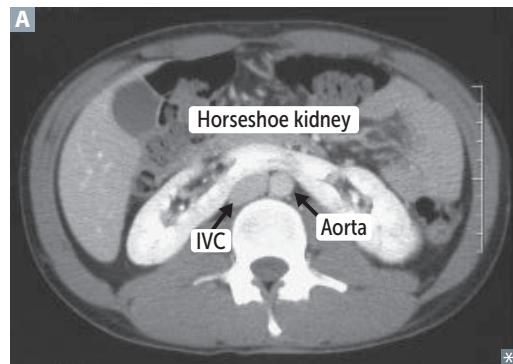
**POTTER** sequence associated with:

- Pulmonary hypoplasia
- Oligohydramnios (trigger)
- Twisted face
- Twisted skin
- Extremity defects
- Renal failure (in utero)

**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 can function normally, but associated with hydronephrosis (eg, ureteropelvic junction obstruction), renal stones, infection, ↑ risk of renal cancer.

Higher incidence in chromosomal aneuploidy (eg, Turner syndrome, trisomies 13, 18, 21).

**Congenital solitary functioning kidney**

Condition of being born with only one functioning kidney. Majority asymptomatic with compensatory hypertrophy of contralateral kidney, but anomalies in contralateral kidney are common. Often diagnosed prenatally via ultrasound.

**Unilateral renal agenesis**

Ureteric bud fails to develop and induce differentiation of metanephric mesenchyme → complete absence of kidney and ureter.

**Multicystic dysplastic kidney**

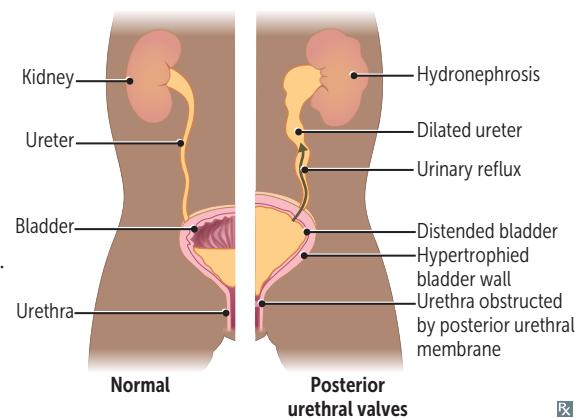
Ureteric bud develops, but fails to induce differentiation of metanephric mesenchyme → nonfunctional kidney consisting of cysts and connective tissue. Predominantly nonhereditary and usually unilateral; bilateral leads to Potter sequence.

**Duplex collecting system**

Bifurcation of ureteric bud before it enters the metanephric blastema creates a Y-shaped bifid ureter. Duplex collecting system can alternatively occur through two ureteric buds reaching and interacting with metanephric blastema. Strongly associated with vesicoureteral reflux and/or ureteral obstruction, ↑ risk for UTIs. Frequently presents with hydronephrosis.

**Posterior urethral valves**

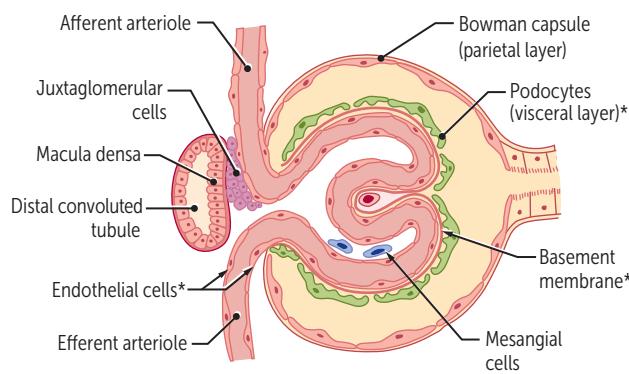
Membrane remnant in the posterior (prostatic) urethra in males; its persistence can lead to urethral obstruction. Can be diagnosed prenatally by bilateral hydronephrosis and dilated or thick-walled bladder on ultrasound. Most common cause of bladder outlet obstruction in male infants. Associated with oligohydramnios in cases of severe obstruction.

**Vesicoureteral reflux**

Retrograde flow of urine from bladder toward upper urinary tract. Can be 1° due to abnormal/insufficient insertion of the ureter within the vesicular wall (ureterovesical junction [UVJ]) or 2° due to abnormally high bladder pressure resulting in retrograde flow via the UVJ. ↑ risk of recurrent UTIs.

## ► RENAL—ANATOMY

## Kidney anatomy and glomerular structure



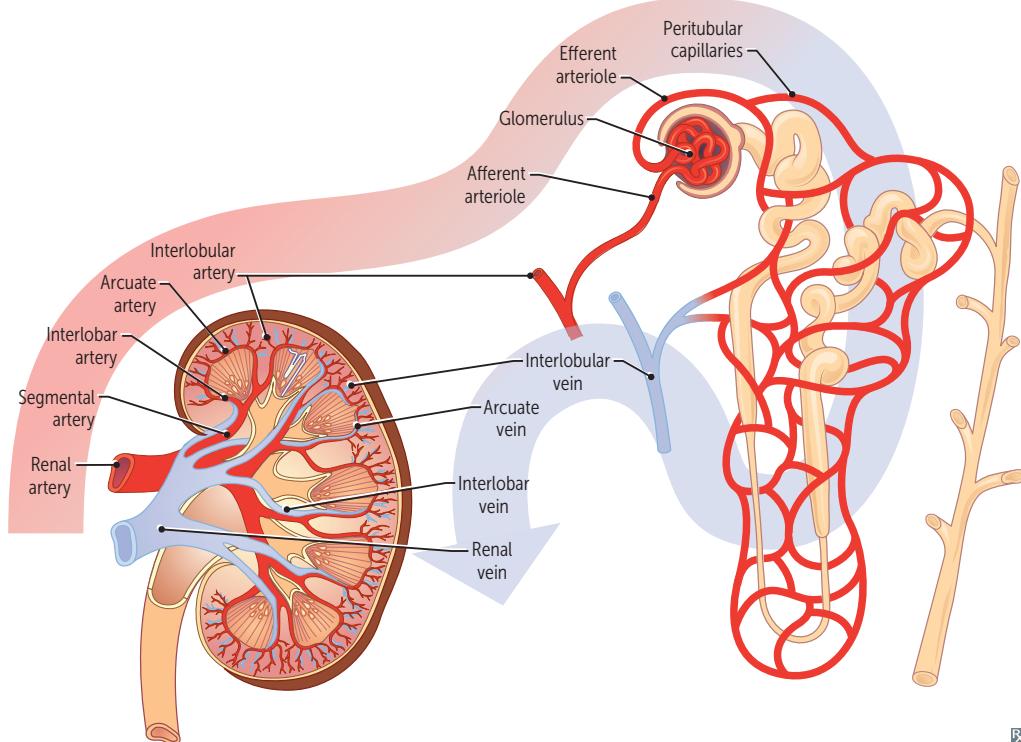
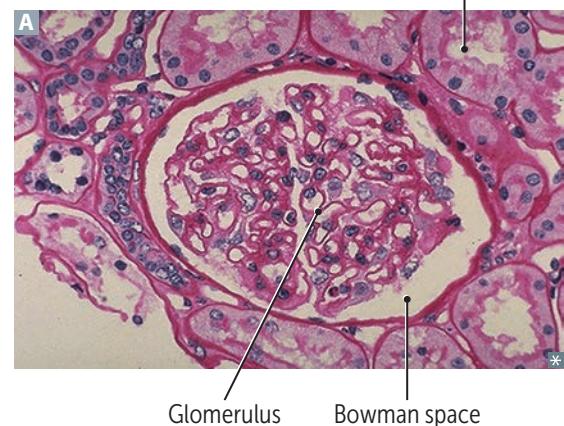
Cross-section of glomerulus A

Left renal vein receives two additional veins: left suprarenal and left gonadal veins.

Despite high overall renal blood flow, renal medulla receives significantly less blood flow than renal cortex → very sensitive to hypoxia → vulnerable to ischemic damage.

Left kidney is taken during living donor transplantation because it has a longer renal vein.

Distal convoluted tubule



Rx

**Course of ureters**

Course of ureter **A**: arises from renal pelvis, travels under gonadal arteries → **over** common iliac artery → **under** uterine artery/vas deferens (retroperitoneal).

Gynecologic procedures (eg, ligation of uterine or ovarian vessels) may damage ureter → ureteral obstruction or leak.

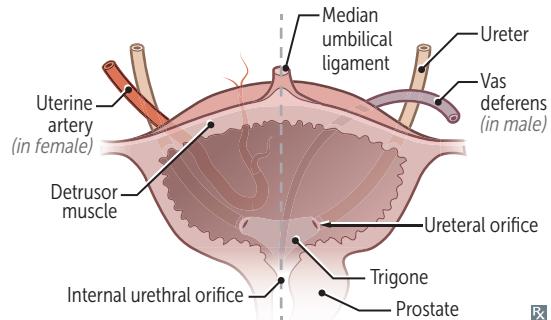
Bladder contraction compresses the intramural ureter, preventing urine reflux.

Blood supply to ureter:

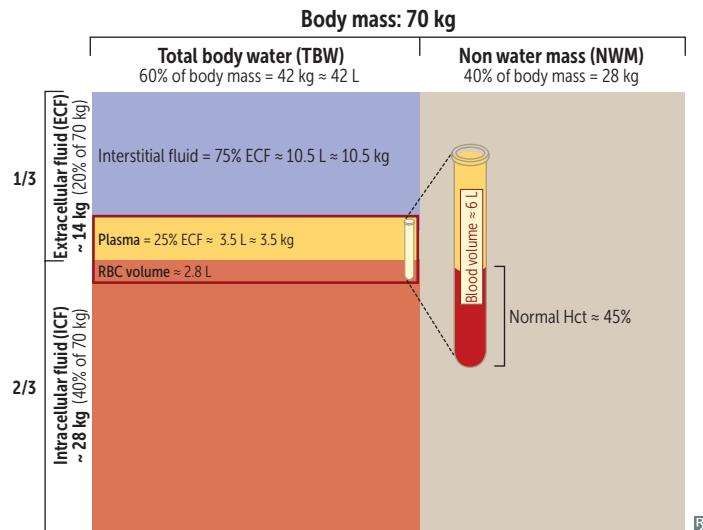
- Proximal—renal arteries
- Middle—gonadal artery, aorta, common and internal iliac arteries
- Distal—internal iliac and superior vesical arteries

3 common points of ureteral obstruction:  
ureteropelvic junction, pelvic inlet,  
ureterovesical junction.

Water (ureters) flows **over** the iliacs and **under** the bridge (uterine artery or vas deferens).



## ▶ RENAL—PHYSIOLOGY

**Fluid compartments**

**HIKIN:** HIgh K<sup>+</sup> INtracellularly.

60–40–20 rule (% of body weight for average person):

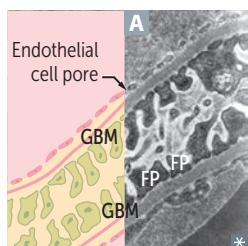
- 60% total body water
- 40% ICF, mainly composed of K<sup>+</sup>, Mg<sup>2+</sup>, organic phosphates (eg, ATP)
- 20% ECF, mainly composed of Na<sup>+</sup>, Cl<sup>-</sup>, HCO<sub>3</sub><sup>-</sup>, albumin

Plasma volume can be measured by radiolabeling albumin.

Extracellular volume can be measured by inulin or mannitol.

Serum osmolality = 275–295 mOsm/kg H<sub>2</sub>O.

Plasma volume = TBV × (1 – Hct).

**Glomerular filtration barrier**

Responsible for filtration of plasma according to size and charge selectivity.

Composed of:

- Fenestrated capillary endothelium
- Basement membrane with type IV collagen chains and heparan sulfate
- Visceral epithelial layer consisting of podocyte foot processes (FPs) **A**

Charger barrier—glomerular filtration barrier contains  $\ominus$  charged glycoproteins that prevent entry of  $\ominus$  charged molecules (eg, albumin).

Size barrier—fenestrated capillary endothelium (prevents entry of > 100 nm molecules/blood cells); podocyte foot processes interpose with glomerular basement membrane (GBM); slit diaphragm (prevents entry of molecules > 4–5 nm).

**Renal clearance**

$C_x = (U_x V)/P_x$  = volume of plasma from which the substance is completely cleared in the urine per unit time.

If  $C_x < \text{GFR}$ : net tubular reabsorption and/or not freely filtered.

If  $C_x > \text{GFR}$ : net tubular secretion of X.

If  $C_x = \text{GFR}$ : 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**

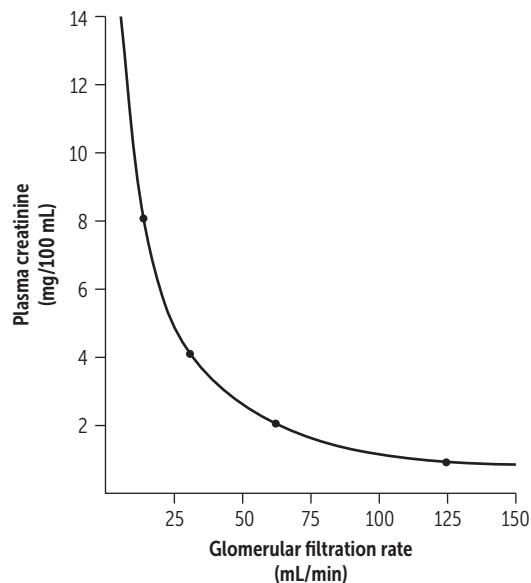
Inulin clearance can be used to calculate GFR because it is freely filtered and is neither reabsorbed nor secreted.

$$C_{\text{inulin}} = \text{GFR} = U_{\text{inulin}} \times V/P_{\text{inulin}} \\ = K_f [(P_{\text{GC}} - P_{\text{BS}}) - (\pi_{\text{GC}} - \pi_{\text{BS}})]$$

(GC = glomerular capillary; BS = Bowman space;  $\pi_{\text{BS}}$  normally equals zero;  $K_f$  = filtration coefficient).

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.

**Effective renal plasma flow**

Effective renal plasma flow (eRPF) can be estimated using *para*-aminohippuric acid (PAH) clearance. Between filtration and secretion, there is nearly 100% excretion of all PAH that enters the kidney.

$$\text{eRPF} = U_{\text{PAH}} \times V/P_{\text{PAH}} = C_{\text{PAH}}.$$

Renal blood flow (RB $F$ ) = RPF/(1 – Hct). Usually 20–25% of cardiac output, remaining constant due to autoregulation.

eRPF underestimates true renal plasma flow (RPF) slightly.

**Filtration**

Filtration fraction (FF) = GFR/RPF.

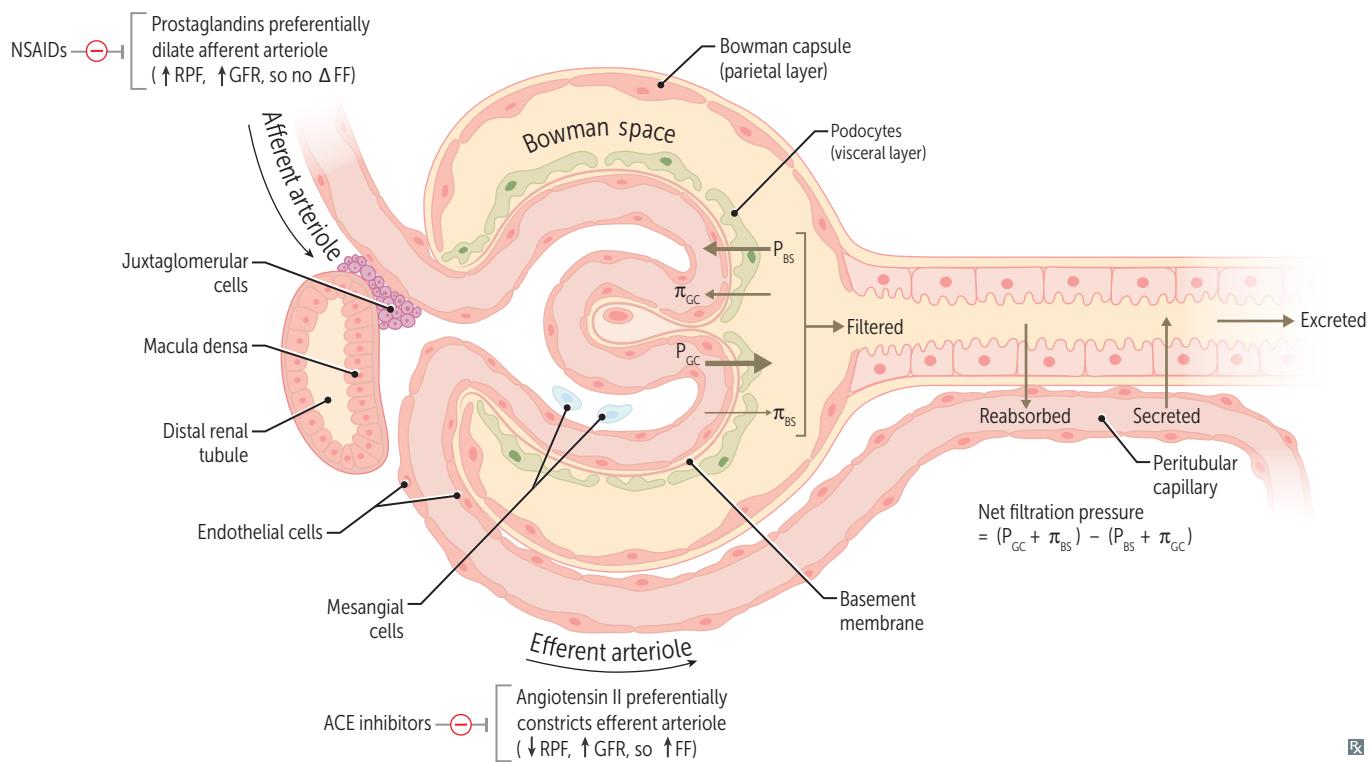
Normal FF = 20%.

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.

**Prostaglandins Dilate Afferent arteriole (PDA).**  
**Angiotensin II Constricts Efferent arteriole (ACE).**

**Changes in glomerular dynamics**

	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 =  $GFR \times P_x$ .

Excretion rate =  $V \times U_x$ .

Reabsorption rate = filtered – excreted.

Secretion rate = excreted – filtered.

$Fe_{Na}$  = fractional excretion of sodium.

$$Fe_{Na} = \frac{Na^+ \text{ excreted}}{Na^+ \text{ filtered}} = \frac{V \times U_{Na}}{GFR \times P_{Na}} = \frac{P_{Cr} \times U_{Na}}{U_{Cr} \times P_{Na}} \text{ where } GFR = \frac{U_{Cr} \times V}{P_{Cr}}$$

### Glucose clearance

Glucose at a normal plasma level (range 60–120 mg/dL) is completely reabsorbed in proximal convoluted tubule (PCT) by  $Na^+$ /glucose cotransport.

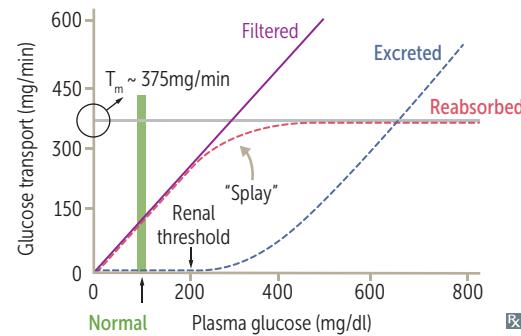
In adults, at plasma glucose of ~ 200 mg/dL, glucosuria begins (threshold). At rate of ~ 375 mg/min, all transporters are fully saturated ( $T_m$ ).

Normal pregnancy is associated with ↑ GFR. With ↑ filtration of all substances, including glucose, the glucose threshold occurs at lower plasma glucose concentrations → glucosuria at normal plasma glucose levels.

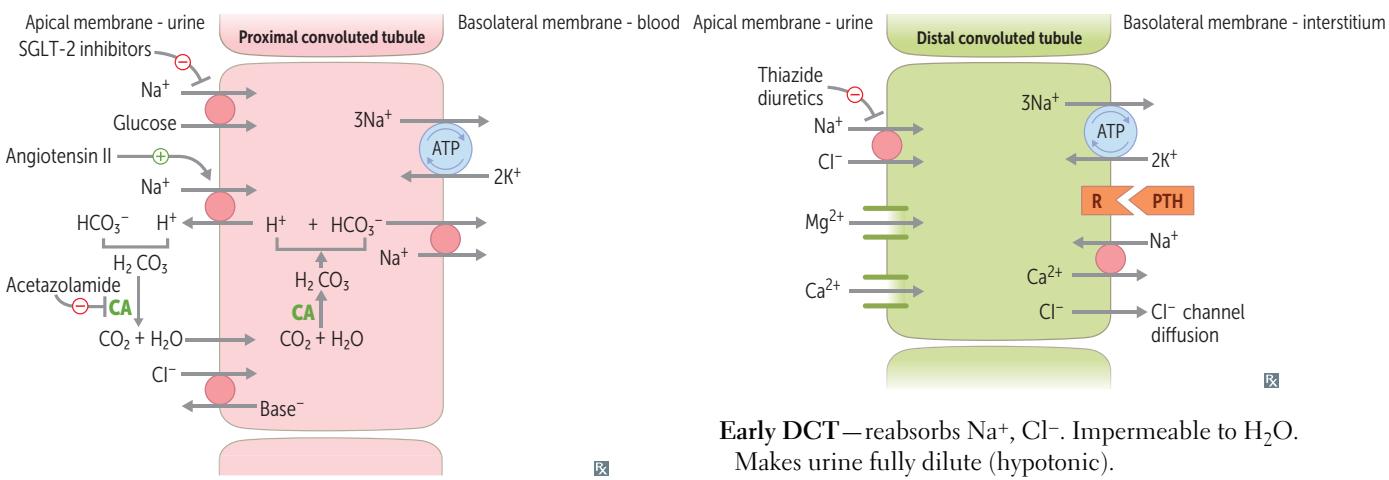
Sodium-glucose cotransporter 2 (SGLT2) inhibitors (eg, -floxin drugs) result in glucosuria at plasma concentrations < 200 mg/dL.

Glucosuria is an important clinical clue to diabetes mellitus.

Splay phenomenon— $T_m$  for glucose is reached gradually rather than sharply due to the heterogeneity of nephrons (ie, different  $T_m$  points); represented by the portion of the titration curve between threshold and  $T_m$ .



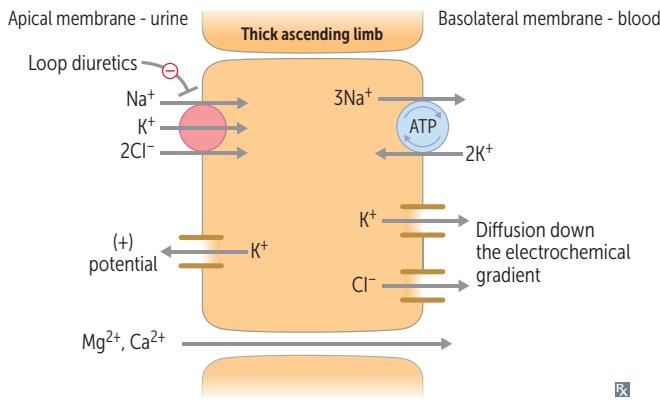
## Nephron transport physiology



**Early PCT**—contains brush border. Reabsorbs all glucose and amino acids and most HCO<sub>3</sub><sup>-</sup>, Na<sup>+</sup>, Cl<sup>-</sup>, PO<sub>4</sub><sup>3-</sup>, K<sup>+</sup>, H<sub>2</sub>O, and uric acid. Isotonic absorption. Generates and secretes NH<sub>3</sub>, which enables the kidney to secrete more H<sup>+</sup>.

PTH—inhibits Na<sup>+</sup>/PO<sub>4</sub><sup>3-</sup> cotransport → ↑ PO<sub>4</sub><sup>3-</sup> excretion. AT II—stimulates Na<sup>+</sup>/H<sup>+</sup> exchange → ↑ Na<sup>+</sup>, H<sub>2</sub>O, and HCO<sub>3</sub><sup>-</sup> reabsorption (permitting contraction alkalosis). 65–80% Na<sup>+</sup> and H<sub>2</sub>O reabsorbed.

**Thin descending loop of Henle**—passively reabsorbs H<sub>2</sub>O via medullary hypertonicity (impermeable to Na<sup>+</sup>). Concentrating segment. Makes urine hypertonic.



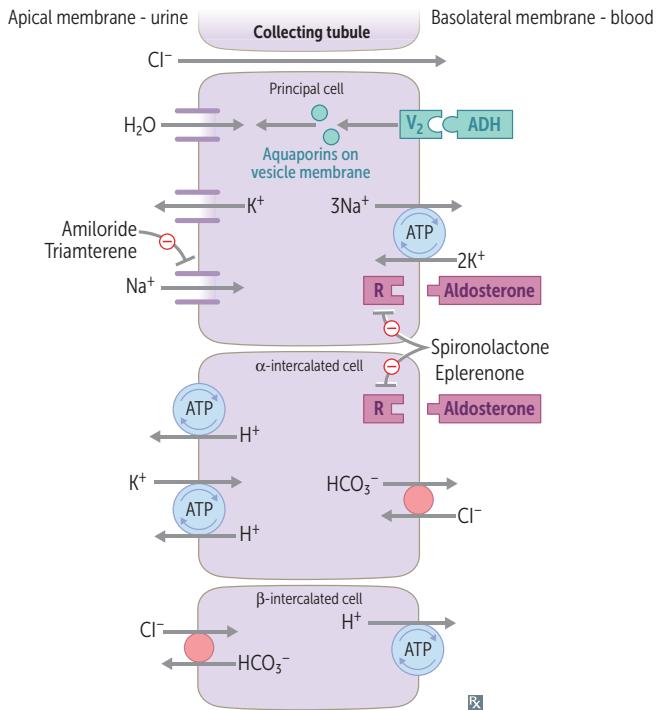
**Thick ascending loop of Henle**—reabsorbs Na<sup>+</sup>, K<sup>+</sup>, and Cl<sup>-</sup>. Indirectly induces paracellular reabsorption of Mg<sup>2+</sup> and Ca<sup>2+</sup> through + lumen potential generated by K<sup>+</sup> backleak. Impermeable to H<sub>2</sub>O. Makes urine less concentrated as it ascends. 10–20% Na<sup>+</sup> reabsorbed.

**Early DCT**—reabsorbs Na<sup>+</sup>, Cl<sup>-</sup>. Impermeable to H<sub>2</sub>O.

Makes urine fully dilute (hypotonic).

PTH—↑ Ca<sup>2+</sup>/Na<sup>+</sup> exchange → ↑ Ca<sup>2+</sup> reabsorption.

5–10% Na<sup>+</sup> reabsorbed.



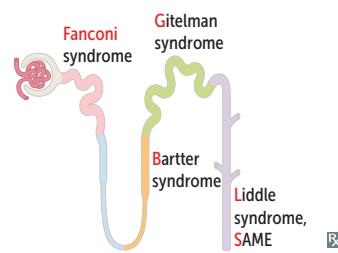
**Collecting tubule**—reabsorbs Na<sup>+</sup> in exchange for secreting K<sup>+</sup> and H<sup>+</sup> (regulated by aldosterone).

Aldosterone—acts on mineralocorticoid receptor → mRNA

→ protein synthesis. In principal cells: ↑ apical K<sup>+</sup> conductance, ↑ Na<sup>+</sup>/K<sup>+</sup> pump, ↑ epithelial Na<sup>+</sup> channel (ENaC) activity → lumen negativity → K<sup>+</sup> secretion. In α-intercalated cells: lumen negativity → ↑ H<sup>+</sup> ATPase activity → ↑ H<sup>+</sup> secretion → ↑ HCO<sub>3</sub><sup>-</sup>/Cl<sup>-</sup> exchanger activity.

ADH—acts at V<sub>2</sub> receptor → insertion of aquaporin H<sub>2</sub>O channels on apical side.

3–5% Na<sup>+</sup> reabsorbed.

**Renal tubular defects** Order: Fanconi's BaGeLS

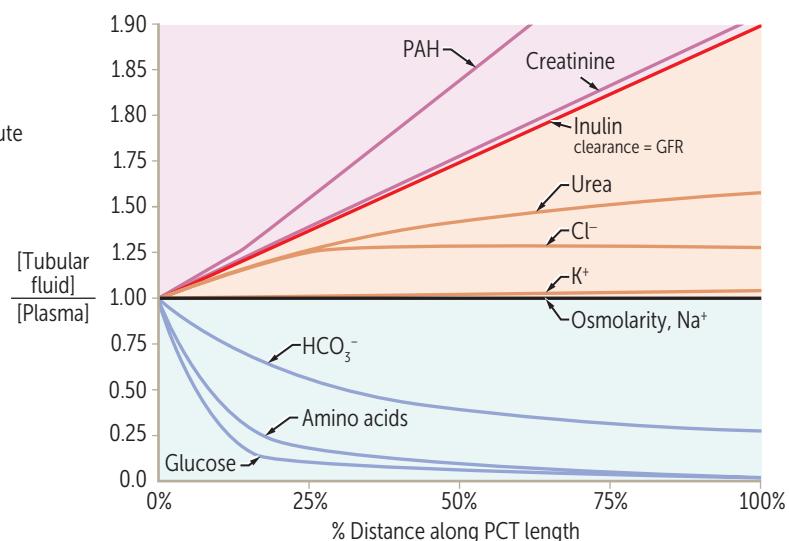
	DEFECTS	EFFECTS	CAUSES	NOTES
<b>Fanconi syndrome</b>	Generalized reabsorption defect in PCT → ↑ excretion of amino acids, glucose, $\text{HCO}_3^-$ , and $\text{PO}_4^{3-}$ , and all substances reabsorbed by the PCT	Metabolic acidosis (proximal RTA), hypophosphatemia, hypokalemia	Hereditary defects (eg, Wilson disease, tyrosinemia, glycogen storage disease), ischemia, multiple myeloma, nephrotoxins/drugs (eg, ifosfamide, cisplatin), lead poisoning	Growth retardation and rickets/osteopenia common due to hypophosphatemia Volume depletion also common
<b>Bartter syndrome</b>	Reabsorption defect in thick ascending loop of Henle (affects $\text{Na}^+/\text{K}^+/2\text{Cl}^-$ cotransporter)	Metabolic alkalosis, hypokalemia, hypercalciuria	Autosomal recessive	Presents similarly to chronic loop diuretic use
<b>Gitelman syndrome</b>	Reabsorption defect of NaCl in DCT	Metabolic alkalosis, hypomagnesemia, hypokalemia, hypocalciumuria	Autosomal recessive	Presents similarly to lifelong thiazide diuretic use Less severe than Bartter syndrome
<b>Liddle syndrome</b>	Gain of function mutation → ↓ $\text{Na}^+$ channel degradation → ↑ $\text{Na}^+$ reabsorption in collecting tubules	Metabolic alkalosis, hypokalemia, hypertension, ↓ aldosterone	Autosomal dominant	Presents similarly to hyperaldosteronism, but aldosterone is nearly undetectable Treatment: amiloride
<b>Syndrome of Apparent Mineralocorticoid Excess</b>	Cortisol activates mineralocorticoid receptors; $11\beta$ -HSD converts cortisol to cortisone (inactive on these receptors) Hereditary $11\beta$ -HSD deficiency → ↑ cortisol → ↑ mineralocorticoid receptor activity	Metabolic alkalosis, hypokalemia, hypertension ↓ serum aldosterone level; cortisol tries to be the <b>SAME</b> as aldosterone	Autosomal recessive Can acquire disorder from glycyrrhetic acid (present in licorice), which blocks activity of $11\beta$ -hydroxysteroid dehydrogenase	Treatment: $\text{K}^+$ -sparing diuretics (↓ mineralocorticoid effects) or corticosteroids (exogenous corticosteroid ↓ endogenous cortisol production → ↓ mineralocorticoid receptor activation)

### Relative concentrations along proximal convoluted tubules

$[TF/P] > 1$   
when solute is reabsorbed less quickly than water or when solute is secreted

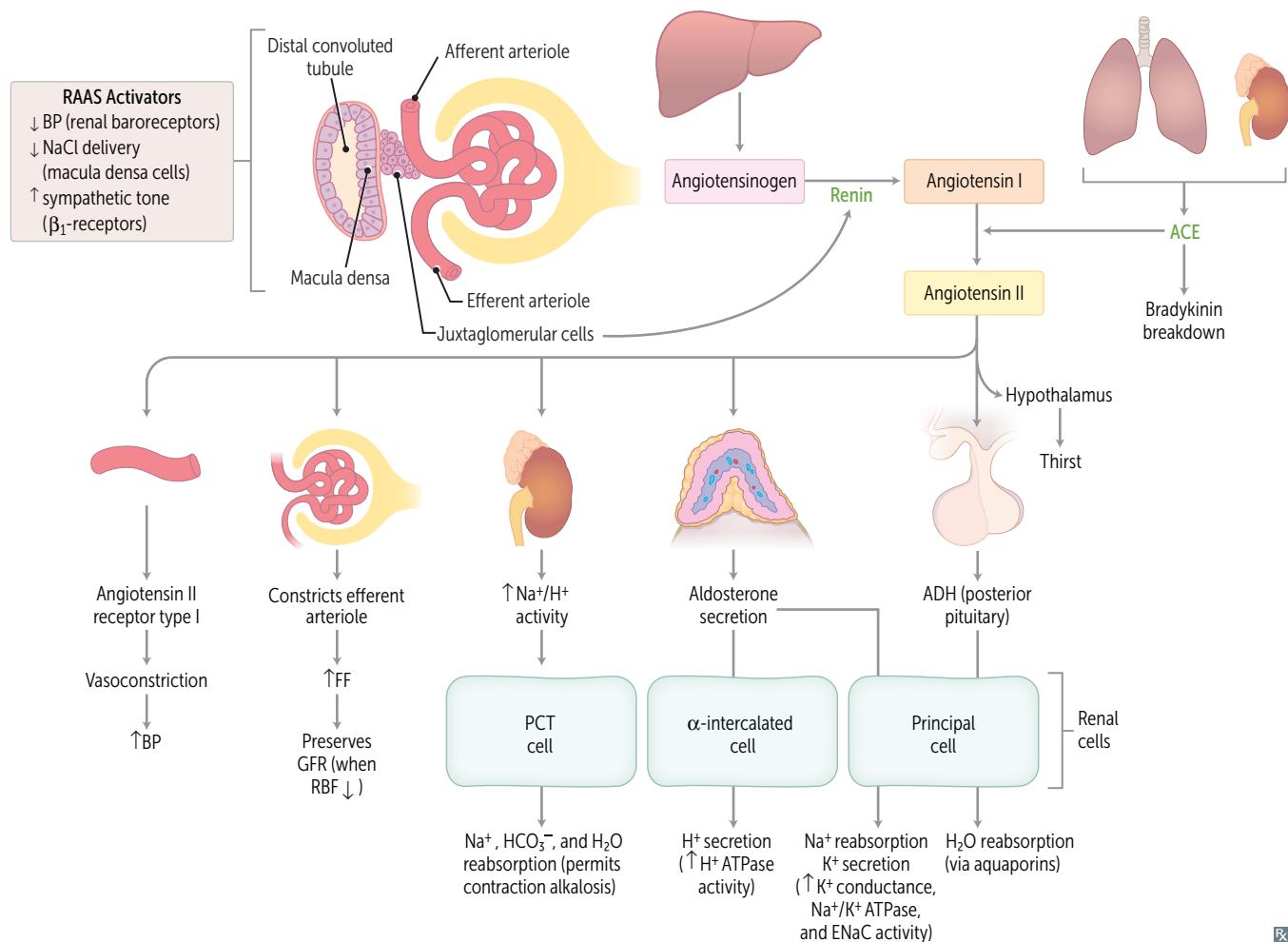
$[TF/P] = 1$   
when solute and water are reabsorbed at the same rate

$[TF/P] < 1$   
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<sup>-</sup> reabsorption occurs at a slower rate than Na<sup>+</sup> in early PCT and then matches the rate of Na<sup>+</sup> reabsorption more distally. Thus, its relative concentration ↑ before it plateaus.

### Renin-angiotensin-aldosterone system



#### Renin

Secreted by JG cells in response to ↓ renal perfusion pressure (detected by renal baroreceptors in afferent arteriole), ↑ renal sympathetic discharge ( $\beta_1$  effect), and ↓ NaCl delivery to macula densa cells.

#### ACE

Catalyzes conversion of angiotensin I to angiotensin II. Located in many tissues but conversion occurs most extensively in the lung. Produced by vascular endothelial cells in the lung.

#### AT II

Helps maintain blood volume and blood pressure. Affects baroreceptor function; limits reflex bradycardia, which would normally accompany its pressor effects.

#### ANP, BNP

Released from atria (ANP) and ventricles (BNP) in response to ↑ volume; inhibits renin-angiotensin-aldosterone system; relaxes vascular smooth muscle via cGMP → ↑ GFR, ↓ renin. Dilates afferent arteriole, promotes natriuresis.

#### ADH (vasopressin)

Primarily regulates serum osmolality; also responds to low blood volume states. Stimulates reabsorption of water in collecting ducts. Also stimulates reabsorption of urea in collecting ducts to maximize corticopapillary osmotic gradient.

#### Aldosterone

Primarily regulates ECF volume and  $\text{Na}^+$  content; ↑ release in hypovolemic states. Responds to hyperkalemia by ↑  $\text{K}^+$  excretion.

**Juxtaglomerular apparatus**

Consists of mesangial cells, JG cells (modified smooth muscle of afferent arteriole), and the macula densa (NaCl sensor located at the DCT). JG cells secrete renin in response to ↓ renal blood pressure and ↑ sympathetic tone ( $\beta_1$ ). Macula densa cells sense ↓ NaCl delivery to DCT → ↑ renin release → efferent arteriole vasoconstriction → ↑ GFR.

JGA maintains GFR via renin-angiotensin-aldosterone system.

In addition to vasodilatory properties,  $\beta$ -blockers can decrease BP by inhibiting  $\beta_1$ -receptors of the JGA → ↓ renin release.

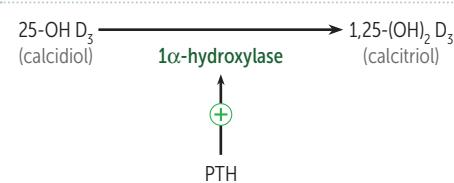
**Kidney hormone functions****Erythropoietin**

Released by interstitial cells in peritubular capillary bed in response to hypoxia.

Stimulates RBC proliferation in bone marrow. Administered for anemia secondary to chronic kidney disease. ↑ risk of HTN.

**Calciferol (vitamin D)**

PCT cells convert 25-OH vitamin D<sub>3</sub> to 1,25-(OH)<sub>2</sub> vitamin D<sub>3</sub> (calcitriol, active form). Increases calcium absorption in small bowel.

**Prostaglandins**

Paracrine secretion vasodilates afferent arterioles to ↑ RBF.

NSAIDs block renal-protective prostaglandin synthesis → constriction of afferent arteriole and ↓ GFR; this may result in acute kidney injury in low renal blood flow states.

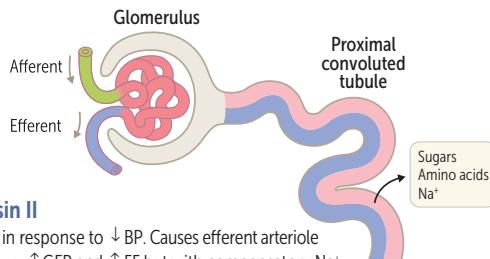
**Dopamine**

Secreted by PCT cells, promotes natriuresis. At low doses; dilates interlobular arteries, afferent arterioles, efferent arterioles → ↑ RBF, little or no change in GFR. At higher doses; acts as vasoconstrictor.

## Hormones acting on kidney

### Atrial natriuretic peptide

Secreted in response to ↑ atrial pressure. Causes ↑ GFR and ↑  $\text{Na}^+$  filtration with no compensatory  $\text{Na}^+$  reabsorption in distal nephron. Net effect:  $\text{Na}^+$  loss and volume loss.

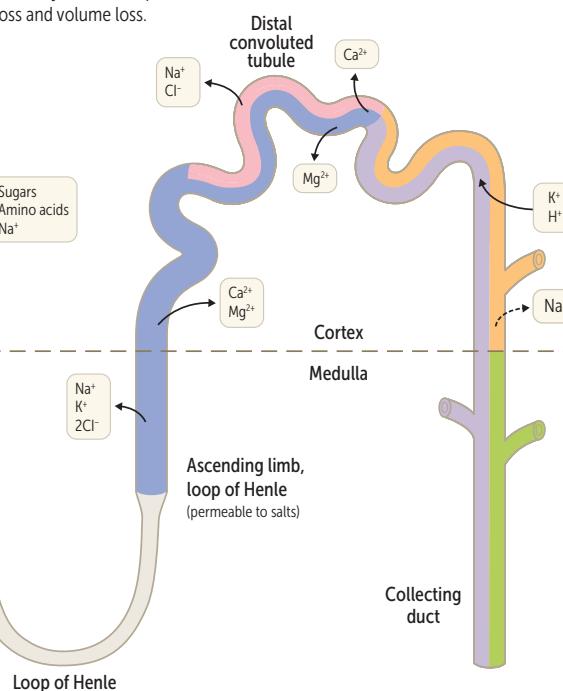


### Angiotensin II

Synthesized in response to ↓ BP. Causes efferent arteriole constriction → ↑ GFR and ↑ FF but with compensatory  $\text{Na}^+$  reabsorption in proximal and distal nephron. Net effect: preservation of renal function (↑ FF) in low-volume state with simultaneous  $\text{Na}^+$  reabsorption (both proximal and distal) to maintain circulating volume.

### Parathyroid hormone

Secreted in response to ↓ plasma  $[\text{Ca}^{2+}]$ , ↑ plasma  $[\text{PO}_4^{3-}]$ , or ↓ plasma  $1,25\text{-}(\text{OH})_2 \text{D}_3$ . Causes ↑  $[\text{Ca}^{2+}]$  reabsorption (DCT), ↓  $[\text{PO}_4^{3-}]$  reabsorption (PCT), and ↑  $1,25\text{-}(\text{OH})_2 \text{D}_3$  production (↑  $\text{Ca}^{2+}$  and  $\text{PO}_4^{3-}$  absorption from gut via vitamin D).



### Aldosterone

Secreted in response to ↓ blood volume (via AT II) and ↑ plasma  $[\text{K}^+]$ ; causes ↑  $\text{Na}^+$  reabsorption, ↑  $\text{K}^+$  secretion, ↑  $\text{H}^+$  secretion.

### ADH (vasopressin)

Secreted in response to ↑ plasma osmolarity and ↓ blood volume. Binds to receptors on principal cells, causing ↑ number of aquaporins and ↑  $\text{H}_2\text{O}$  reabsorption. ↑ reabsorption of urea in collecting ducts to maximize corticopapillary osmotic gradient.



## Potassium shifts

### SHIFTS $\text{K}^+$ INTO CELL (CAUSING HYPOKALEMIA)

Hypo-osmolarity

Alkalosis

$\beta$ -adrenergic agonist (↑  $\text{Na}^+/\text{K}^+$  ATPase)

Insulin (↑  $\text{Na}^+/\text{K}^+$  ATPase)

Insulin shifts  $\text{K}^+$  into cells

### SHIFTS $\text{K}^+$ OUT OF CELL (CAUSING HYPERKALEMIA)

Digoxin (blocks  $\text{Na}^+/\text{K}^+$  ATPase)

HyperOsmolarity

Lysis of cells (eg, crush injury, rhabdomyolysis, tumor lysis syndrome)

Acidosis

$\beta$ -blocker

High blood Sugar (insulin deficiency)

Succinylcholine (↑ risk in burns/muscle trauma)

Hyperkalemia? **DO LA $\beta$ SS**

**Electrolyte disturbances**

ELECTROLYTE	LOW SERUM CONCENTRATION	HIGH SERUM CONCENTRATION
<b>Sodium</b>	Nausea, malaise, stupor, coma, seizures	Irritability, stupor, coma
<b>Potassium</b>	U waves and flattened T waves on ECG, arrhythmias, muscle cramps, spasm, weakness	Wide QRS and peaked T waves on ECG, arrhythmias, muscle weakness
<b>Calcium</b>	Tetany, seizures, QT prolongation, twitching (eg, Chvostek sign), spasm (eg, Trousseau sign)	<b>Stones</b> (renal), <b>bones</b> (pain), <b>groans</b> (abdominal pain), <b>thrones</b> ( $\uparrow$ urinary frequency), <b>psychiatric overtones</b> (anxiety, altered mental status)
<b>Magnesium</b>	Tetany, torsades de pointes, hypokalemia, hypocalcemia (when $[Mg^{2+}] < 1.0 \text{ mEq/L}$ )	$\downarrow$ DTRs, lethargy, bradycardia, hypotension, cardiac arrest, hypocalcemia
<b>Phosphate</b>	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 $Ca^{2+}$
<b>SIADH</b>	$-/\uparrow$	$\downarrow$	$\downarrow$	—	—
<b>Primary hyperaldosteronism</b>	$\uparrow$	$\downarrow$	$\uparrow$	—	—
<b>Renin-secreting tumor</b>	$\uparrow$	$\uparrow$	$\uparrow$	—	—
<b>Bartter syndrome</b>	—	$\uparrow$	$\uparrow$	—	$\uparrow$
<b>Gitelman syndrome</b>	—	$\uparrow$	$\uparrow$	$\downarrow$	$\downarrow$
<b>Liddle syndrome, syndrome of apparent mineralocorticoid excess</b>	$\uparrow$	$\downarrow$	$\downarrow$	—	—

$\uparrow$   $\downarrow$  = important differentiating feature.

### Acid-base physiology

	pH	P <sub>CO<sub>2</sub></sub>	[HCO <sub>3</sub> <sup>-</sup> ]	COMPENSATORY RESPONSE
<b>Metabolic acidosis</b>	↓	↓	↓	Hyperventilation (immediate)
<b>Metabolic alkalosis</b>	↑	↑	↑	Hypoventilation (immediate)
<b>Respiratory acidosis</b>	↓	↑	↑	↑ renal [HCO <sub>3</sub> <sup>-</sup> ] reabsorption (delayed)
<b>Respiratory alkalosis</b>	↑	↓	↓	↓ renal [HCO <sub>3</sub> <sup>-</sup> ] reabsorption (delayed)

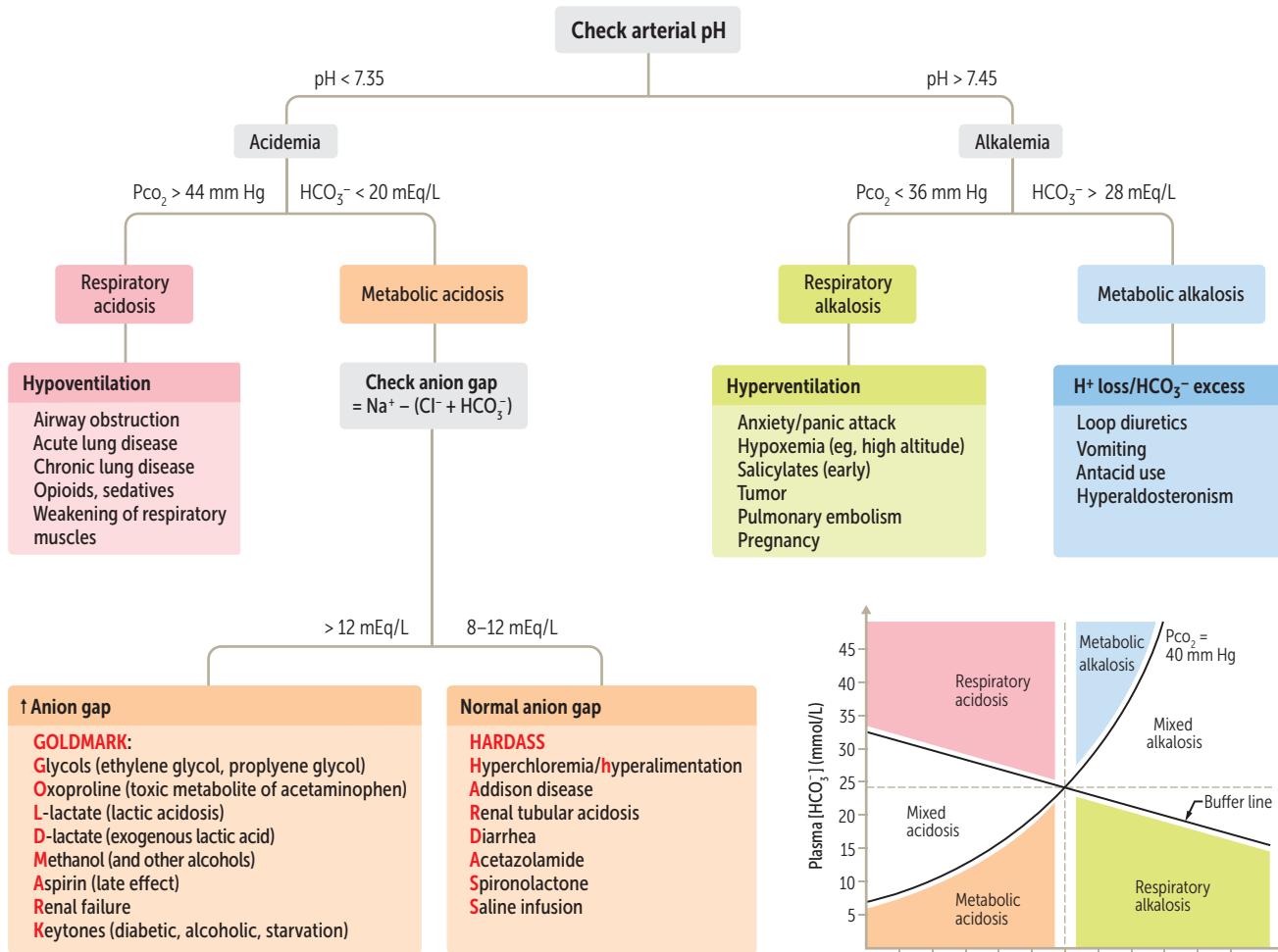
Key: ↓ ↑ = compensatory response.

$$\text{Henderson-Hasselbalch equation: } \text{pH} = 6.1 + \log \frac{[\text{HCO}_3^-]}{0.03 \text{ PCO}_2}$$

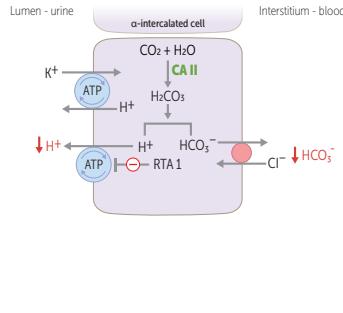
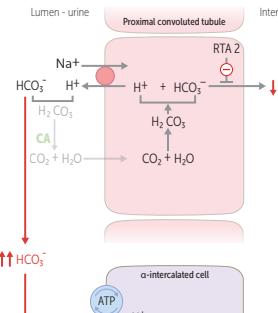
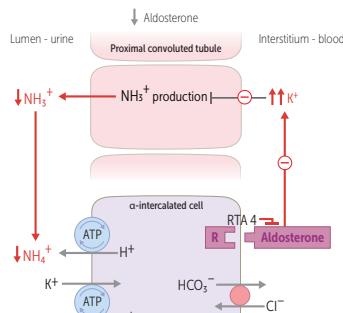
Predicted respiratory compensation for a simple metabolic acidosis can be calculated using the Winters formula. If measured P<sub>CO<sub>2</sub></sub> > predicted P<sub>CO<sub>2</sub></sub> → concomitant respiratory acidosis; if measured P<sub>CO<sub>2</sub></sub> < predicted P<sub>CO<sub>2</sub></sub> → concomitant respiratory alkalosis:

$$\text{PCO}_2 = 1.5 [\text{HCO}_3^-] + 8 \pm 2$$

### Acidosis and alkalosis



**Renal tubular acidosis**

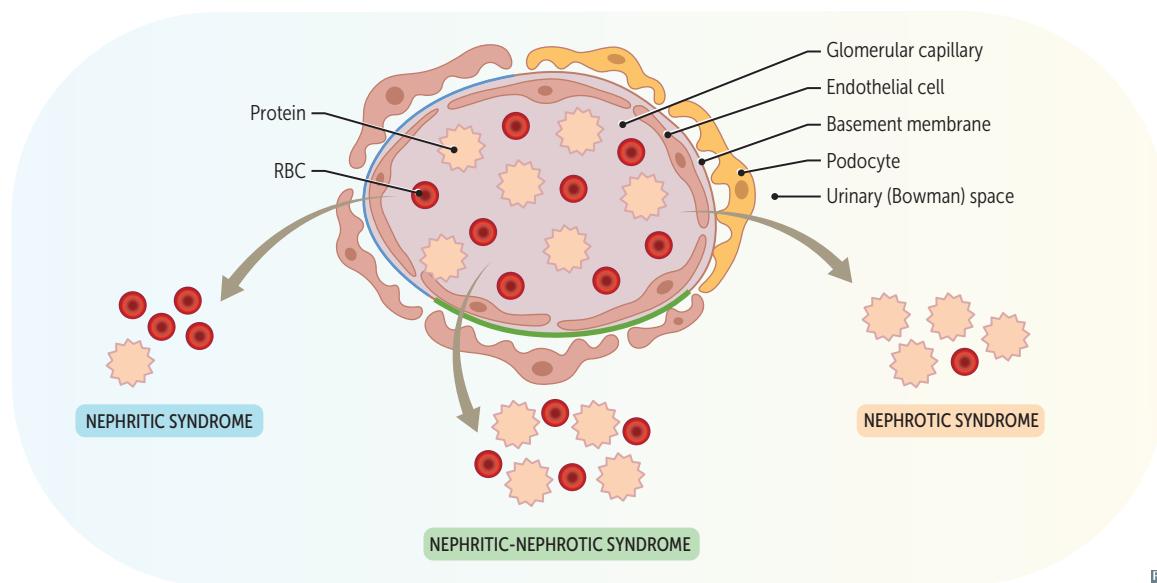
	<b>Distal renal tubular acidosis (RTA type 1)</b>	<b>Proximal renal tubular acidosis (RTA type 2)</b>	<b>Hyperkalemic tubular acidosis (RTA type 4)</b>
	Inability of $\alpha$ -intercalated cells to secrete $H^+$ $\rightarrow$ no new $HCO_3^-$ is generated $\rightarrow$ metabolic acidosis		
<b>DEFECT</b>	Inability of $\alpha$ -intercalated cells to secrete $H^+$ $\rightarrow$ no new $HCO_3^-$ is generated $\rightarrow$ metabolic acidosis	Defect in PCT $HCO_3^-$ reabsorption $\rightarrow$ $\uparrow$ excretion of $HCO_3^-$ in urine $\rightarrow$ metabolic acidosis Urine can be acidified by $\alpha$ -intercalated cells in collecting duct, but not enough to overcome $\uparrow HCO_3^-$ excretion	Hypoaldosteronism or aldosterone resistance; hyperkalemia $\rightarrow$ $\downarrow NH_3^+$ synthesis in PCT $\rightarrow$ $\downarrow NH_4^+$ excretion
<b>URINE pH</b>	$> 5.5$	$< 5.5$ when plasma $HCO_3^-$ below reduced resorption threshold $> 5.5$ when filtered $HCO_3^-$ exceeds resorptive threshold	$< 5.5$ (or variable)
<b>SERUM <math>K^+</math></b>	$\downarrow$	$\downarrow$	$\uparrow$
<b>CAUSES</b>	Amphotericin B toxicity, analgesic nephropathy, congenital anomalies (obstruction) of urinary tract, autoimmune diseases (eg, SLE)	Fanconi syndrome, multiple myeloma, carbonic anhydrase inhibitors	$\downarrow$ aldosterone production (eg, diabetic hyporeninism, ACE inhibitors, ARB, NSAIDs, heparin, cyclosporine, adrenal insufficiency) or aldosterone resistance (eg, $K^+$ -sparing diuretics, nephropathy due to obstruction, TMP-SMX)
<b>ASSOCIATIONS</b>	$\uparrow$ risk for calcium phosphate kidney stones (due to $\uparrow$ urine pH and $\uparrow$ bone turnover related to buffering)	$\uparrow$ risk for hypophosphatemic rickets (in Fanconi syndrome)	

## ▶ RENAL—PATHOLOGY

<b>Casts in urine</b>	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.
<b>RBC casts A</b>	Glomerulonephritis, hypertensive emergency.
<b>WBC casts B</b>	Tubulointerstitial inflammation, acute pyelonephritis, transplant rejection.
<b>Granular casts C</b>	Acute tubular necrosis (ATN). Can be “muddy brown” in appearance.
<b>Fatty casts (“oval fat bodies”)</b>	Nephrotic syndrome. Associated with “Maltese cross” sign D.
<b>Waxy casts</b>	End-stage renal disease/chronic kidney disease.
<b>Hyaline casts E</b>	Nonspecific, can be a normal finding with dehydration, exercise, or diuretic therapy. Form via solidification of Tamm-Horsfall mucoprotein (uromodulin), secreted by renal tubular cells to prevent UTIs.

**Nomenclature of glomerular disorders**

TYPE	CHARACTERISTICS	EXAMPLE
<b>Focal</b>	< 50% of glomeruli are involved	Focal segmental glomerulosclerosis
<b>Diffuse</b>	> 50% of glomeruli are involved	Diffuse proliferative glomerulonephritis
<b>Proliferative</b>	Hypercellular glomeruli	Membranoproliferative glomerulonephritis
<b>Membranous</b>	Thickening of glomerular basement membrane (GBM)	Membranous nephropathy
<b>Primary glomerular disease</b>	1° disease of the kidney specifically impacting the glomeruli	Minimal change disease
<b>Secondary glomerular disease</b>	Systemic disease or disease of another organ system that also impacts the glomeruli	SLE, diabetic nephropathy

**Glomerular diseases**

Rx

TYPE	ETIOLOGY	CLINICAL PRESENTATION	EXAMPLES
<b>Nephritic syndrome</b>	Glomerular inflammation → GBM damage → loss of RBCs into urine → dysmorphic RBCs, hematuria	Hematuria, RBC casts in urine ↓ GFR → oliguria, azotemia ↑ renin release, HTN Proteinuria often in the subnephrotic range (< 3.5 g/day) but in severe cases may be in nephrotic range	<ul style="list-style-type: none"> <li>Acute poststreptococcal glomerulonephritis</li> <li>Goodpasture syndrome</li> <li>IgA nephropathy (Berger disease)</li> <li>Alport syndrome</li> <li>Membranoproliferative glomerulonephritis</li> </ul>
<b>Nephrotic syndrome</b>	Podocyte damage → impaired charge barrier → proteinuria	Massive proteinuria (> 3.5 g/day) with hypoalbuminemia, edema  Frothy urine with fatty casts  Associated with hypercoagulable state due to antithrombin III loss in urine and ↑ risk of infection (loss of IgGs in urine and soft tissue compromise by edema)	<p>May be 1° (eg, direct podocyte damage) or 2° (podocyte damage from systemic process):</p> <ul style="list-style-type: none"> <li>Focal segmental glomerulosclerosis (1° or 2°)</li> <li>Minimal change disease (1° or 2°)</li> <li>Membranous nephropathy (1° or 2°)</li> <li>Amyloidosis (2°)</li> <li>Diabetic glomerulonephropathy (2°)</li> </ul>
<b>Nephritic-nephrotic syndrome</b>	Severe GBM damage → loss of RBCs into urine + impaired charge barrier → hematuria + proteinuria	Nephrotic-range proteinuria (> 3.5 g/day) and concomitant features of nephritic syndrome	Can occur with any form of nephritic syndrome, but is most common with: <ul style="list-style-type: none"> <li>Diffuse proliferative glomerulonephritis</li> <li>Membranoproliferative glomerulonephritis</li> </ul>

**Nephritic syndrome****Acute poststreptococcal glomerulonephritis**

Nephritic syndrome = inflammatory process.

Most frequently seen in children. ~ 2–4 weeks after group A streptococcal infection of pharynx or skin. Also called postinfectious glomerulonephritis when caused by non-streptococcal pathogens. Resolves spontaneously in most children; may progress to renal insufficiency in adults. Type III hypersensitivity reaction. Presents with peripheral and periorbital edema, tea or cola-colored urine, HTN. ↑ strep titers/serologies, ↓ complement levels (C3) due to consumption.

- LM—glomeruli enlarged and hypercellular **A**
- IF—(“starry sky”) granular appearance (“lumpy-bumpy”) **B** due to IgG, IgM, and C3 deposition along GBM and mesangium
- EM—subepithelial IC humps

**Rapidly progressive (crescentic) glomerulonephritis**

Poor prognosis, rapidly deteriorating renal function (days to weeks).

- LM—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 which may be delineated via IF pattern.

- Linear IF due to antibodies to GBM and alveolar basement membrane: **Goodpasture syndrome**—hematuria/hemoptysis; type II hypersensitivity reaction. Treatment: plasmapheresis
- Negative IF/Pauci-immune (no Ig/C3 deposition): **granulomatosis with polyangiitis** (formerly Churg-Strauss syndrome)—PR3-ANCA/c-ANCA, **eosinophilic granulomatosis with polyangiitis** or **Microscopic polyangiitis**—MPO-ANCA/p-ANCA
- Granular IF—PSGN or DPGN

**Diffuse proliferative glomerulonephritis**

Often due to SLE (think “wire lupus”). DPGN and MPGN often present as nephrotic syndrome and nephritic syndrome concurrently.

- LM—“wire looping” of capillaries **D**
- IF—granular; EM—subendothelial, sometimes subepithelial or intramembranous IgG-based ICs often with C3 deposition

**IgA nephropathy (Berger disease)**

Episodic hematuria that usually occurs concurrently with respiratory or GI tract infections (IgA is secreted by mucosal linings). Renal pathology of IgA vasculitis (HSP).

- LM—mesangial proliferation
- IF—IgA-based IC deposits in mesangium; EM—mesangial IC deposition

**Alport syndrome**

Mutation in type IV collagen → irregular thinning and thickening and splitting of glomerular basement membrane.

Most commonly X-linked dominant. Eye problems (eg, retinopathy, anterior lenticonus), glomerulonephritis, sensorineural deafness; “can’t see, can’t pee, can’t hear a bee.”

- EM—“basket-weave” appearance due to irregular thickening of GBM

**Membrano-proliferative glomerulonephritis**

MPGN is a nephritic syndrome that often co-presents with nephrotic syndrome.

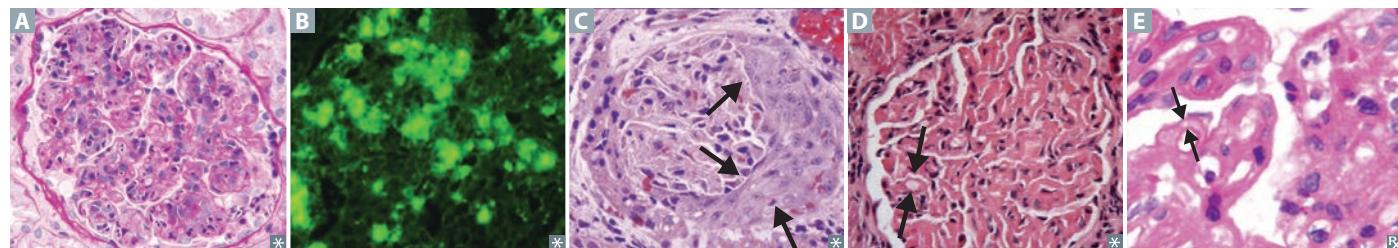
Type I may be 2° to hepatitis B or C infection. May also be idiopathic.

- Subendothelial IC deposits with granular IF

Type II is associated with C3 nephritic factor (IgG autoantibody that stabilizes C3 convertase → persistent complement activation → ↓ C3 levels).

- Intramembranous deposits, also called dense deposit disease

Both types: mesangial ingrowth → GBM splitting → “tram-track” on H&E and PAS **E** stains.



**Nephrotic syndrome**

Nephrotic syndrome—massive proteinuria ( $> 3.5 \text{ g/day}$ )

**Minimal change disease**

Also known as lipoid nephrosis. Most common cause of nephrotic syndrome in children.

Often 1° (idiopathic) and may be triggered by recent infection, immunization, immune stimulus (4 I's of MCD). Rarely, may be 2° to lymphoma (eg, cytokine-mediated damage).

1° disease has excellent response to corticosteroids.

- LM—Normal glomeruli (lipid may be seen in PCT cells)
- IF— $\ominus$
- EM—effacement of podocyte foot processes **A**

**Focal segmental glomerulosclerosis**

Higher prevalence in Black people.

Can be 1° (idiopathic) or 2° to other conditions (eg, HIV infection, sickle cell disease, heroin use, obesity, interferon treatment, or congenital malformations).

1° disease has inconsistent response to steroids. May progress to CKD.

- LM—segmental sclerosis and hyalinosis **B**
- IF—often  $\ominus$  but may be  $\oplus$  for nonspecific focal deposits of IgM, C3, C1
- EM—effacement of foot processes similar to minimal change disease

**Membranous nephropathy**

Also known as membranous glomerulonephritis.

Can be 1° (eg, antibodies to phospholipase A<sub>2</sub> receptor) or 2° to drugs (eg, NSAIDs, penicillamine, gold), infections (eg, HBV, HCV, syphilis), SLE, or solid tumors.

1° disease has poor response to steroids. May progress to CKD.

- LM—diffuse capillary and GBM thickening **C**
- IF—granular due to immune complex (IC) deposition
- EM—“Spike and dome” appearance of subepithelial deposits

**Amyloidosis**

Kidney is the most commonly involved organ (systemic amyloidosis). Associated with chronic conditions that predispose to amyloid deposition (eg, AL amyloid, AA amyloid, prolonged dialysis).

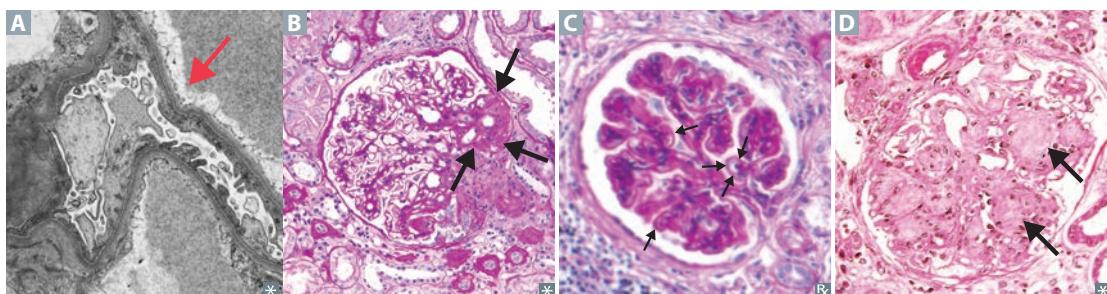
- LM—Congo red stain shows apple-green birefringence under polarized light due to amyloid deposition in the mesangium

**Diabetic glomerulonephropathy**

Most common cause of ESRD in the United States.

Hyperglycemia → nonenzymatic glycation of tissue proteins → mesangial expansion; GBM thickening and ↑ permeability. Hyperfiltration (glomerular HTN and ↑ GFR) → glomerular hypertrophy and glomerular scarring (glomerulosclerosis) → further progression of nephropathy.

- LM—Mesangial expansion, GBM thickening, eosinophilic nodular glomerulosclerosis (Kimmelstiel-Wilson lesions **D**)

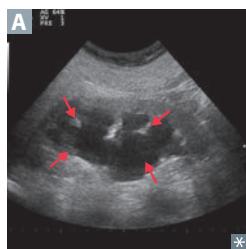


**Kidney stones**

Can lead to severe complications such as hydronephrosis, pyelonephritis, and acute kidney injury. Obstructed stone presents with unilateral flank tenderness, colicky pain radiating to groin, hematuria. Treat and prevent by encouraging fluid intake.

CONTENT	PRECIPITATES WITH	X-RAY FINDINGS	CT FINDINGS	URINE CRYSTAL	NOTES
<b>Calcium</b>	Calcium oxalate: hypocitraturia	Radiopaque	Radiopaque	Shaped like envelope <b>A</b> or dumbbell	Calcium stones most common (80%); calcium oxalate more common than calcium phosphate stones. Can result from ethylene glycol (antifreeze) ingestion, vitamin C overuse, hypocitraturia (associated with ↓ urine pH), malabsorption (eg, Crohn disease). Treatment: thiazides, citrate, low-sodium diet.
	Calcium phosphate: ↑ pH	Radiopaque	Radiopaque	Wedge-shaped prism	Treatment: low-sodium diet, thiazides.
<b>Ammonium magnesium phosphate (struvite)</b>	↑ pH	Radiopaque	Radiopaque	Coffin lid <b>B</b>	Account for 15% of stones. Caused by infection with urease $\oplus$ bugs (eg, <i>Proteus mirabilis</i> , <i>Staphylococcus saprophyticus</i> , <i>Klebsiella</i> ) that hydrolyze urea to ammonia → urine alkalinization. Commonly form staghorn calculi <b>C</b> . Treatment: eradication of underlying infection, surgical removal of stone.
<b>Uric acid</b>	↓ pH	Radiolucent	Visible	Rhomboid <b>D</b> or rosettes	About 5% of all stones. Risk factors: ↓ urine volume, arid climates, acidic pH. Strong association with hyperuricemia (eg, gout). Often seen in diseases with ↑ cell turnover (eg, leukemia). Treatment: alkalinization of urine, allopurinol.
<b>Cystine</b>	↓ pH	Faintly radiopaque	Moderately radiopaque	Hexagonal <b>E</b>	Hereditary (autosomal recessive) condition in which <b>Cystine</b> -reabsorbing PCT transporter loses function, causing cystinuria. Transporter defect also results in poor reabsorption of <b>Ornithine</b> , <b>Lysine</b> , <b>Arginine</b> ( <b>COLA</b> ). Cystine is poorly soluble, thus stones form in urine. Usually begins in childhood. Can form staghorn calculi. Sodium cyanide nitroprusside test $\oplus$ . “Sixtine” stones have <b>six</b> sides. Treatment: low sodium diet, alkalinization of urine, chelating agents (eg, tiopronin, penicillamine) if refractory.

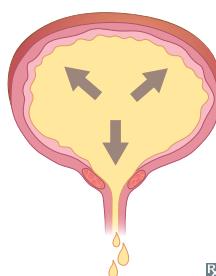


**Hydronephrosis**

Distention/dilation of renal pelvis and/or calyces **A**. Usually caused by urinary tract obstruction (eg, renal stones, severe BPH, congenital obstructions, cervical cancer, injury to ureter); other causes include retroperitoneal fibrosis, vesicoureteral reflux. Dilation occurs proximal to site of pathology. Serum creatinine becomes elevated if obstruction is bilateral or if patient has an obstructed solitary kidney. Leads to compression and possible atrophy of renal cortex and medulla.

**Urinary incontinence**

Mixed incontinence has features of both stress and urgency incontinence.

**Stress incontinence****Urgency incontinence****Overflow incontinence****MECHANISM**

Outlet incompetence (urethral hypermobility or intrinsic sphincter deficiency) → leak with ↑ intra-abdominal pressure (eg, sneezing, lifting)  
⊕ bladder stress test (directly observed leakage from urethra upon coughing or Valsalva maneuver)

Detrusor overactivity → leak with urge to void immediately

Incomplete emptying (detrusor underactivity or outlet obstruction) → leak with overfilling, ↑ postvoid residual on catheterization or ultrasound

**ASSOCIATIONS**

Obesity, pregnancy, vaginal delivery, prostate surgery

UTI

Polyuria (eg, diabetes), bladder outlet obstruction (eg, BPH), spinal cord injury (eg, MS)

**TREATMENT**

Pelvic floor muscle strengthening (Kegel) exercises, weight loss, pessaries

Kegel exercises, bladder training (timed voiding, distraction or relaxation techniques), antimuscarinics (eg, oxybutynin for overactive bladder), mirabegron

Catheterization, relieve obstruction (eg, α-blockers for BPH)

**Acute cystitis**

Inflammation of urinary bladder. Presents as suprapubic pain, dysuria, urinary frequency, urgency.

Systemic signs (eg, high fever, chills) are usually absent.

Risk factors include female sex (short urethra), sexual intercourse, indwelling catheter, diabetes mellitus, impaired bladder emptying.

Causes:

- *E. coli* (most common)
- *Staphylococcus saprophyticus*—seen in sexually active young women (*E. coli* is still more common in this group)
- *Klebsiella*
- *Proteus mirabilis*—urine has ammonia scent

Labs: + leukocyte esterase. + nitrites (indicates presence of Enterobacteriaceae). Sterile pyuria (pyuria with - urine cultures) could suggest urethritis by *Neisseria gonorrhoeae* or *Chlamydia trachomatis*.

Treatment: antibiotics (eg, TMP-SMX, nitrofurantoin).

**Pyelonephritis****Acute pyelonephritis**

Neutrophils infiltrate renal interstitium **A**. Affects cortex with relative sparing of glomeruli/vessels.

Presents with fevers, flank pain (costovertebral angle tenderness), nausea/vomiting, chills.

Causes include ascending UTI (*E. coli* is most common), hematogenous spread to kidney. Presents with WBCs in urine +/- WBC casts. CT would show striated parenchymal enhancement **B**.

Risk factors include indwelling urinary catheter, urinary tract obstruction, vesicoureteral reflux, diabetes mellitus, pregnancy.

Complications include chronic pyelonephritis, renal papillary necrosis, perinephric abscess, urosepsis.

Treatment: antibiotics.

**Chronic pyelonephritis**

The result of recurrent or inadequately treated episodes of acute pyelonephritis. Typically requires predisposition to infection such as vesicoureteral reflux or chronically obstructing kidney stones.

Coarse, asymmetric corticomedullary scarring, blunted calyces. Tubules can contain eosinophilic casts resembling thyroid tissue **C** (thyroidization of kidney).

**Xanthogranulomatous pyelonephritis**—rare; grossly orange nodules that can mimic tumor nodules; characterized by widespread kidney damage due to granulomatous tissue containing foamy macrophages. Associated with *Proteus* infection.



**Acute kidney injury**

	<b>Prerenal azotemia</b>	<b>Intrinsic renal failure</b>	<b>Postrenal azotemia</b>
<b>ETIOLOGY</b>	Hypovolemia ↓ cardiac output ↓ effective circulating volume (eg, HF, liver failure)	Tubules and interstitium: ■ Acute tubular necrosis (ischemia, nephrotoxins) ■ Acute interstitial nephritis  Glomerulus: ■ Acute glomerulonephritis  Vascular: ■ Vasculitis ■ Malignant hypertension ■ TTP-HUS	Stones BPH Neoplasm Congenital anomalies
<b>PATHOPHYSIOLOGY</b>	↓ RBF → ↓ GFR → ↑ reabsorption of Na <sup>+</sup> /H <sub>2</sub> O and urea	In ATN, patchy necrosis → debris obstructing tubules and fluid backflow → ↓ GFR	Outflow obstruction (bilateral)
<b>URINE OSMOLALITY (mOsm/kg)</b>	>500	<350	<350
<b>URINE Na<sup>+</sup> (mEq/L)</b>	<20	>40	Varies
<b>FE<sub>Na</sub></b>	<1%	>2%	Varies
<b>SERUM BUN/Cr</b>	>20	<15	Varies

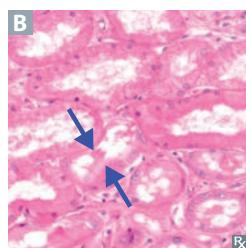
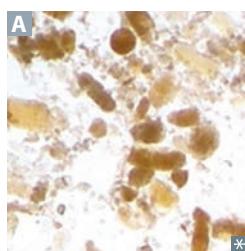
**Acute interstitial nephritis**

Also called tubulointerstitial nephritis. Acute interstitial renal inflammation. Pyuria (classically eosinophils) and azotemia occurring after administration of drugs that act as haptens, inducing hypersensitivity (eg, diuretics, NSAIDs, penicillin derivatives, proton pump inhibitors, rifampin, quinolones, sulfonamides). Less commonly may be 2° to other processes such as systemic infections (eg, *Mycoplasma*) or autoimmune diseases (eg, Sjögren syndrome, SLE, sarcoidosis).

Associated with fever, rash, pyuria, hematuria, and costovertebral angle tenderness, but can be asymptomatic.

Remember these **5 P'S**:

- Pee (diuretics)
- Pain-free (NSAIDs)
- Penicillins and cephalosporins
- Proton pump inhibitors
- RifamPin
- Sulfa drugs

**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. ↑ FE<sub>Na</sub>.

Key finding: granular casts (often muddy brown in appearance) **A**.

3 stages:

1. Inciting event
2. Maintenance phase—oliguric; lasts 1–3 weeks; risk of hyperkalemia, metabolic acidosis, uremia
3. Recovery phase—polyuric; BUN and serum creatinine fall; risk of hypokalemia and renal wasting of other electrolytes and minerals

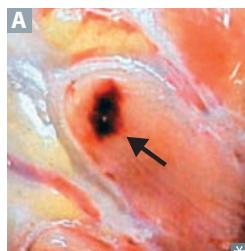
Can be caused by ischemic or nephrotoxic injury:

- 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, ethylene glycol), crush injury (myoglobinuria), hemoglobinuria. Proximal tubules are particularly susceptible to injury.

**Diffuse cortical necrosis**

Acute generalized cortical infarction of both kidneys. Likely due to a combination of vasospasm and DIC.

Associated with obstetric catastrophes (eg, abruptio placentae), septic shock.

**Renal papillary necrosis**

Sloughing of necrotic renal papillae **A** → gross hematuria. May be triggered by recent infection or immune stimulus.

Associated with:

- Sickle cell disease or trait
- Acute pyelonephritis
- Analgesics (eg, NSAIDs)
- Diabetes mellitus

**SAAD papa** with papillary necrosis.

**Consequences of renal failure**

Decline in renal filtration can lead to excess retained nitrogenous waste products and electrolyte disturbances.

Consequences (**MAD HUNGER**):

- **M**etabolic **A**cidosis
- **D**yslipidemia (especially ↑ triglycerides)
- **H**igh potassium
- **U**remia
- **N**a<sup>+</sup>/H<sub>2</sub>O retention (HF, pulmonary edema, hypertension)
- **G**rowth retardation and developmental delay
- **E**rythropoietin deficiency (anemia)
- **R**enal osteodystrophy

2 forms of renal failure: acute (eg, ATN) and chronic (eg, hypertension, diabetes mellitus, congenital anomalies).

Incremental reductions in GFR define the stages of chronic kidney disease.

Normal phosphate levels are maintained during early stages of CKD due to ↑ levels of fibroblast growth factor 23 (FGF23), which promotes renal excretion of phosphate.

**Uremia**—syndrome resulting from high serum urea. Can present with nausea, anorexia, encephalopathy (seen with asterixis), pericarditis, platelet dysfunction. Management: dialysis.

**Renal osteodystrophy**

Hypocalcemia, hyperphosphatemia, and failure of vitamin D hydroxylation associated with chronic kidney disease → 2° hyperparathyroidism → 3° hyperparathyroidism (if 2° poorly managed). High serum phosphate can bind with  $\text{Ca}^{2+}$  → tissue deposits → ↓ serum  $\text{Ca}^{2+}$ . ↓ 1,25-(OH)<sub>2</sub>D<sub>3</sub> → ↓ intestinal  $\text{Ca}^{2+}$  absorption. Causes subperiosteal thinning of bones.

**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 combinations of 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).

Complications include chronic kidney disease and hypertension (caused by ↑ renin production).

Associated with berry aneurysms, mitral valve prolapse, benign hepatic cysts, diverticulosis.

Treatment: If hypertension or proteinuria develops, treat with ACE inhibitors or ARBs.

**Autosomal recessive polycystic kidney disease**

Cystic dilation of collecting ducts **B**. Often presents in infancy. Associated with congenital hepatic fibrosis. Significant oliguric renal failure in utero can lead to Potter sequence. Concerns beyond neonatal period include systemic hypertension, progressive renal insufficiency, and portal hypertension from congenital hepatic fibrosis.

**Autosomal dominant tubulointerstitial kidney disease**

Also called medullary cystic kidney disease. Causes tubulointerstitial fibrosis and progressive renal insufficiency with inability to concentrate urine. Medullary cysts usually not visualized; smaller kidneys on ultrasound. Poor prognosis.

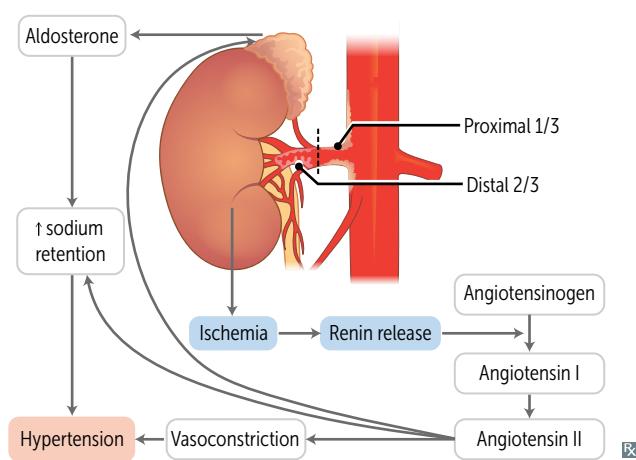
**Simple vs complex renal cysts**

Simple cysts are filled with ultrafiltrate (anechoic on ultrasound **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 possibility of renal cell carcinoma.



### Renovascular disease



Unilateral or bilateral renal artery stenosis (RAS) → ↓ renal perfusion → ↑ renin → ↑ angiotensin → HTN. Most common cause of 2° HTN in adults.

Main causes of RAS:

- Atherosclerotic plaques: proximal 1/3 of renal artery, usually in older males, smokers.
- Fibromuscular dysplasia: distal 2/3 of renal artery or segmental branches, usually young or middle-aged females

For unilateral RAS, affected kidney can atrophy → asymmetric kidney size. Renal venous sampling will show ↑ renin in affected kidney, ↓ renin in unaffected kidney.

For bilateral RAS, patients can have a sudden rise in creatinine after starting an ACE inhibitor, ARB, or renin inhibitor, due to their interference on RAAS-mediated renal perfusion.

Can present with severe/refractory HTN, flash pulmonary edema, epigastric/flank bruit. Patients with RAS may also have stenosis in other large vessels.

### Renal cell carcinoma

Polygonal clear cells **A** filled with accumulated lipids and carbohydrate. Often golden-yellow **B** due to ↑ lipid content.

Originates from PCT → invades renal vein (may develop varicocele if left sided) → IVC → hematogenous spread → metastasis to lung and bone.

Manifests with hematuria, palpable masses, 2° polycythemia, flank pain, fever, weight loss.

Treatment: surgery/ablation for localized disease. Immunotherapy (eg, ipilimumab) or targeted therapy for metastatic disease, rarely curative. Resistant to chemotherapy and radiation therapy.

Class triad: flank pain, palpable mass, hematuria.

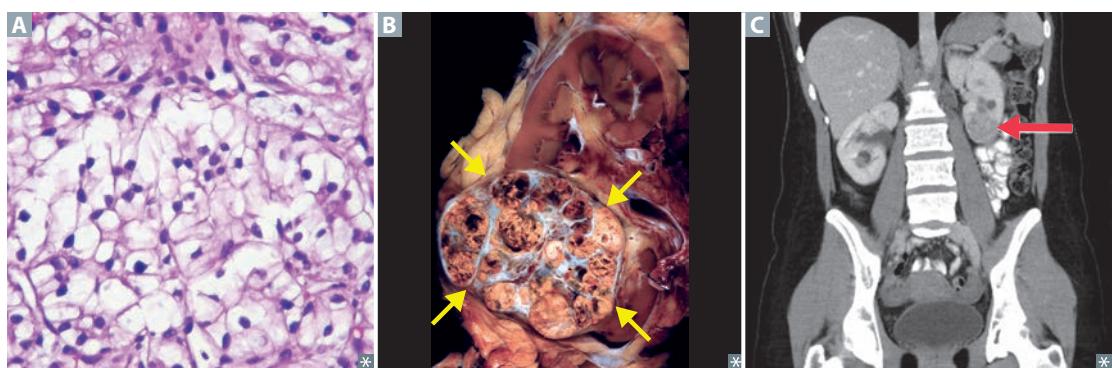
Most common 1° renal malignancy **C**.

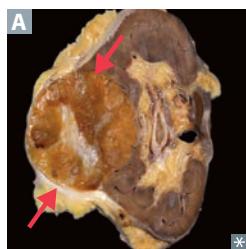
Most common in males 50–70 years old, ↑ incidence with tobacco smoking and obesity.

Associated with paraneoplastic syndromes, eg, PTHrP, Ectopic EPO, ACTH, Renin (“PEAR”-aneoplastic).

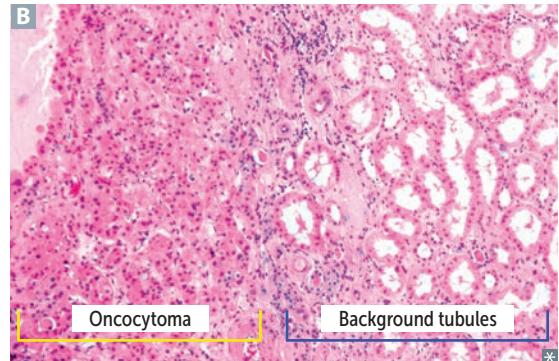
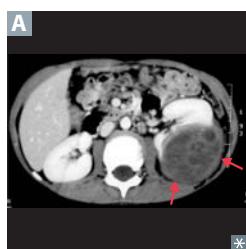
Clear cell (most common subtype) associated with gene deletion on chromosome 3 (sporadic, or inherited as von Hippel-Lindau syndrome).

**RCC** = 3 letters = chromosome 3 = associated with **VHL** (also 3 letters).



**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).

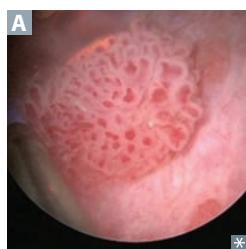
**Nephroblastoma**

Also called Wilms tumor. Most common renal malignancy of early childhood (ages 2–4). Contains embryonic glomerular structures. Most often present with large, palpable, unilateral flank mass **A** and/or hematuria and possible HTN.

Can be associated with loss-of-function mutations of tumor suppressor genes *WT1* or *WT2* on chromosome 11.

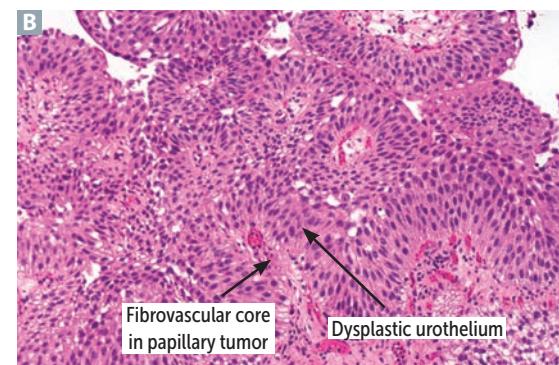
May be a part of several syndromes:

- **WAGR complex**—Wilms tumor, **Aniridia** (absence of iris), **Genitourinary malformations**, **Range** of developmental delays (*WT1* deletion)
- **Denys-Drash syndrome**—Wilms tumor, **Diffuse mesangial sclerosis** (early-onset nephrotic syndrome), **Dysgenesis of gonads** (male pseudohermaphroditism), *WT1* mutation
- **Beckwith-Wiedemann syndrome**—Wilms tumor, macroglossia, organomegaly, hemihyperplasia (*WT2* mutation), omphalocele

**Urothelial carcinoma of the bladder**

Also called transitional cell carcinoma. Most common tumor of urinary tract system (can occur in renal calyces, renal pelvis, ureters, and bladder) **A** **B**. Can be suggested by painless hematuria (no casts).

Associated with problems in your **Pee SAC**: **P**henacetin, **S**tobacco **S**moking, **A**romatic amines (found in dyes), **C**yclophosphamide.

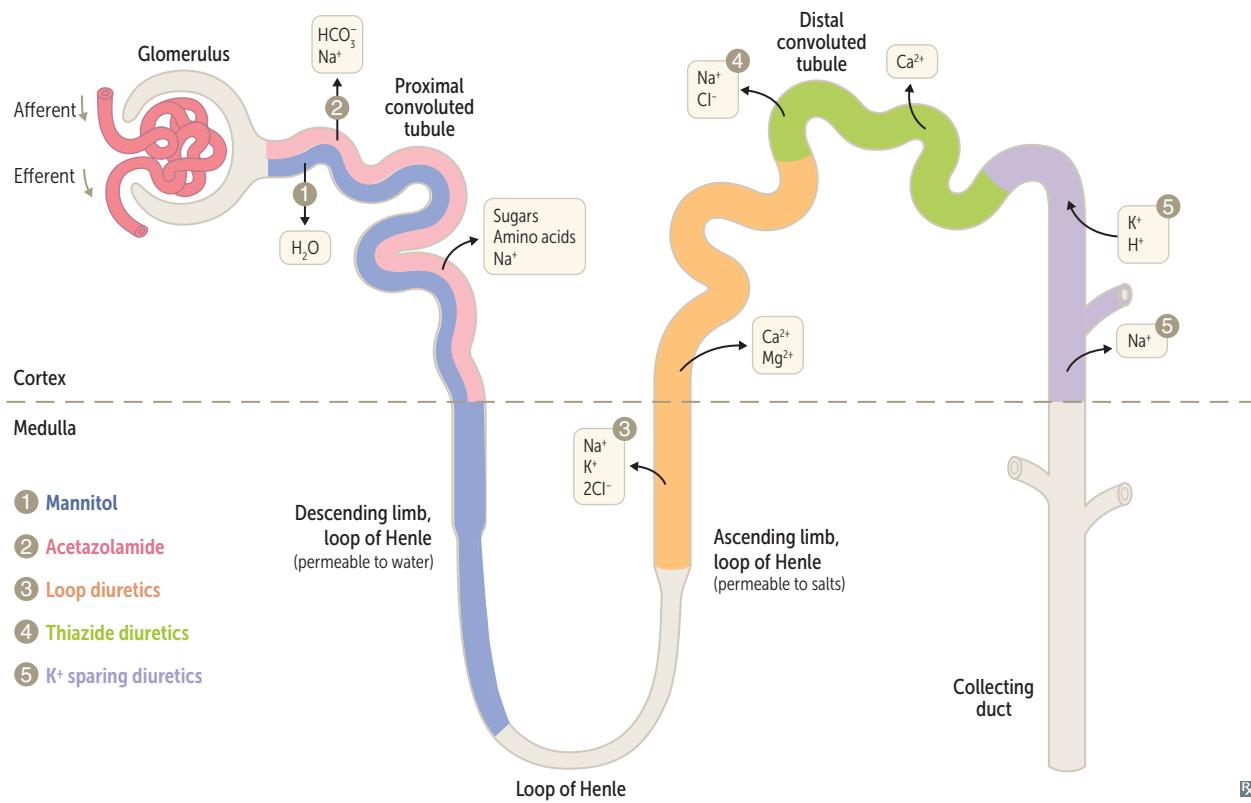
**Squamous cell carcinoma of the bladder**

Chronic irritation of urinary bladder → squamous metaplasia → dysplasia and squamous cell carcinoma.

Risk factors include **4 S's**: ***Schistosoma haematobium*** infection (Middle East), chronic cystitis ("systitis"), **smoking**, **chronic nephrolithiasis** (stones). Presents with painless hematuria (no casts).

## ► RENAL—PHARMACOLOGY

## Diuretics site of action

**Mannitol**

## MECHANISM

Osmotic diuretic. ↑ tubular fluid osmolarity → ↑ urine flow, ↓ intracranial/intraocular pressure.

## CLINICAL USE

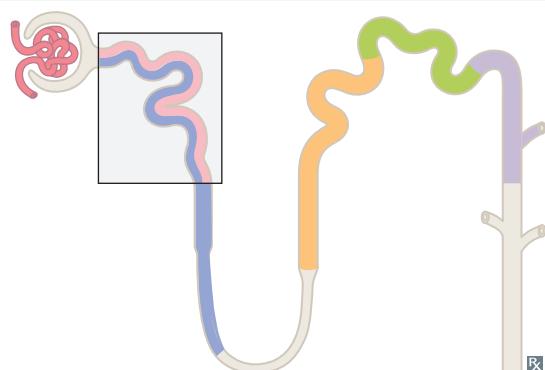
Drug overdose, elevated intracranial/intraocular pressure.

## ADVERSE EFFECTS

Dehydration, hypo- or hypernatremia, pulmonary edema. Contraindicated in anuria, HF.

**Acetazolamide**

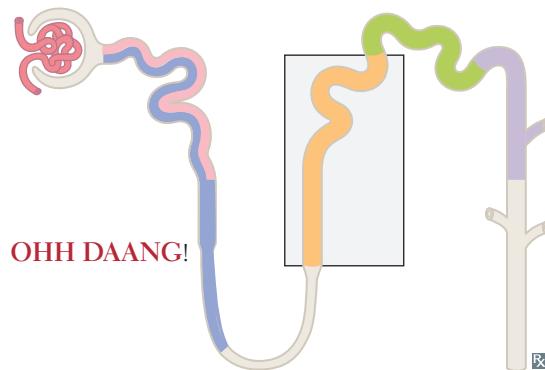
MECHANISM	Carbonic anhydrase inhibitor. Causes self-limited $\text{NaHCO}_3$ diuresis and $\downarrow$ total body $\text{HCO}_3^-$ stores. Alkalinizes urine.
CLINICAL USE	Glaucoma, metabolic alkalosis, altitude sickness (by offsetting respiratory alkalosis), idiopathic intracranial hypertension.
ADVERSE EFFECTS	Proximal renal tubular acidosis (type 2 RTA), paresthesias, NH <sub>3</sub> toxicity, sulfa allergy, hypokalemia. Promotes calcium phosphate stone formation (insoluble at high pH).



“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. Associated with $\uparrow$ PGE (vasodilatory effect on afferent arteriole); inhibited by NSAIDs. $\uparrow \text{Ca}^{2+}$ excretion. Loops lose $\text{Ca}^{2+}$ .
CLINICAL USE	Edematous states (HF, cirrhosis, nephrotic syndrome, pulmonary edema), hypertension, hypercalcemia.
ADVERSE EFFECTS	Ototoxicity, Hypokalemia, Hypomagnesemia, Dehydration, Allergy (sulfa), metabolic Alkalosis, Nephritis (interstitial), Gout.

**Ethacrynic acid**

MECHANISM	Nonsulfonamide inhibitor of cotransport system ( $\text{Na}^+/\text{K}^+/2\text{Cl}^-$ ) of thick ascending limb of <b>loop</b> of Henle.
CLINICAL USE	Diuresis in patients allergic to sulfa drugs.
ADVERSE EFFECTS	Similar to furosemide, but more <b>ototoxic</b> .

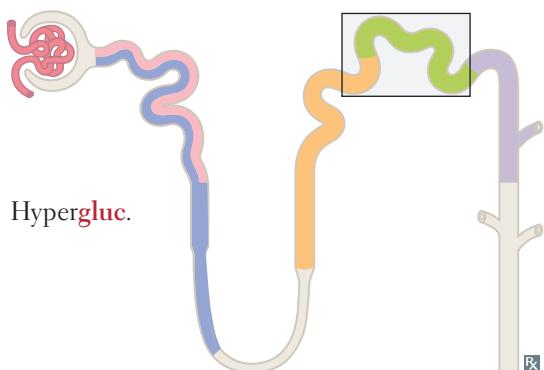
Loop earrings hurt your ears.

**Thiazide diuretics**

Hydrochlorothiazide, chlorthalidone, metolazone.

**MECHANISM**

Inhibit NaCl reabsorption in early DCT  
→ ↓ diluting capacity of nephron. ↓ Ca<sup>2+</sup> excretion.

**CLINICAL USE**

Hypertension, HF, idiopathic hypercalciuria, nephrogenic diabetes insipidus, osteoporosis.

**ADVERSE EFFECTS**

Hypokalemic metabolic alkalosis, hyponatremia, hyperglycemia, hyperlipidemia, hyperuricemia, hypercalcemia. Sulfa allergy.

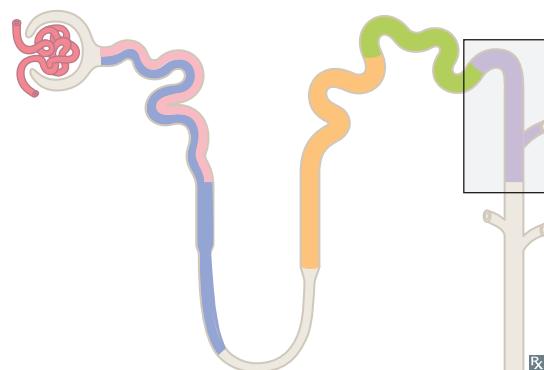
Keep your SEAT.

**Potassium-sparing diuretics**

Spironolactone, Eplerenone, Amiloride, Triamterene.

**MECHANISM**

Spironolactone and eplerenone are competitive aldosterone receptor antagonists in cortical collecting tubule. Triamterene and amiloride block Na<sup>+</sup> channels at the same part of the tubule.

**CLINICAL USE**

Hyperaldosteronism, K<sup>+</sup> depletion, HF, hepatic ascites (spironolactone), nephrogenic DI (amiloride), antiandrogen (spironolactone).

**ADVERSE EFFECTS**

Hyperkalemia (can lead to arrhythmias), endocrine effects with spironolactone (eg, gynecomastia, antiandrogen effects).

**Diuretics: electrolyte changes****Urine NaCl**

↑ with all diuretics (concentration varies based on potency of diuretic effect). Serum NaCl may decrease as a result.

**Urine K<sup>+</sup>**

↑ especially with loop and thiazide diuretics, excluding K<sup>+</sup>-sparing diuretics.

**Blood pH**

↓ (acidemia): carbonic anhydrase inhibitors: ↓ HCO<sub>3</sub><sup>-</sup> reabsorption. K<sup>+</sup> sparing: aldosterone blockade prevents K<sup>+</sup> secretion and H<sup>+</sup> secretion. Additionally, hyperkalemia leads to K<sup>+</sup> entering all cells (via H<sup>+</sup>/K<sup>+</sup> exchanger) in exchange for H<sup>+</sup> exiting cells.

↑ (alkalemia): loop diuretics and thiazides cause alkalemia through several mechanisms:

- Volume contraction → ↑ AT II → ↑ Na<sup>+</sup>/H<sup>+</sup> exchange in PCT → ↑ HCO<sub>3</sub><sup>-</sup> reabsorption (“contraction alkalosis”)
- K<sup>+</sup> loss leads to K<sup>+</sup> exiting all cells (via H<sup>+</sup>/K<sup>+</sup> exchanger) in exchange for H<sup>+</sup> entering cells
- In low K<sup>+</sup> state, H<sup>+</sup> (rather than K<sup>+</sup>) is exchanged for Na<sup>+</sup> in cortical collecting tubule → alkalemia and “paradoxical aciduria”

**Urine Ca<sup>2+</sup>**

↑ with loop diuretics: ↓ paracellular Ca<sup>2+</sup> reabsorption → hypocalcemia.

↓ with thiazides: enhanced Ca<sup>2+</sup> reabsorption.

### **Angiotensin-converting enzyme inhibitors**

<b>MECHANISM</b>	Captopril, enalapril, lisinopril, ramipril.
<b>CLINICAL USE</b>	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.
<b>ADVERSE EFFECTS</b>	Hypertension, HF (↓ mortality), proteinuria, diabetic nephropathy. Prevent unfavorable heart remodeling as a result of chronic hypertension.
	In chronic kidney disease (eg, diabetic nephropathy), ↓ intraglomerular pressure, slowing GBM thickening.
	Cough, Angioedema (both due to ↑ bradykinin; contraindicated in Cl esterase inhibitor deficiency), Teratogen (fetal renal malformations), ↑ Creatinine (↓ GFR), Hyperkalemia, and Hypotension. Used with caution in bilateral renal artery stenosis because ACE inhibitors will further ↓ GFR → renal failure.
	Captopril's <b>CATCHH</b> .

### **Angiotensin II receptor blockers**

<b>MECHANISM</b>	Selectively block binding of angiotensin II to AT <sub>1</sub> receptor. Effects similar to ACE inhibitors, but ARBs do not increase bradykinin.
<b>CLINICAL USE</b>	Hypertension, HF, proteinuria, or chronic kidney disease (eg, diabetic nephropathy) with intolerance to ACE inhibitors (eg, cough, angioedema).
<b>ADVERSE EFFECTS</b>	Hyperkalemia, ↓ GFR, hypotension; teratogen.

### **Aliskiren**

<b>MECHANISM</b>	Direct renin inhibitor, blocks conversion of angiotensinogen to angiotensin I. Aliskiren kills renin.
<b>CLINICAL USE</b>	Hypertension.
<b>ADVERSE EFFECTS</b>	Hyperkalemia, ↓ GFR, hypotension, angioedema. Relatively contraindicated in patients already taking ACE inhibitors or ARBs and contraindicated in pregnancy.

▶ NOTES

# Reproductive

*“Life is always a rich and steady time when you are waiting for something to happen or to hatch.”*

—E.B. White, *Charlotte’s Web*

*“Love is only a dirty trick played on us to achieve continuation of the species.”*

—W. Somerset Maugham

*“In pregnancy, there are two bodies, one inside the other. Two people live under one skin. When so much of life is dedicated to maintaining our integrity as distinct beings, this bodily tandem is an uncanny fact.”*

—Joan Raphael-Leff, *Pregnancy: The Inside Story*

*“Life is a sexually transmitted disease and the mortality rate is one hundred percent.”*

—R.D. Laing

Organizing the reproductive system by key concepts such as embryology, endocrinology, pregnancy, and oncology can help with understanding this complex topic. Study the endocrine and reproductive chapters together, because mastery of the hypothalamic-pituitary-gonadal axis is key to answering questions on ovulation, menstruation, disorders of sexual development, contraception, and many pathologies.

Embryology is a nuanced subject that spans multiple organ systems. Approach it from a clinical perspective. For instance, make the connection between the presentation of DiGeorge syndrome and the 3rd/4th pharyngeal pouch, and between the Müllerian/Wolffian systems and disorders of sexual development.

As for oncology, don’t worry about remembering screening or treatment guidelines. It is more important to recognize the clinical presentation (eg, signs and symptoms) of reproductive cancers and their associated labs, histopathology, and risk factors. In addition, some of the testicular and ovarian cancers have distinct patterns of hCG, AFP, LH, or FSH derangements that serve as helpful clues in exam questions.

► Embryology	636
► Anatomy	648
► Physiology	653
► Pathology	661
► Pharmacology	679

## ► REPRODUCTIVE—EMBRYOLOGY

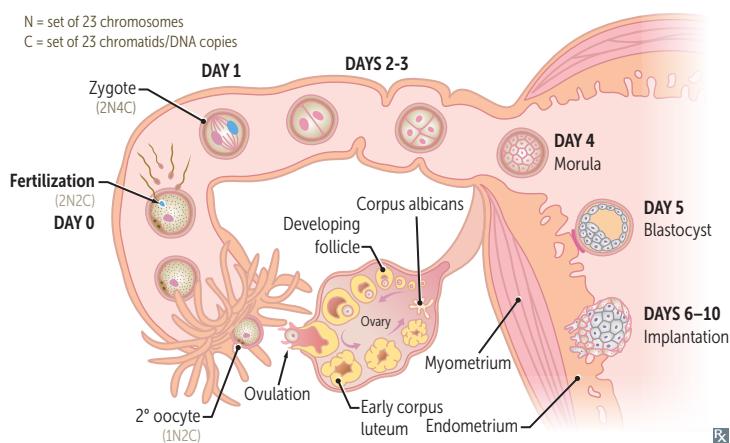
## Important genes of embryogenesis

GENE	LOCATION	FUNCTION	NOTES
<b>Sonic hedgehog (SHH) gene</b>	Zone of polarizing activity at base of limb buds	Anterior-posterior axis patterning, CNS development	Mutations → holoprosencephaly
<b>Wnt-7 gene</b>	Apical ectodermal ridge at distal end of each limb	Dorsal-ventral axis patterning, limb development	"Vnt-7"
<b>Fibroblast growth factor (FGF) gene</b>	Apical ectodermal ridge	Limb lengthening (via mitosis of mesoderm)	"Look at that Fetus, Growing Fingers"
<b>Homeobox (Hox) genes</b>	Multiple	Segmental organization in cranial-caudal direction, transcription factor coding	Mutations → appendages in wrong locations. Isotretinoin → ↑ Hox gene expression

## Early fetal development

Timeline shown is based on developmental age (ie, time since fertilization) rather than gestational age (ie, time since first day of last menstrual period).

## 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 and induces overlying ectoderm to become 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. Cardiac activity visible by transvaginal ultrasound.  
Upper and lower limb buds begin to form.

4 weeks = 4 limbs and 4 heart chambers.

## Week 6

Fetal movements start.

## Week 8

Genitalia have male/female characteristics.

## Embryologic derivatives

<b>Ectoderm</b>		<b>External/outer layer</b>
Surface ectoderm	Epidermis; adenohypophysis (from Rathke pouch); lens of eye; epithelial linings of oral cavity, sensory organs of ear, and olfactory epithelium; anal canal below the pectinate line; parotid, sweat, mammary glands.	<b>Craniopharyngioma</b> —benign Rathke pouch tumor with cholesterol crystals, calcifications.
Neural tube	Brain (neurohypophysis, CNS neurons, oligodendrocytes, astrocytes, ependymal cells, pineal gland), retina, spinal cord.	Neuroectoderm—think CNS.
Neural crest	Enterochromaffin cells, Leptomeninges (arachnoid, pia), Melanocytes, Odontoblasts, PNS ganglia (cranial, dorsal root, autonomic), Adrenal medulla, Schwann cells, Spiral membrane (aorticopulmonary septum), Endocardial cushions (also derived partially from mesoderm), Skull bones.	<b>ELMO PASSES</b> Neural crest—think PNS and non-neural structures nearby.
<b>Mesoderm</b>		<b>Middle/“meat” layer.</b> Mesodermal defects = <b>VACTERL</b> association: <b>V</b> ertebral defects <b>A</b> nal atresia <b>C</b> ardiac defects <b>T</b> racheo- <b>E</b> sophageal fistula <b>R</b> enal defects <b>E</b> limb defects (bone and muscle)
Endoderm	Gut tube epithelium (including anal canal above the pectinate line), most of urethra and lower 1/3 of vagina (derived from urogenital sinus), luminal epithelial derivatives (eg, lungs, liver, gallbladder, pancreas, eustachian tube, thymus, parathyroid, thyroid follicular and parafollicular [C] cells).	“ <b>E</b> ntral” layer.

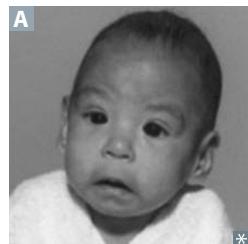
## Types of errors in morphogenesis

<b>Agenesis</b>	Absent organ due to absent primordial tissue.
<b>Aplasia</b>	Absent organ despite presence of primordial tissue.
<b>Hypoplasia</b>	Incomplete organ development; primordial tissue present.
<b>Disruption</b>	2° breakdown of previously normal tissue or structure (eg, amniotic band syndrome).
<b>Deformation</b>	Extrinsic mechanical distortion (eg, congenital torticollis); occurs after embryonic period.
<b>Malformation</b>	Intrinsic developmental defect; occurs during embryonic period (weeks 3–8 of development).
<b>Sequence</b>	Abnormalities result from a single 1° embryologic event (eg, oligohydramnios → Potter sequence).
<b>Field defect</b>	Disturbance of tissues that develop in a contiguous physical space (eg, holoprosencephaly).

**Teratogens**

Most susceptible in 3rd–8th weeks (embryonic period—organogenesis) of development. Before week 3, “all-or-none” effects. After week 8, growth and function affected.

TERATOGEN	EFFECTS ON FETUS	NOTES
<b>Medications</b>		
<b>ACE inhibitors</b>	Renal failure, oligohydramnios, hypocalvaria	
<b>Alkylating agents</b>	Absence of digits, multiple anomalies	
<b>Aminoglycosides</b>	Ototoxicity	<b>A mean guy</b> hit the baby in the <b>ear</b>
<b>Antiepileptic drugs</b>	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
<b>Diethylstilbestrol</b>	Vaginal clear cell adenocarcinoma, congenital Müllerian anomalies	
<b>Fluoroquinolones</b>	Cartilage damage	
<b>Folate antagonists</b>	Neural tube defects	Antiepileptics, trimethoprim, methotrexate
<b>Isotretinoin</b>	Craniofacial (eg, microtia, dysmorphism), CNS, cardiac, and thymic defects	Contraception mandatory. Pronounce “ <b>isotretinoin</b> .”
<b>Lithium</b>	Ebstein anomaly	
<b>Methimazole</b>	Aplasia cutis congenita (congenital absence of skin, particularly on scalp)	
<b>Tetracyclines</b>	Discolored teeth, inhibited bone growth	“ <b>Teeth</b> racyclines”
<b>Thalidomide</b>	Limb defects (phocomelia, micromelia—“flipper” limbs)	<b>Limb</b> defects with “tha- <b>limb</b> -domide”
<b>Warfarin</b>	Bone and cartilage deformities (stippled epiphyses, nasal and limb hypoplasia), optic nerve atrophy, fetal cerebral hemorrhage	Do not wage <b>warfare</b> on the baby; keep it <b>heppy</b> with <b>heparin</b> (does not cross placenta)
<b>Substance use</b>		
<b>Alcohol</b>	Fetal alcohol syndrome	
<b>Cocaine</b>	Low birth weight, preterm birth, IUGR, placental abruption	Cocaine → vasoconstriction
<b>Smoking</b>	Low birth weight (leading cause in developed countries), preterm labor, placental problems, IUGR, SIDS, ADHD	Nicotine → vasoconstriction CO → impaired O <sub>2</sub> delivery
<b>Other</b>		
<b>Iodine lack or excess</b>	Congenital hypothyroidism (cretinism), congenital goiter	
<b>Diabetes in pregnancy</b>	Caudal regression syndrome, cardiac defects (eg, VSD), neural tube defects, macrosomia, neonatal hypoglycemia (due to islet cell hyperplasia), polycythemia, neonatal respiratory distress syndrome	
<b>Methylmercury</b>	Neurotoxicity	Higher concentrations in top-predator fish (eg, shark, swordfish, king mackerel, tilefish)
<b>X-rays</b>	Microcephaly, intellectual disability	Minimized by lead shielding

**Fetal alcohol syndrome**

One of the leading preventable causes of intellectual disability in the US. Newborns of patients who consumed alcohol during any stage of pregnancy have ↑ incidence of congenital abnormalities, including pre- and postnatal developmental delay, microcephaly, facial abnormalities **A** (eg, smooth philtrum, thin vermillion border, small palpebral fissures), limb dislocation, heart defects. Heart-lung fistulas and holoprosencephaly may occur in more severe presentations. One mechanism is due to impaired migration of neuronal and glial cells.

**Neonatal abstinence syndrome**

Complex disorder involving CNS, ANS, and GI systems. Secondary to substance use (most commonly opioids) during pregnancy.

Universal screening for substance use is recommended in all pregnant patients.

Newborns may present with uncoordinated sucking reflexes, irritability, high-pitched crying, tremors, tachypnea, sneezing, diarrhea, and possibly seizures.

Treatment (for opiate use): methadone, morphine, buprenorphine.

**Placenta**

1° site of nutrient and gas exchange between pregnant patient and fetus.

**Fetal component****Cytrophoblast**

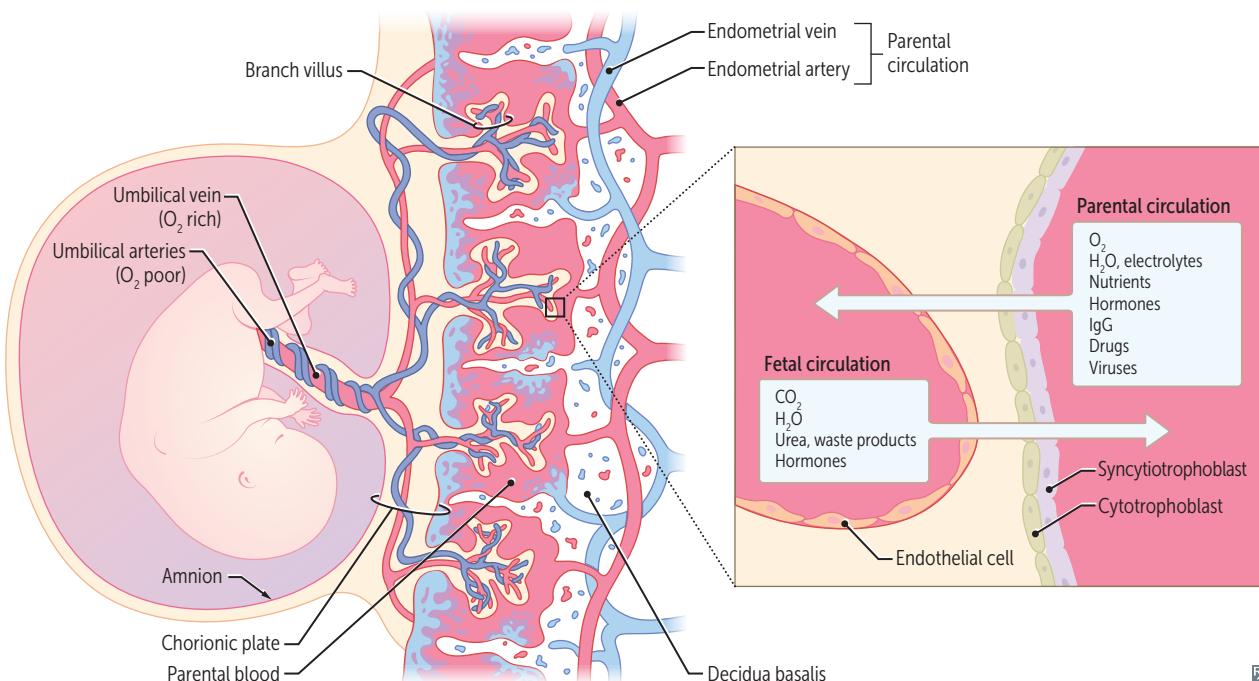
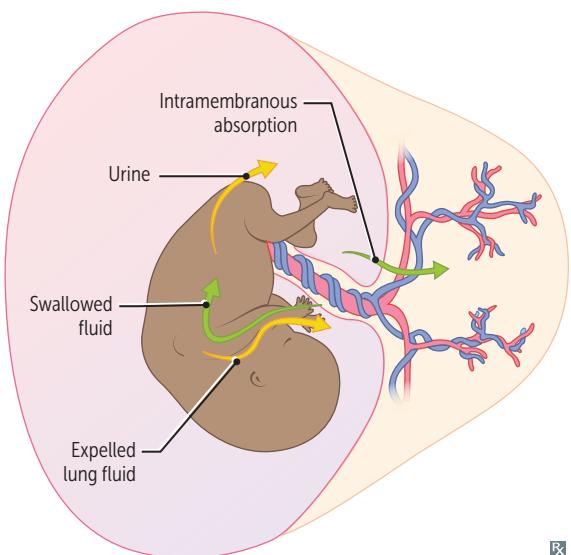
Inner layer of chorionic villi; makes **cells**.

**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). Lacks MHC I expression → ↓ chance of attack by maternal immune system.

**Parental component****Decidua basalis**

Derived from endometrium. Parental blood in lacunae.

**Amniotic fluid**

Derived from fetal urine (mainly) and fetal lung liquid.

Cleared by fetal swallowing (mainly) and intramembranous absorption.

**Polyhydramnios**—too much amniotic fluid.

May be idiopathic or associated with fetal malformations (eg, esophageal/duodenal atresia, anencephaly; both result in inability to swallow amniotic fluid), diabetes in pregnant patient, fetal anemia, multiple gestations.

**Oligohydramnios**—too little amniotic fluid.

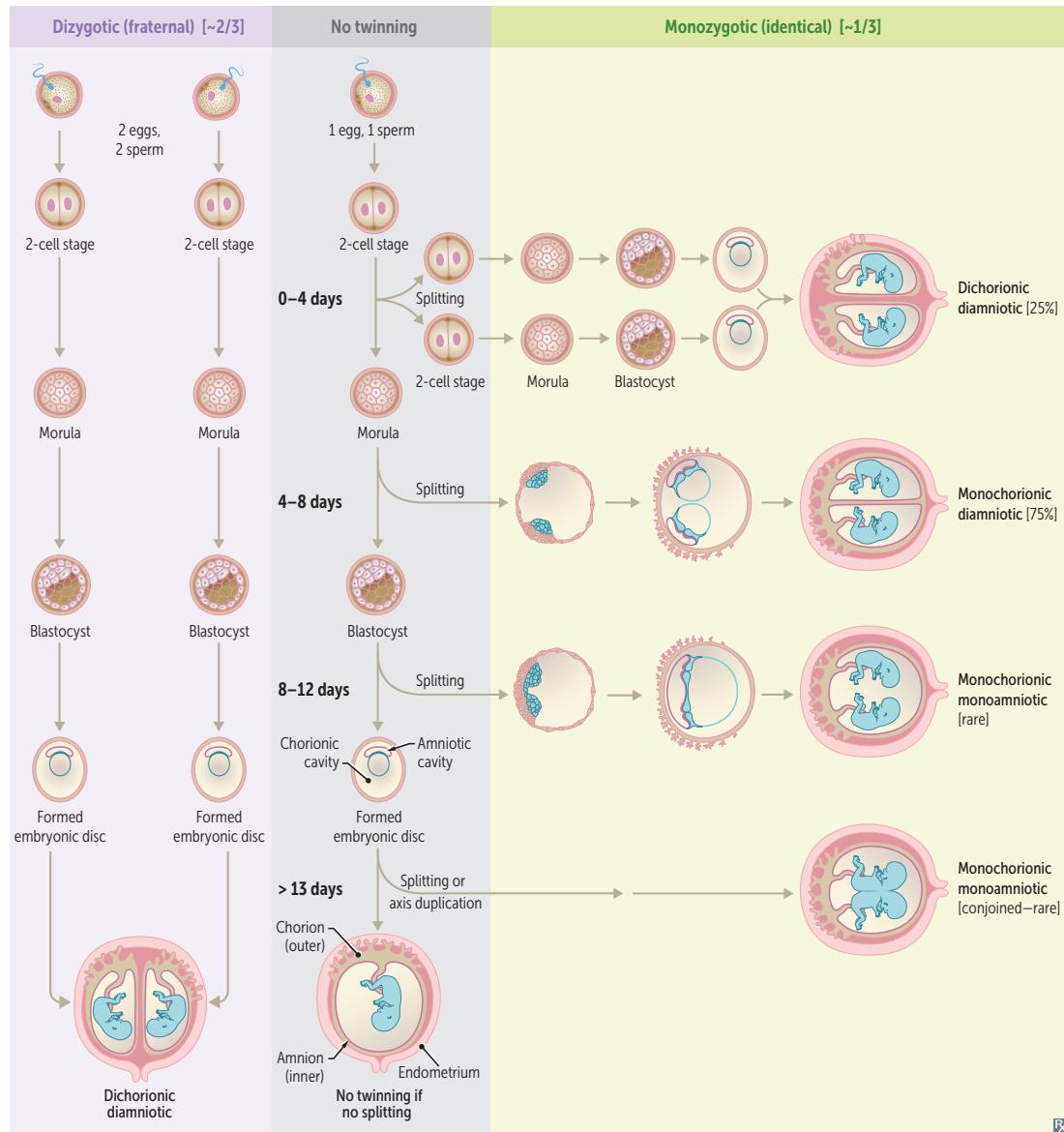
Associated with placental insufficiency, bilateral renal agenesis, posterior urethral valves (in males); these result in inability to excrete urine. Profound oligohydramnios can cause Potter sequence.

**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 splitting determines chorionicity (number of chorions) and amniocyticity (number of amnions) (take **separate** cars or **share a CCAB**):

- Splitting 0–4 days: **separate** chorion and amnion (di-di)
- Splitting 4–8 days: **shared Chorion** (mo-di)
- Splitting 8–12 days: **shared Chorion and Amnion** (mo-mo)
- Splitting 13+ days: **shared Body** (conjoined)

**Twin-twin transfusion syndrome**

Occurs in monochorionic twin gestations. Unbalanced vascular connections between twins in shared placenta → net blood flow from one twin to the other.

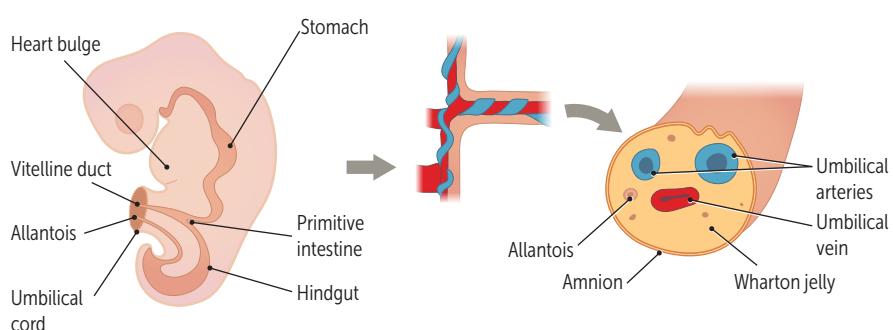
Donor twin → hypovolemia and oligohydramnios (“stuck twin” appearance).

Recipient twin → hypervolemia and polyhydramnios.

**Umbilical cord**

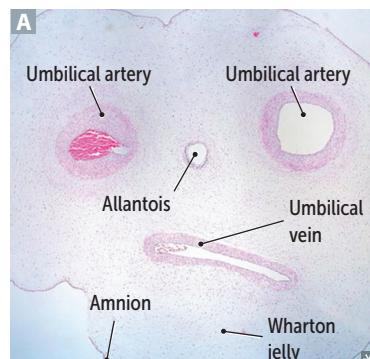
Two umbilical arteries return deoxygenated blood from fetal internal iliac arteries to placenta **A**.

One umbilical vein supplies oxygenated blood from placenta to fetus; drains into IVC via liver or via ductus venosus.



Single umbilical artery (2-vessel cord) is associated with congenital and chromosomal anomalies.

Umbilical arteries and vein are derived from allantois.

**Urachus**

Allantois forms from hindgut and extends into urogenital sinus. Allantois becomes the urachus, a duct between fetal bladder and umbilicus. Failure of urachus to involute can lead to anomalies that may increase risk of infection and/or malignancy (eg, adenocarcinoma) if not treated. Obliterated urachus is represented by the median umbilical ligament after birth, which is covered by median umbilical fold of the peritoneum.

**Patent urachus**

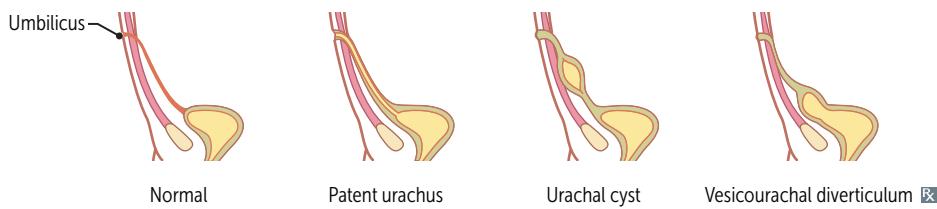
Total failure of urachus to obliterate → urine discharge from umbilicus.

**Urachal cyst**

Partial failure of urachus to obliterate; fluid-filled cavity lined with uroepithelium, between umbilicus and bladder. Cyst can become infected and present as painful mass below umbilicus.

**Vesicourachal diverticulum**

Slight failure of urachus to obliterate → outpouching of bladder.

**Vitelline duct**

Also called omphalomesenteric duct. Connects yolk sac to midgut lumen. Obliterates during week 7 of development.

**Patent vitelline duct**

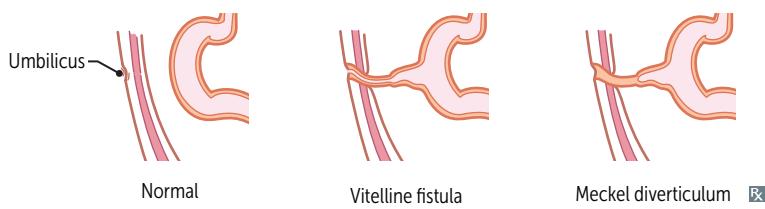
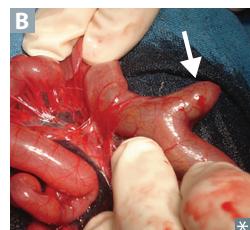
Total failure of vitelline duct to obliterate → meconium discharge from umbilicus.

**Vitelline duct cyst**

Partial failure of vitelline duct to obliterate. ↑ risk for volvulus.

**Meckel diverticulum**

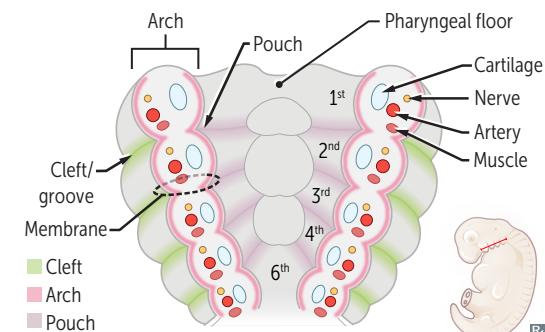
Slight failure of vitelline duct to obliterate → outpouching of ileum (true diverticulum, arrow in **B**). Usually asymptomatic. May have heterotopic gastric and/or pancreatic tissue → melena, hematochezia, abdominal pain.



**Pharyngeal apparatus**

Composed of pharyngeal (branchial) clefts, arches, pouches.  
 Pharyngeal clefts—derived from ectoderm. Also called pharyngeal grooves.  
 Pharyngeal arches—derived from mesoderm (muscles, arteries) and neural crest (bones, cartilage).  
 Pharyngeal pouches—derived from endoderm.

CAP covers outside to inside:  
 Clefts = ectoderm  
 Arches = mesoderm + neural crest  
 Pouches = endoderm

**Pharyngeal cleft derivatives**

1st cleft develops into external auditory meatus.  
 2nd through 4th clefts form temporary cervical sinuses, which are obliterated by proliferation of 2nd arch mesenchyme.  
**Pharyngeal cleft cyst**—persistent cervical sinus; presents as lateral neck mass anterior to sternocleidomastoid muscle that does not move with swallowing (vs thyroglossal duct cyst).

**Pharyngeal arch derivatives** 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).

ARCH	CARTILAGE	MUSCLES	NERVES <sup>a</sup>	NOTES
<b>1st pharyngeal arch</b>	Maxillary process → <b>maxilla</b> , zygomatic bone  <b>Mandibular process</b> → <b>meckel cartilage</b> → <b>mandible</b> , <b>malleus</b> and <b>incus</b> , sphenom <b>mandibular</b> ligament	Muscles of mastication (temporalis, masseter, lateral and medial pterygoids), <b>mylohyoid</b> , anterior belly of digastric, tensor tympani, anterior 2/3 of tongue, tensor veli palatini	CN V <sub>3</sub> <b>chew</b>	Pierre Robin sequence—micrognathia, glossoptosis, cleft palate, airway obstruction  <b>Treacher Collins syndrome</b> —autosomal dominant neural crest dysfunction → craniofacial abnormalities (eg, zygomatic bone and mandibular hypoplasia), hearing loss, airway compromise
<b>2nd pharyngeal arch</b>	Reichert cartilage: <b>stapes</b> , <b>styloid process</b> , <b>lesser horn of hyoid</b> , <b>stylohyoid ligament</b>	Muscles of facial expression, <b>stapedius</b> , <b>stylohyoid</b> , <b>platysma</b> , posterior belly of digastric	CN VII ( <b>seven smile</b> (facial expression))	
<b>3rd pharyngeal arch</b>	Greater horn of hyoid	<b>Stylopharyngeus</b>	CN IX ( <b>stylo-pharyngeus</b> ) <b>swallow stylishly</b>	
<b>4th and 6th pharyngeal arches</b>	<b>Arytenoids</b> , <b>Cricoid</b> , <b>Corniculate</b> , <b>Cuneiform</b> , <b>Thyroid</b> (used to sing and <b>ACCCT</b> )	4th arch: most pharyngeal constrictors; cricothyroid, levator veli palatini 6th arch: all intrinsic muscles of larynx except cricothyroid	4th arch: CN X (superior laryngeal branch) simply swallow 6th arch: CN X (recurrent/inferior laryngeal branch) <b>speak</b>	Arches 3 and 4 form posterior 1/3 of tongue Arch 5 makes no major developmental contributions

<sup>a</sup>Sensory and motor nerves are not pharyngeal arch derivatives. They grow into the arches and are derived from neural crest (sensory) and neuroectoderm (motor).

**Pharyngeal pouch derivatives** **Ear, tonsils, bottom-to-top:** 1 (**ear**), 2 (**tonsils**), 3 dorsal (**bottom** for inferior parathyroids), 3 ventral (**to = thymus**), 4 (**top = superior** parathyroids)

POUCH	DERIVATIVES	NOTES
<b>1st pharyngeal pouch</b>	Middle ear cavity, eustachian tube, mastoid air cells	1st pouch contributes to endoderm-lined structures of ear
<b>2nd pharyngeal pouch</b>	Epithelial lining of palatine tonsil	
<b>3rd pharyngeal pouch</b>	Dorsal wings → <b>inferior parathyroids</b> Ventral wings → thymus	<b>Third</b> pouch contributes to <b>thymus</b> and both <b>inferior parathyroids</b> Structures from 3rd pouch end up <b>below</b> those from 4th pouch
<b>4th pharyngeal pouch</b>	Dorsal wings → <b>superior parathyroids</b> Ventral wings → ultimopharyngeal body → parafollicular (C) cells of thyroid	<b>4th</b> pharyngeal pouch forms para“ <b>4</b> ”llicular cells

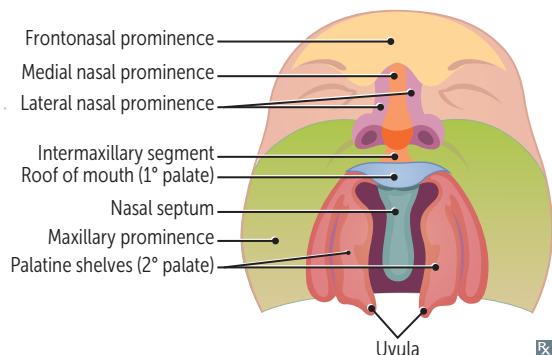
**Orofacial clefts****Cleft lip**

Cleft lip and cleft palate have distinct, multifactorial etiologies, but often occur together.

**Cleft lip** Due to failure of fusion of the maxillary and merged medial nasal processes (formation of 1° palate).

**Cleft palate**

**Cleft palate** Due to failure of fusion of the two lateral palatine shelves or failure of fusion of lateral palatine shelf with the nasal septum and/or 1° palate (formation of 2° palate).

**Genital embryology****Female**

Default development. Mesonephric duct degenerates and paramesonephric duct develops.

**Male**

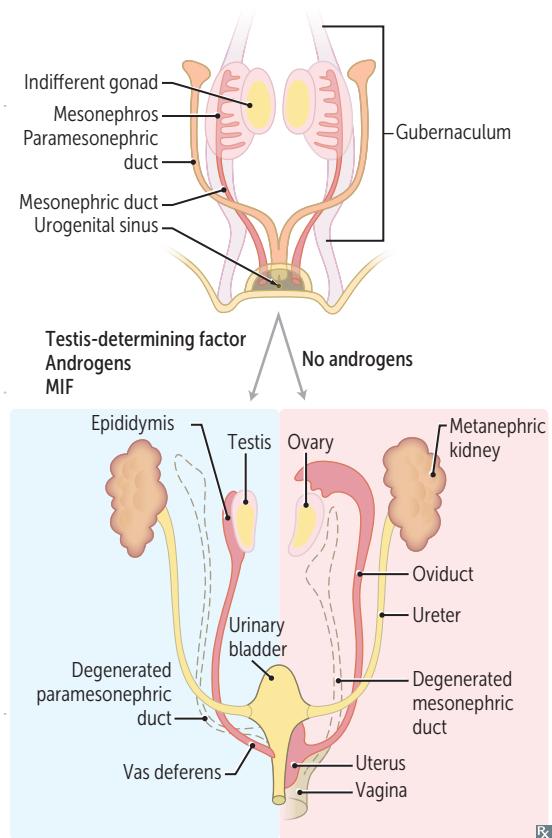
SRY gene on Y chromosome—produces testis-determining factor → testes development. Sertoli cells secrete Müllerian inhibitory factor (MIF, also called antimüllerian hormone) that suppresses development of paramesonephric ducts. Leydig cells secrete androgens that stimulate development of mesonephric ducts.

**Paramesonephric (Müllerian) duct**

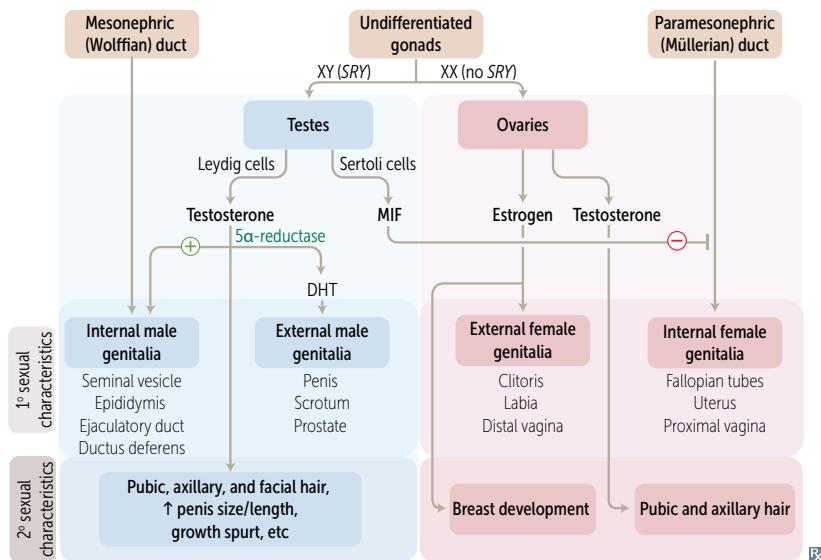
Develops into female internal structures—fallopian tubes, uterus, upper portion of vagina (lower portion from urogenital sinus). Male remnant is appendix testis. **Müllerian agenesis (Mayer-Rokitansky-Küster-Hauser syndrome)**—may present as 1° amenorrhea (due to a lack of uterine development) in females with fully developed 2° sexual characteristics (functional ovaries).

**Mesonephric (Wolffian) duct**

Develops into male internal structures (except prostate)—**Seminal vesicles, Epididymis, Ejaculatory duct, Ductus deferens (SEED)**. Female remnant is Gartner duct.



### Sexual differentiation



Absence of Sertoli cells or lack of Müllerian inhibitory factor → develop both male and female internal genitalia and male external genitalia (streak gonads)

$5\alpha$ -reductase deficiency—ability to convert testosterone into DHT → male internal genitalia, ambiguous external genitalia until puberty (when ↑ testosterone levels cause masculinization)

In the testes:

Leydig leads to male (internal and external) sexual differentiation.

Sertoli shuts down female (internal) sexual differentiation.

### Uterine (Müllerian duct) anomalies

↓ fertility and ↑ risk of complicated pregnancy (eg, spontaneous abortion, prematurity, IUGR, malpresentation). Contrast with normal uterus **A**.

#### Septate uterus

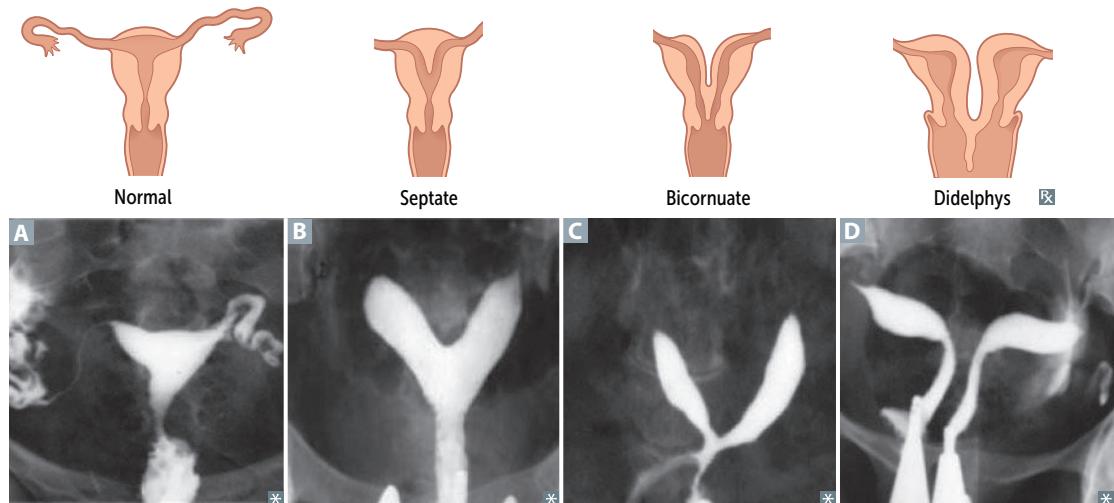
Incomplete resorption of septum **B**. Common anomaly. Treat with septoplasty.

#### Bicornuate uterus

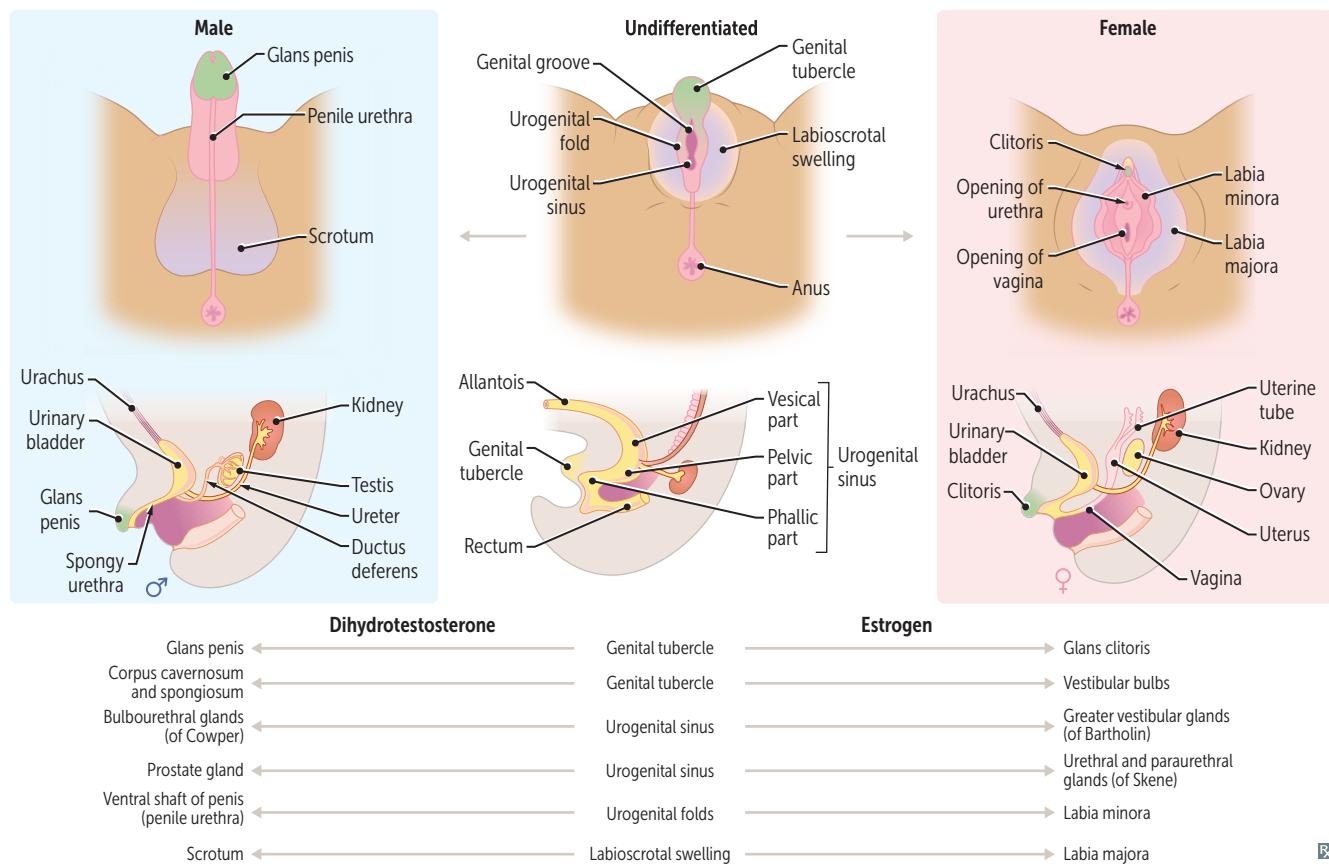
Incomplete fusion of Müllerian ducts **C**.

#### Uterus didelphys

Complete failure of fusion → double uterus, cervix, vagina **D**.

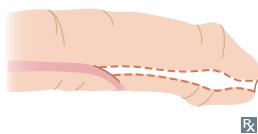


### Male/female genital homologs



### Congenital penile abnormalities

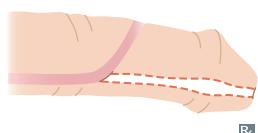
#### Hypospadias



Abnormal opening of penile urethra on ventral (under) surface due to failure of urethral folds to fuse.

Hypospadias is more common than epispadias. Associated with inguinal hernia, cryptorchidism, chordee (downward or upward bending of penis). Can be seen in 5α-reductase deficiency.

#### Epispadias



Abnormal opening of penile urethra on dorsal (top) surface due to faulty positioning of genital tubercle.

Exstrophy of the bladder is associated with epispadias.

**Descent of testes and ovaries**

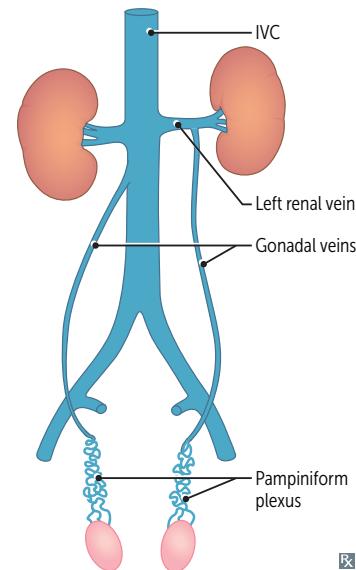
	DESCRIPTION	MALE REMNANT	FEMALE REMNANT
<b>Gubernaculum</b>	Band of fibrous tissue	Anchors testes within scrotum	Ovarian ligament + round ligament of uterus
<b>Processus vaginalis</b>	Evagination of peritoneum	Forms tunica vaginalis Persistent patent processus vaginalis → hydrocele	Obliterated

## ► REPRODUCTIVE—ANATOMY

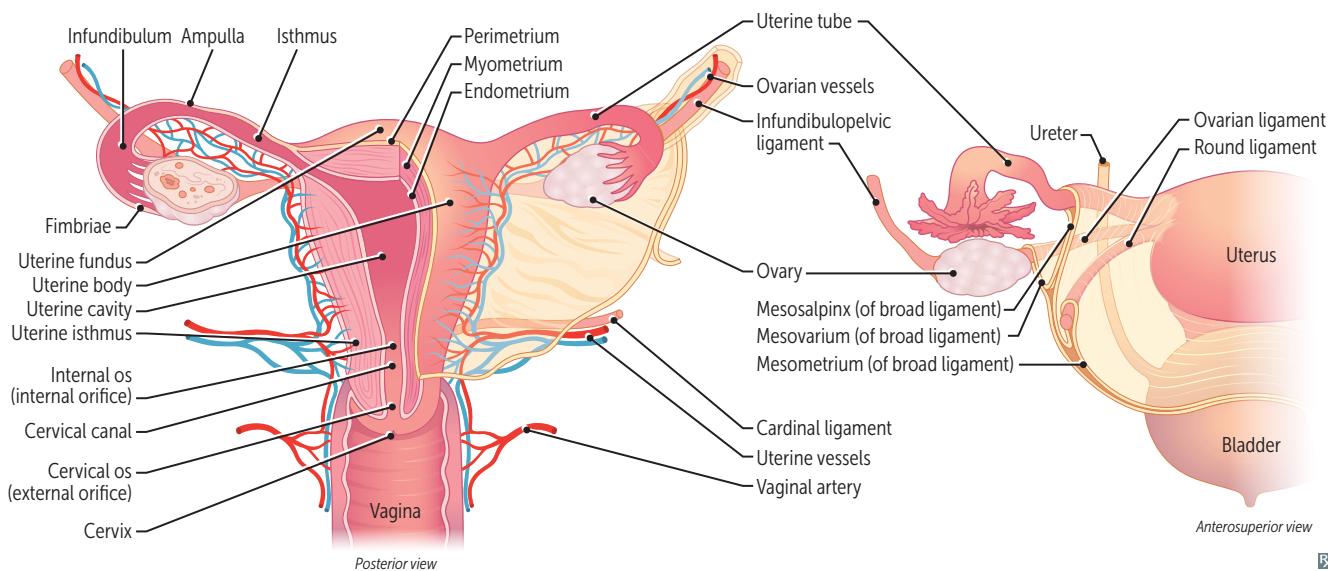
**Gonadal drainage****Venous drainage**

Left ovary/testis → left gonadal vein → left renal vein → IVC.  
 Right ovary/testis → right gonadal vein → IVC.  
 Because the left spermatic vein enters the left renal vein at a 90° angle, flow is less laminar on left than on right → left venous pressure > right venous pressure → varicocele more common on the left.

“Left gonadal vein takes the longer way.”

**Lymphatic drainage**

Ovaries/testes/fundus of uterus → para-aortic lymph nodes.  
 Body of uterus/cervix/superior part of bladder → external iliac nodes.  
 Prostate/cervix/corpus cavernosum/proximal vagina → internal iliac nodes.  
 Distal vagina/vulva/scrotum/distal anus → superficial inguinal nodes.  
 Clitoris/glans penis → deep inguinal nodes.

**Female reproductive anatomy**

LIGAMENT	CONNECTS	STRUCTURES CONTAINED	NOTES
<b>Infundibulopelvic (suspensory) ligament</b>	Ovaries to lateral pelvic wall	Ovarian vessels	Ureter courses retroperitoneally, close to gonadal vessels → ligation of ovarian vessels during oophorectomy presents risk to ureter
<b>Cardinal (transverse cervical) ligament</b>	Cervix to side wall of pelvis	Uterine vessels	Ligation of uterine vessels during hysterectomy presents risk to ureter
<b>Round ligament of the uterus</b>	Uterine horn to labia majora		Derivative of gubernaculum. Travels through <b>round</b> inguinal canal; above the artery of Sampson
<b>Broad ligament</b>	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
<b>Ovarian ligament</b>	Medial pole of ovary to uterine horn		Derivative of gubernaculum Ovarian ligament latches to lateral uterus

**Adnexal torsion**

Twisting of ovary and fallopian tube around infundibulopelvic ligament and ovarian ligament → compression of ovarian vessels in infundibulopelvic ligament → blockage of lymphatic and venous outflow. Continued arterial perfusion → ovarian edema → complete blockage of arterial inflow → necrosis, local hemorrhage. Associated with ovarian masses. Presents with acute pelvic pain, adnexal mass, nausea/vomiting. Surgical emergency.

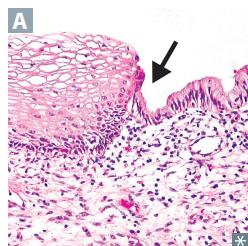
**Pelvic organ prolapse**

Herniation of pelvic organs to or beyond the vaginal walls (anterior, posterior) or apex. Associated with multiparity, ↑ age, obesity. Presents with pelvic pressure, tissue protrusion from vagina, urinary frequency, constipation, sexual dysfunction.

- Anterior compartment prolapse—bladder (cystocele). Most common.
- Posterior compartment prolapse—rectum (rectocele) or small bowel (enterocele).
- Apical compartment prolapse—uterus, cervix, or vaginal vault.

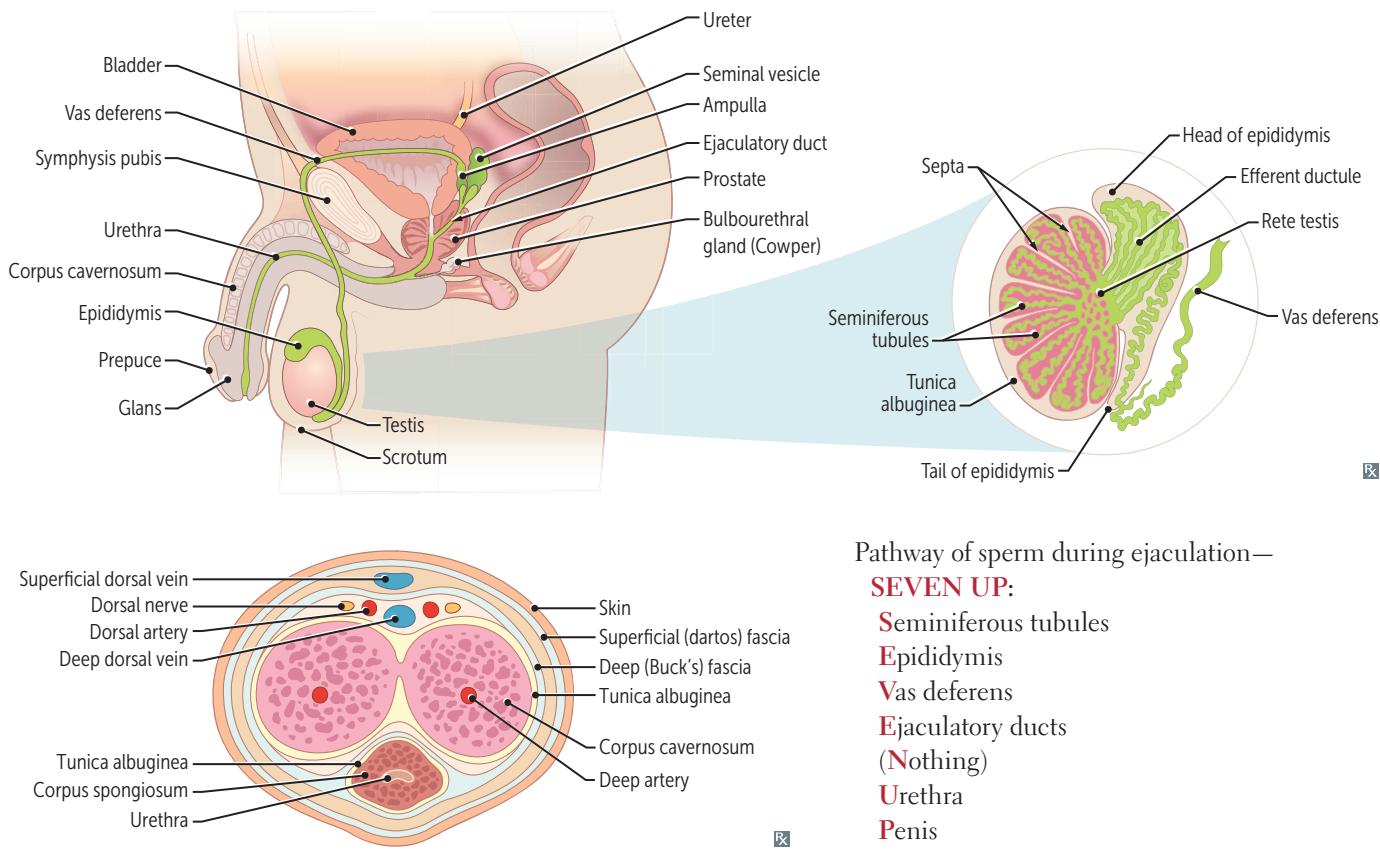
**Uterine procidentia**—herniation involving all 3 compartments.

### Female reproductive epithelial histology



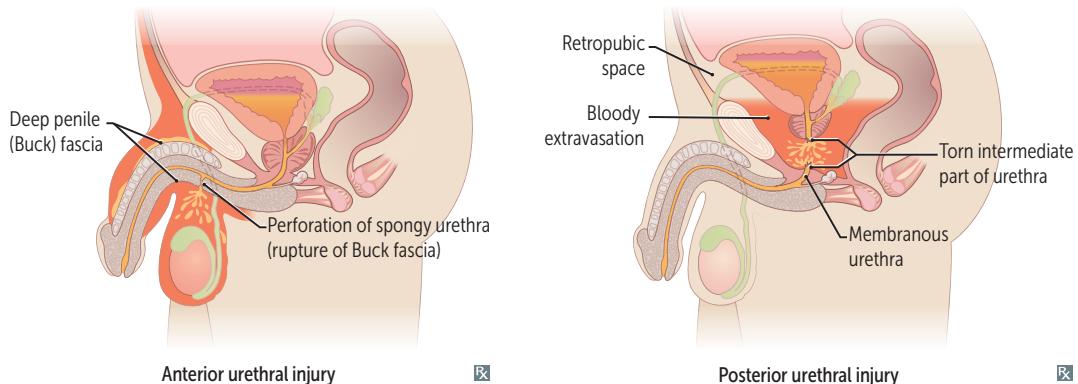
TISSUE	HISTOLOGY/NOTES
Vulva	Stratified squamous epithelium
Vagina	Stratified squamous epithelium, nonkeratinized
Ectocervix	Stratified squamous epithelium, nonkeratinized
Transformation zone	Squamocolumnar junction <b>A</b> (most common area for cervical cancer; sampled in Pap test)
Endocervix	Simple 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

<b>Genitourinary trauma</b>	Most commonly due to blunt trauma (eg, motor vehicle collision).
<b>Renal injury</b>	Presents with bruises, flank pain, hematuria. Caused by direct blows or lower rib fractures.
<b>Bladder injury</b>	Presents with hematuria, suprapubic pain, difficulty voiding. <ul style="list-style-type: none"> <li>▪ Superior bladder wall (dome) injury—direct trauma to full bladder (eg, seatbelt) → abrupt ↑ intravesical pressure → dome rupture (weakest part) → intraperitoneal urine accumulation. Peritoneal absorption of urine → ↑ BUN, ↑ creatinine.</li> <li>▪ Anterior bladder wall or neck injury—pelvic fracture → perforation by bony spicules → extraperitoneal urine accumulation (retropubic space).</li> </ul>
<b>Urethral injury</b>	Occurs almost exclusively in males. Presents with blood at urethral meatus, hematuria, difficulty voiding. Urethral catheterization is relatively contraindicated. <ul style="list-style-type: none"> <li>▪ Anterior urethral injury—perineal straddle injury → disruption of bulbous (spongy) urethra → scrotal hematoma. If Buck fascia is torn, urine escapes into perineal space.</li> <li>▪ Posterior urethral injury—pelvic fracture → disruption at bulbomembranous junction (weakest part) → urine leakage into retropubic space and high-riding prostate.</li> </ul>



### Autonomic innervation of male sexual response

Erection—parasympathetic nervous system (pelvic splanchnic nerves, S2-S4):

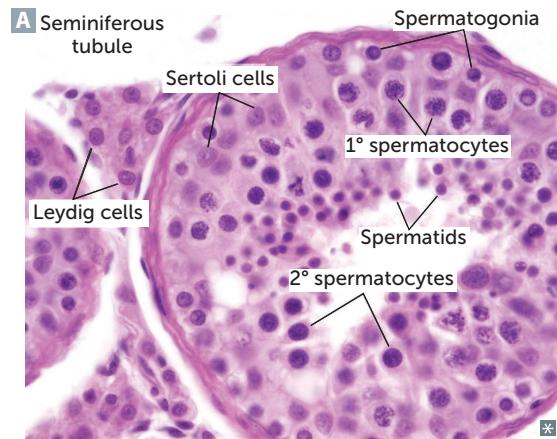
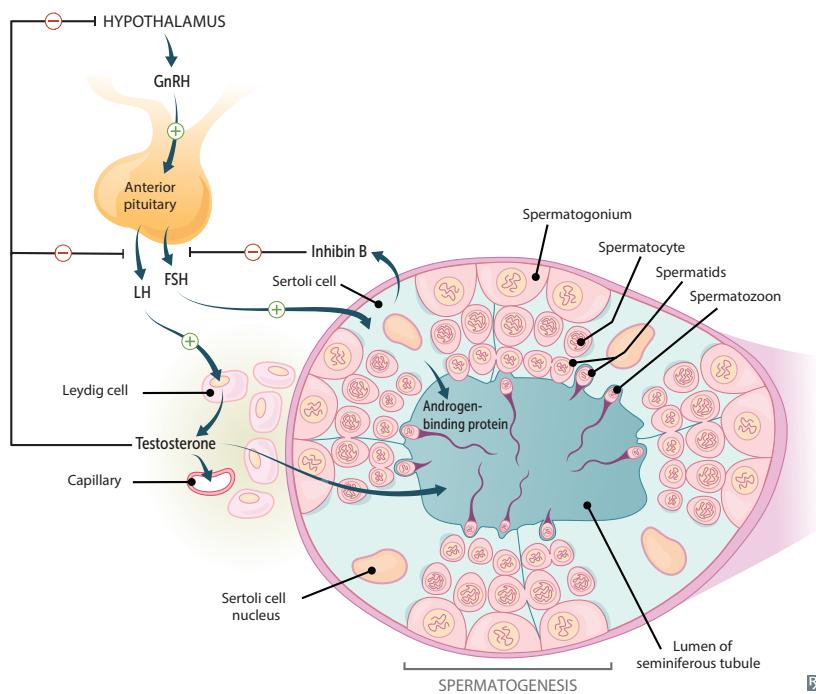
- NO → ↑ cGMP → smooth muscle relaxation → vasodilation → proerectile.
- Norepinephrine → ↑  $[Ca^{2+}]_{in}$  → smooth muscle contraction → vasoconstriction → antierectile.

Emission—sympathetic nervous system (hypogastric nerve, T11-L2).
Expulsion—visceral and somatic nerves (pudendal nerve).

Point, squeeze, and shoot.  
S2, 3, 4 keep the penis off the floor.  
PDE-5 inhibitors (eg, sildenafil) → ↓ cGMP breakdown.

**Seminiferous tubules**

CELL	FUNCTION	LOCATION/NOTES
<b>Spermatogonia</b>	Maintain germ cell pool and produce 1° spermatocytes	Line seminiferous tubules <b>A</b> Germ cells
<b>Sertoli cells</b>	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 Non-germ cells Convert testosterone and androstenedione to estrogens via aromatase <b>Sertoli cells are temperature sensitive, line seminiferous tubules, support sperm synthesis, and inhibit FSH</b> Homolog of female granulosa cells
<b>Leydig cells</b>	Secrete testosterone in the presence of LH; testosterone production unaffected by temperature	↑ temperature seen in varicocele, cryptorchidism Interstitial Endocrine cells Homolog of female theca interna cells



## ► REPRODUCTIVE—PHYSIOLOGY

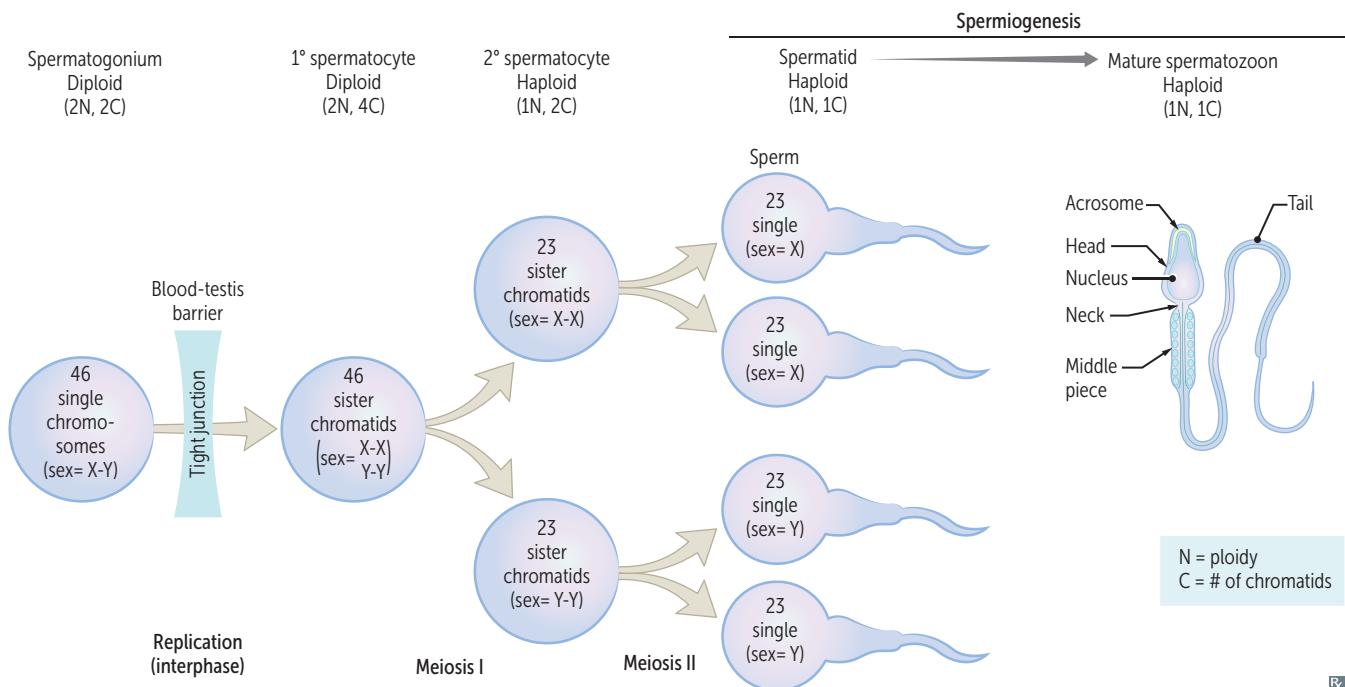
**Spermatogenesis**

Begins at puberty with spermatogonia. Full development takes 2 months. Occurs in seminiferous tubules. Produces spermatids that undergo spermogenesis (loss of cytoplasmic contents, gain of acrosomal cap) to form mature spermatozoa.

“Gonium” is going to be a sperm; “zoon” is “zooming” to egg.

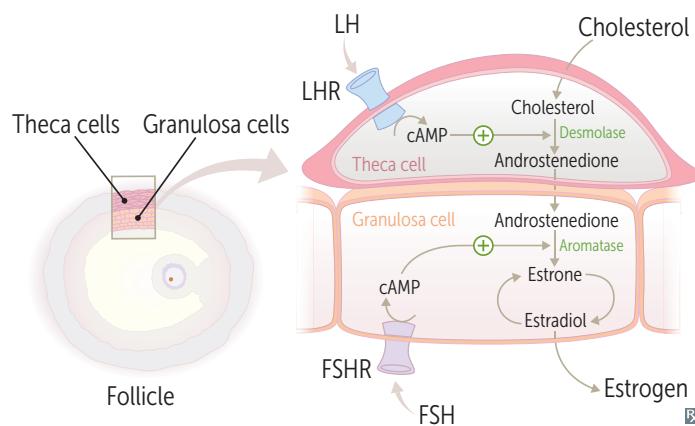
Tail mobility impaired in ciliary dyskinesia/Kartagener syndrome → infertility.

Tail mobility normal in cystic fibrosis (in CF, absent vas deferens → infertility).



**Estrogen**

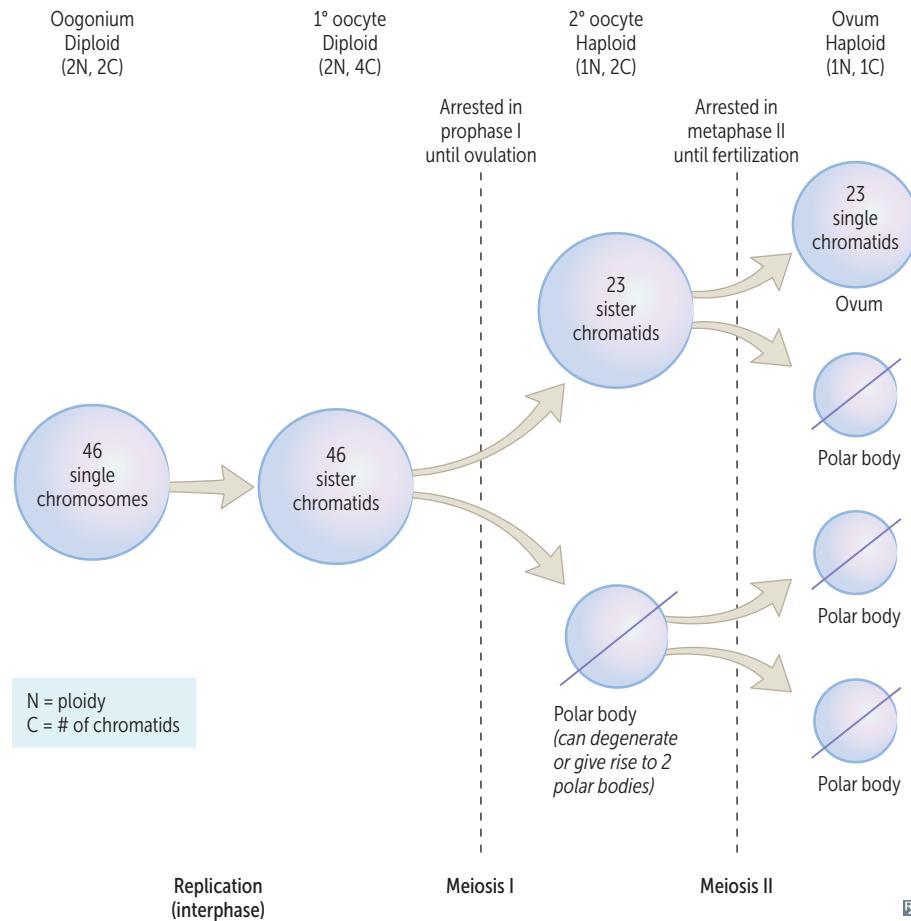
SOURCE	Ovary (17 $\beta$ -estradiol), placenta (estriol), adipose tissue (estrone via aromatization).	Potency: estradiol > estrone > estriol.
FUNCTION	<p>Development of internal/external genitalia, breasts, female fat distribution.</p> <p>Growth of follicle, endometrial proliferation, ↑ myometrial excitability.</p> <p>Upregulation of estrogen, LH, and progesterone receptors; feedback inhibition of FSH and LH, then LH surge; stimulation of prolactin secretion, ↓ prolactin action on breasts.</p> <p>↑ transport proteins, SHBG; ↑ HDL; ↓ LDL.</p>	<p>Pregnancy:</p> <ul style="list-style-type: none"> <li>50-fold ↑ in estradiol and estrone</li> <li>1000-fold ↑ in estriol (indicator of fetal well-being)</li> </ul> <p>Estrogen receptors expressed in cytoplasm; translocate to nucleus when bound by estrogen.</p>

**Progesterone**

SOURCE	Corpus luteum, placenta, adrenal cortex, testes.	Fall in estrogen and progesterone after delivery disinhibits prolactin → lactation. ↑ progesterone is indicative of ovulation.
FUNCTION	<p>During luteal phase, prepares uterus for implantation of fertilized egg:</p> <ul style="list-style-type: none"> <li>Stimulation of endometrial glandular secretions and spiral artery development</li> <li>Production of thick cervical mucus → inhibits sperm entry into uterus</li> <li>Prevention of endometrial hyperplasia</li> <li>↑ body temperature</li> <li>↓ estrogen receptor expression</li> <li>↓ gonadotropin (LH, FSH) secretion</li> </ul> <p>During pregnancy:</p> <ul style="list-style-type: none"> <li>Maintenance of pregnancy</li> <li>↓ myometrial excitability → ↓ contraction frequency and intensity</li> <li>↓ prolactin action on breasts</li> </ul>	<p><b>Progesterone is pro-gestation.</b></p> <p><b>Prolactin is pro-lactation.</b></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 metaphase II until fertilization (2° oocytes). “An egg met a sperm.” If fertilization does not occur within 1 day, the 2° oocyte degenerates.

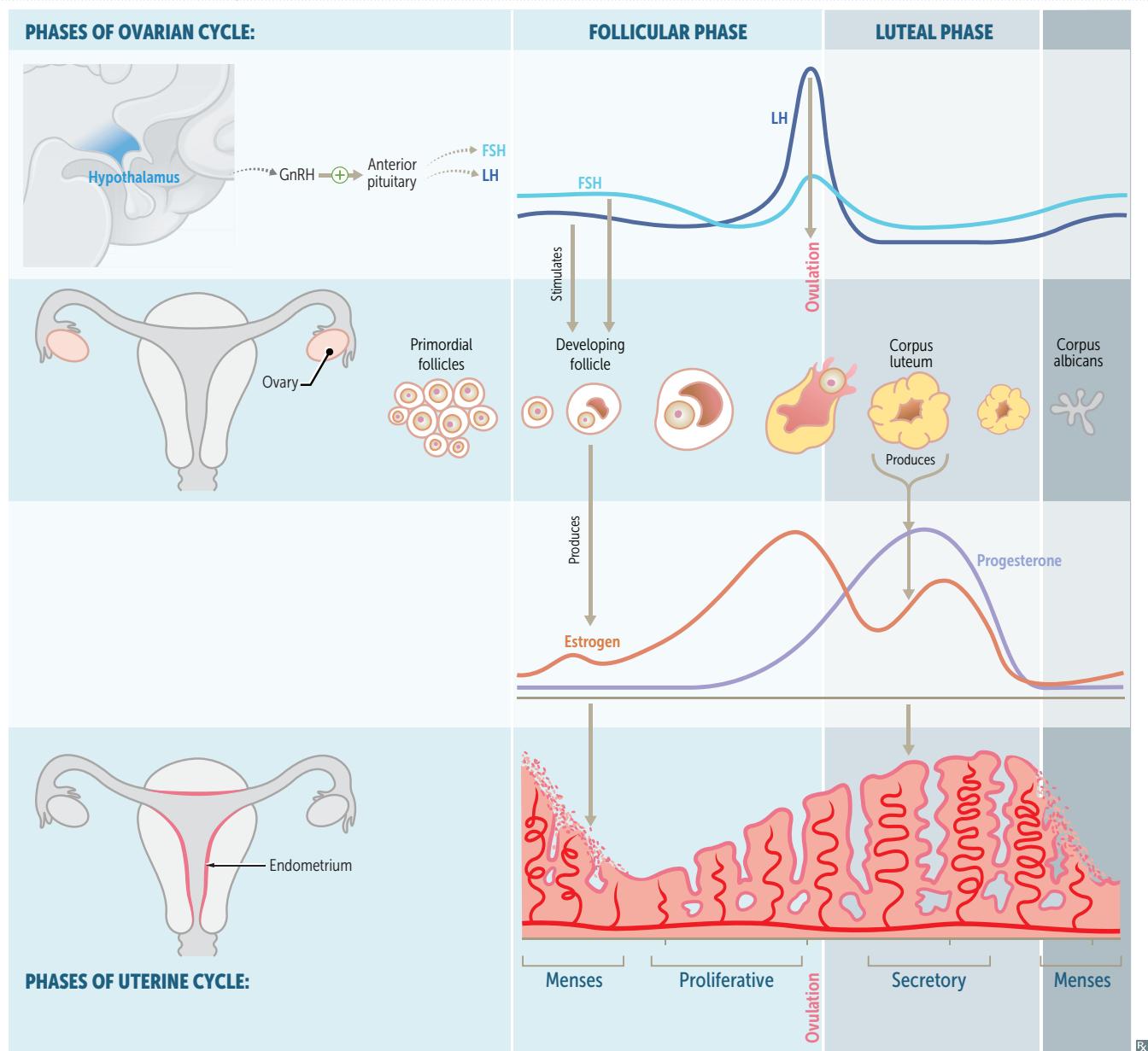
**Ovulation**

↑ estrogen, ↑ GnRH receptors on anterior pituitary. Estrogen rise then stimulates LH surge → 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 fluctuate in length.  
 Follicular growth is fastest during 2nd week of the follicular phase.  
 Luteal phase is a fixed 14 days, after which menstruation occurs.  
 Estrogen stimulates endometrial proliferation.  
 Progesterone maintains endometrium to support implantation.  
 $\downarrow$  progesterone  $\rightarrow$   $\downarrow$  fertility.



**Abnormal uterine bleeding**

Characterized as either heavy menstrual bleeding (AUB/HMB) or intermenstrual bleeding (AUB/IMB).

These are further subcategorized by **PALM-COEIN**:

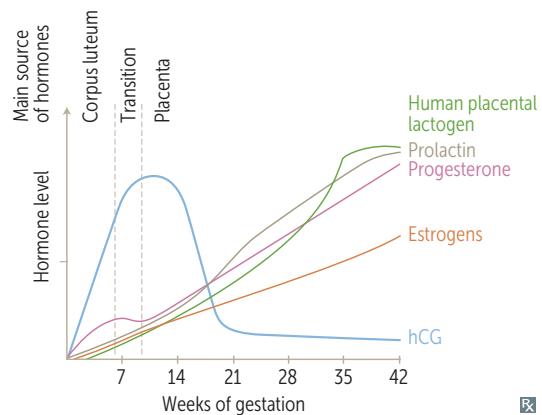
- Structural causes (**PALM**): **Polyp**, **Adenomyosis**, **Leiomyoma**, or **Malignancy/hyperplasia**
- Non-structural causes (**COEIN**): **Coagulopathy**, **Ovulatory**, **Endometrial**, **Iatrogenic**, **Not yet classified**

Terms such as dysfunctional uterine bleeding, menorrhagia, oligomenorrhea are no longer recommended.

**Pregnancy**

Fertilization (conception) most commonly occurs in upper end of fallopian tube (the ampulla). Occurs within 1 day of ovulation. Implantation in the uterine wall occurs 6 days after fertilization. Syncytiotrophoblasts secrete hCG, which is detectable in blood 1 week after fertilization and on home urine tests 2 weeks after fertilization. Embryonic/developmental age—time since fertilization. Used in embryology. Gestational age—time since first day of last menstrual period. Used clinically. Gravidity (“gravida”)—number of pregnancies. Parity (“para”)—number of pregnancies that resulted in live births.

Placental hormone secretion generally increases over the course of pregnancy, but hCG peaks at 8–10 weeks of gestation.

**Physiologic changes in pregnancy**

Changes that nurture the developing fetus and prepare the pregnant patient for labor and delivery. Mediated by ↑ hormones (eg, estrogen, progesterone) and mechanical effects of gravid uterus.

**CARDIOVASCULAR**

↓ SVR (↓ afterload) and ↑ blood volume (↑ preload) → ↑ SV → ↑ CO → ↑ placental perfusion. ↑ HR is the major contributor to ↑ CO in late pregnancy. Hemodilution → ↓ oncotic pressure → peripheral edema.

**ENDOCRINE**

Insulin resistance and hypoglycemia → ↑ lipolysis and fat utilization (to preserve glucose and amino acids for fetus). Pituitary enlargement (lactotroph hyperplasia). ↑ TBG, ↑ CBG, ↑ SHBG.

**GASTROINTESTINAL**

↓ GI motility, ↓ LES tone, gallbladder stasis; predispose to constipation, GERD, gallstones.

**HEMATOLOGIC**

Dilutional anemia (↑↑ plasma volume, ↑ RBC mass), hypercoagulable state (to ↓ blood loss at delivery). ↑ micronutrient requirements predispose to deficiency (eg, iron, folate).

**MUSCULOSKELETAL**

Lordosis (to realign gravity center), joint laxity (to facilitate fetal descent).

**SKIN**

Hyperpigmentation (eg, melasma, linea nigra, areola darkening), striae gravidarum (stretch marks), vascular changes (eg, spider angiomas, palmar erythema, varicosities).

**RENAL**

Vasodilation → ↑ renal plasma flow → ↑ GFR → ↓ BUN and ↓ creatinine. Mild glucosuria, proteinuria. Ureter and renal pelvis dilation (hydroureter and hydronephrosis) predisposes to pyelonephritis.

**RESPIRATORY**

Respiratory center stimulation → chronic hyperventilation (to ↑ fetal CO<sub>2</sub> elimination).

**Human chorionic gonadotropin**

SOURCE	Syncytiotrophoblast of placenta.
FUNCTION	Maintains corpus luteum (and thus progesterone) for first 8–10 weeks of gestation by acting like LH (otherwise no luteal cell stimulation → abortion). Luteal-placental shift is complete after 8–10 weeks; placenta synthesizes its own estriol and progesterone and corpus luteum degenerates. Used to detect pregnancy because it appears early in urine (see above). Has identical $\alpha$ subunit as LH, FSH, TSH (states of ↑ hCG can cause hyperthyroidism). $\beta$ subunit is unique (pregnancy tests detect $\beta$ subunit). hCG is ↑ in multiple gestations, hydatidiform moles, choriocarcinomas, and Down syndrome; hCG is ↓ in ectopic/failing pregnancy, Edwards syndrome, and Patau syndrome.

**Human placental lactogen**

SOURCE	Syncytiotrophoblast of placenta.
FUNCTION	Stimulates insulin production; overall ↑ insulin resistance. Gestational diabetes can occur if pancreatic function cannot overcome the insulin resistance.

**Apgar score**

	Score 2	Score 1	Score 0
<b>A</b> pppearance	 Pink	 Extremities blue	 Pale or blue
<b>P</b> ulse	≥ 100 bpm	< 100 bpm	No pulse
<b>G</b> rimace	Cries and pulls away	Grimaces or weak cry	No response to stimulation
<b>A</b> ctivity	 Active movement	 Arms, legs flexed	 No movement
<b>R</b> espiration	Strong cry	Slow, irregular	No breathing 

Assessment of newborn vital signs following delivery via a 10-point scale evaluated at 1 minute and 5 minutes. **Apgar** score is based on **a**ppearance, **p**ulse, **g**rimace, **a**ctivity, and **r**espiration. Apgar scores < 7 may require further evaluation. If Apgar score remains low at later time points, there is ↑ risk the child will develop long-term neurologic damage.

**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.

**Lactation**

After parturition and delivery of placenta, rapid ↓ in estrogen and progesterone disinhibits prolactin → initiation of lactation. Suckling is required to maintain milk production and ejection, since ↑ nerve stimulation → ↑ oxytocin and prolactin.

Prolactin—induces and maintains lactation and ↓ reproductive function.

Oxytocin—assists in milk letdown; also promotes uterine contractions.

Breast milk is the ideal nutrition for infants < 6 months old. Contains 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. Guidelines recommend exclusively breastfed infants get vitamin D and possibly iron supplementation.

Breastfeeding facilitates bonding with the child. Breastfeeding or donating milk ↓ risk of breast and ovarian cancers.

**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 people who smoke tobacco).

Usually preceded by 4–5 years of abnormal menstrual cycles. Source of estrogen (estrone) after menopause becomes peripheral conversion of androgens, ↑ androgens → hirsutism.

↑↑ FSH is specific for menopause (loss of negative feedback on FSH due to ↓ estrogen).

Hormonal changes: ↓ estrogen, ↑↑ FSH, ↑ LH (no surge), ↑ GnRH.

Causes **HAVOCs:** Hot flashes (most common), Atrophy of the Vagina, Osteoporosis, Coronary artery disease, Sleep disturbances.

Menopause before age 40 suggests 1° ovarian insufficiency (premature ovarian failure); may occur in females who have received chemotherapy and/or radiation therapy.

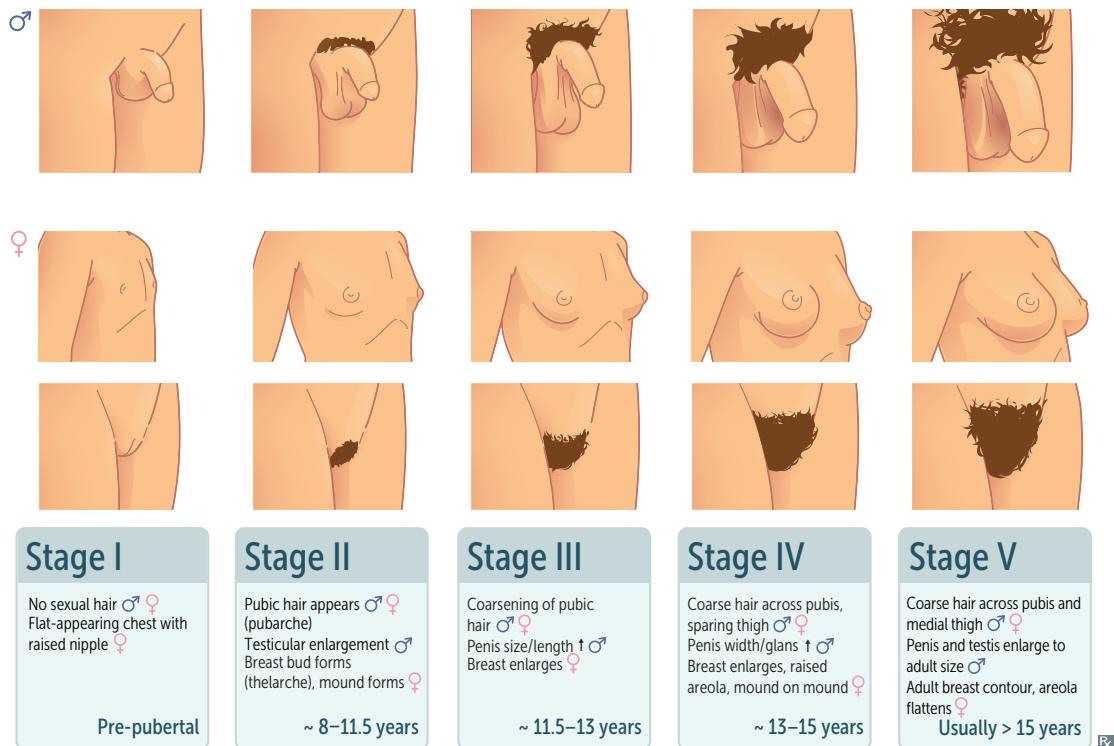
**Androgens**

Testosterone, dihydrotestosterone (DHT), androstenedione.

SOURCE	DHT and testosterone (testis), <b>androstenedione (adrenal)</b>	Potency: DHT > testosterone > androstenedione.
FUNCTION	<p>Testosterone:</p> <ul style="list-style-type: none"> <li>▪ Differentiation of epididymis, vas deferens, seminal vesicles (internal genitalia, except prostate)</li> <li>▪ Growth spurt: penis, seminal vesicles, sperm, muscle, RBCs</li> <li>▪ Deepening of voice</li> <li>▪ Closing of epiphyseal plates (via estrogen converted from testosterone)</li> <li>▪ Libido</li> </ul> <p>DHT:</p> <ul style="list-style-type: none"> <li>▪ Early—differentiation of penis, scrotum, prostate</li> <li>▪ Late—prostate growth, balding, sebaceous gland activity</li> </ul>	<p>Testosterone is converted to DHT by 5α-reductase, which is inhibited by finasteride. In the male, <b>androgens</b> are converted to <b>estrogens</b> by <b>aromatase</b> (primarily in adipose tissue and testes).</p> <p><b>Anabolic-androgenic steroid use</b>—↑ fat-free mass, muscle strength, performance. Suspect in males who present with changes in behavior (eg, aggression), acne, gynecomastia, ↑ Hb and Hct, small testes (exogenous testosterone → hypothalamic-pituitary-gonadal axis inhibition → ↓ intratesticular testosterone → ↓ testicular size, ↓ sperm count, azoospermia). Females may present with virilization (eg, hirsutism, acne, breast atrophy, male pattern baldness).</p>

### Tanner stages of sexual development

Tanner stage is assigned independently to genitalia, pubic hair, and breast (eg, a person can have Tanner stage 2 genitalia, Tanner stage 3 pubic hair). Earliest detectable secondary sexual characteristic is breast bud development in females, testicular enlargement in males.



### Precocious puberty

Appearance of 2° sexual characteristics (eg, adrenarche, thelarche, menarche) before age 8 years in females and 9 years in males. ↑ sex hormone exposure or production → ↑ linear growth, somatic and skeletal maturation (eg, premature closure of epiphyseal plates → short stature). Types include:

- Central precocious puberty (↑ GnRH secretion): idiopathic (most common; early activation of hypothalamic-pituitary gonadal axis), CNS tumors.
- Peripheral precocious puberty (GnRH-independent; ↑ sex hormone production or exposure to exogenous sex steroids): congenital adrenal hyperplasia, estrogen-secreting ovarian tumor (eg, granulosa cell tumor), Leydig cell tumor, McCune-Albright syndrome.

## ► REPRODUCTIVE—PATHOLOGY

**Sex chromosome disorders****Klinefelter syndrome**

Aneuploidy most commonly due to meiotic nondisjunction.

Male, 47,XXY.

Testicular atrophy (small, firm testes), tall stature with eunuchoid proportions (delayed epiphyseal closure → ↑ long bone length), gynecomastia, female hair distribution **A**. May present with developmental delay. Presence of inactivated X chromosome (Barr body). Common cause of hypogonadism seen in infertility workup. ↑ risk of breast cancer.

Dysgenesis of seminiferous tubules

→ ↓ inhibin B → ↑ FSH.

Abnormal Leydig cell function → ↓ testosterone  
→ ↑ LH → ↑ estrogen.

**Turner syndrome**

Female, 45,XO.

Short stature (associated with *SHOX* gene, preventable with growth hormone therapy), ovarian dysgenesis (streak ovary), shield chest **B**, bicuspid aortic valve, coarctation of the aorta (femoral < brachial pulse), lymphatic defects (result in webbed neck or cystic hygroma; lymphedema in feet, hands), horseshoe kidney, high-arched palate, shortened 4th metacarpals.

Most common cause of 1° amenorrhea. No Barr body.

Menopause before menarche.

↓ estrogen leads to ↑ LH, FSH.

Sex chromosome (X, or rarely Y) loss often due to nondisjunction during meiosis or mitosis.

Meiosis errors usually occur in paternal gametes  
→ sperm missing the sex chromosome.

Mitosis errors occur after zygote formation → loss of sex chromosome in some but not all cells  
→ mosaic karyotype (eg. 45,X/46XX).

(45,X/46,XY) mosaicism associated with increased risk for gonadoblastoma.

Pregnancy is possible in some cases (IVF, exogenous estradiol-17 $\beta$  and progesterone).

**Double Y males**

47, XYY.

Phenotypically normal (usually undiagnosed), very tall. Normal fertility. May be associated with severe acne, learning disability, autism spectrum disorders.

**Ovotesticular disorder 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
	↓	↑	Hypergonadotropic hypogonadism (1°)
	↓	↓	Hypogonadotropic hypogonadism (2°)

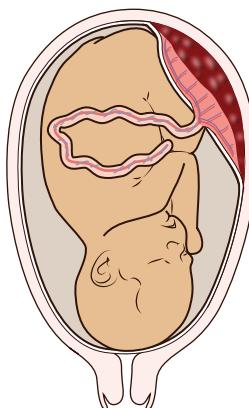
Other disorders of sex development	Disagreement between the phenotypic sex (external genitalia, influenced by hormonal levels) and the gonadal sex (testes vs ovaries, corresponds with Y chromosome). Formerly called hermaphroditism and pseudohermaphroditism; now most commonly referred to as intersex.												
46,XX DSD	Ovaries present, but external genitalia are virilized or ambiguous. Due to excessive and inappropriate exposure to androgenic steroids during early gestation (eg, congenital adrenal hyperplasia or exogenous administration of androgens during pregnancy).												
46,XY DSD	Testes present, but external genitalia are female or ambiguous. Most common form is androgen insensitivity syndrome (testicular feminization).												
Disorders by physical characteristics	<table border="1"> <thead> <tr> <th>UTERUS</th> <th>BREASTS</th> <th>DISORDERS</th> </tr> </thead> <tbody> <tr> <td>+</td> <td>-</td> <td>Hypergonadotropic hypogonadism (eg, Turner syndrome, genetic mosaicism, pure gonadal dysgenesis) Hypogonadotropic hypogonadism (eg, CNS lesions, Kallmann syndrome)</td> </tr> <tr> <td>-</td> <td>+</td> <td>Uterovaginal agenesis in genotypic female or androgen insensitivity in genotypic male</td> </tr> <tr> <td>-</td> <td>-</td> <td>Male genotype with insufficient production of testosterone</td> </tr> </tbody> </table>	UTERUS	BREASTS	DISORDERS	+	-	Hypergonadotropic hypogonadism (eg, Turner syndrome, genetic mosaicism, pure gonadal dysgenesis) Hypogonadotropic hypogonadism (eg, CNS lesions, Kallmann syndrome)	-	+	Uterovaginal agenesis in genotypic female or androgen insensitivity in genotypic male	-	-	Male genotype with insufficient production of testosterone
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<b>Placental aromatase deficiency</b>	Inability to synthesize estrogens from androgens. Masculinization of female (46,XX DSD) infants (ambiguous genitalia), ↑ serum testosterone and androstenedione. Can present with virilization of pregnant patient (fetal androgens cross the placenta).
<b>Androgen insensitivity syndrome</b>	Defect in androgen receptor resulting in female-appearing genetic male (46,XY DSD); female external genitalia with scant axillary and pubic hair, rudimentary vagina; uterus and fallopian tubes absent due to persistence of anti-Müllerian hormone from testes. Patients develop normal functioning testes (often found in labia majora; surgically removed to prevent malignancy). ↑ testosterone, estrogen, LH (vs sex chromosome disorders).
<b>5α-reductase deficiency</b>	Autosomal recessive; sex limited to genetic males (46,XY DSD). Inability to convert testosterone to DHT. Ambiguous genitalia until puberty, when ↑ testosterone causes masculinization/↑ growth of external genitalia. Testosterone/estrogen levels are normal; LH is normal or ↑. Internal genitalia are normal.
<b>Kallmann syndrome</b>	Failure to complete puberty; a form of hypogonadotropic hypogonadism. Defective migration of neurons and subsequent failure of olfactory bulbs to develop → ↓ synthesis of GnRH in the hypothalamus; hyposmia/anosmia; ↓ GnRH, FSH, LH, testosterone. Infertility (low sperm count in males; amenorrhea in females).

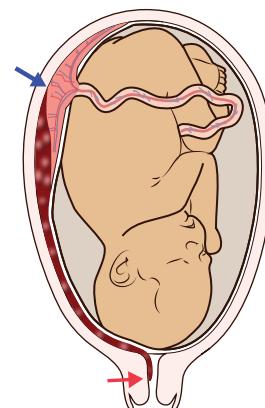
### Pregnancy complications

#### Abruptio placentae

Premature separation (partial or complete) of placenta from uterine wall before delivery of infant. Risk factors: trauma (eg, motor vehicle accident), smoking, hypertension, preeclampsia, cocaine use. Presentation: **abrupt**, painful bleeding (concealed or apparent) in third trimester; possible DIC (mediated by tissue factor activation), shock, fetal distress. May be life threatening for patient and fetus.



Complete abruption with concealed hemorrhage



Partial abruption (blue arrow) with apparent hemorrhage (red arrow)

#### Placenta accreta spectrum

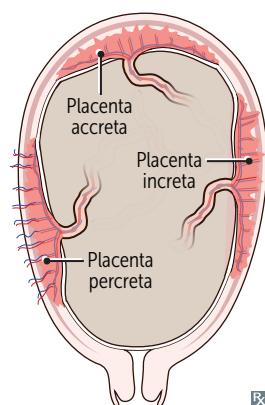
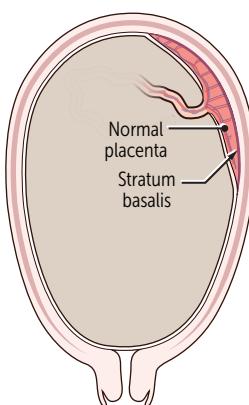
Defective decidual layer → abnormal attachment and separation after delivery. Risk factors: prior C-section or uterine surgery involving myometrium, inflammation, placenta previa, advanced age during pregnancy, multiparity. Three types distinguishable by the depth of penetration:

**Placenta accreta**—placenta **attaches** to myometrium without penetrating it; most common type.

**Placenta increta**—placenta penetrates **into** myometrium.

**Placenta percreta**—placenta penetrates (“**perforates**”) through myometrium and into uterine serosa (invades entire uterine wall); can result in placental attachment to rectum or bladder (can result in hematuria).

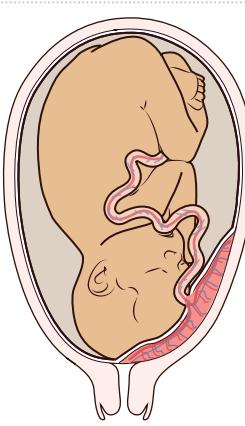
Presentation: often detected on ultrasound prior to delivery. No separation of placenta after delivery → postpartum hemorrhage (can cause Sheehan syndrome).



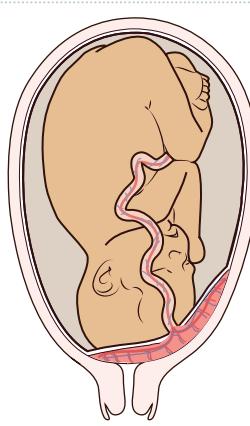
#### Placenta previa

Attachment of placenta over internal cervical os. Risk factors: multiparity, prior C-section. Associated with painless third-trimester bleeding. A “**preview**” of the **placenta** is visible through cervix.

Low-lying placenta is located < 2 cm from, but not covering, the internal cervical os.



Partial placenta previa

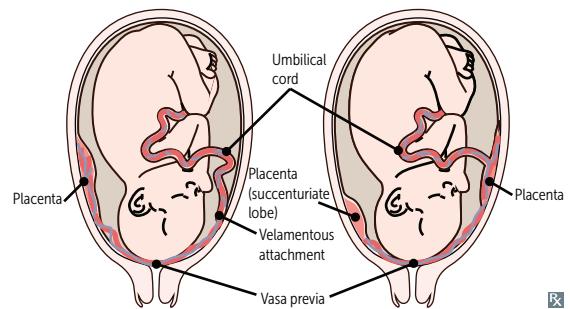


Complete placenta previa

### 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**: tone (uterine atony → soft, boggy uterus; most common), trauma (lacerations, incisions, uterine rupture), thrombin (coagulopathy), tissue (retained products of conception).

Treatment: uterine massage, oxytocin. If refractory, surgical ligation of uterine or internal iliac artery (will preserve fertility since ovarian arteries provide collateral circulation).

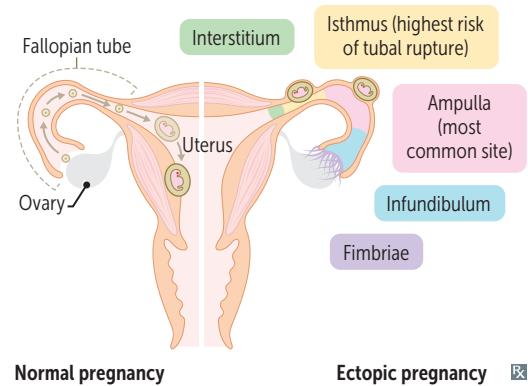
#### Ectopic pregnancy

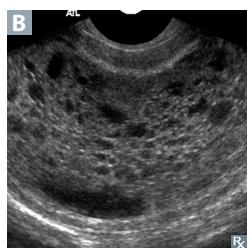
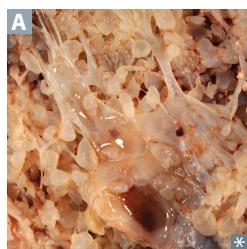


Implantation of fertilized ovum in a site other than the uterus, most often in ampulla of fallopian tube **A**. Risk factors: tubal pathologies (eg, scarring from salpingitis [PID] or surgery), previous ectopic pregnancy, IUD, IVF.

Presents with first-trimester bleeding and/or lower abdominal pain. Often clinically mistaken for appendicitis. Suspect in patients with history of amenorrhea, lower-than-expected rise in hCG based on dates. Confirm with ultrasound, which may show extraovarian adnexal mass.

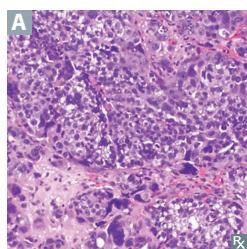
Treatment: methotrexate, surgery.



**Hydatidiform mole**

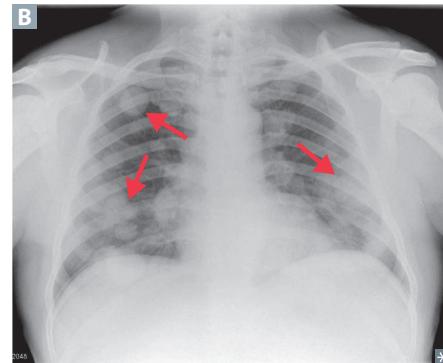
Cystic swelling of chorionic villi and proliferation of chorionic epithelium (only trophoblast).  
Presents with vaginal bleeding, emesis, uterine enlargement more than expected, pelvic pressure/pain. Associated with hCG-mediated sequelae: early preeclampsia (before 20 weeks of gestation), theca-lutein cysts, hyperemesis gravidarum, hyperthyroidism.  
Treatment: dilation and curettage +/- methotrexate. Monitor hCG.

	<b>Complete mole</b>	<b>Partial mole</b>
<b>KARYOTYPE</b>	46,XX (most common); 46,XY	69,XXX; 69,XXY; 69,XYY
<b>COMPONENTS</b>	Most commonly enucleated egg + single sperm (subsequently duplicates paternal DNA)	2 sperm + 1 egg
<b>HISTOLOGY</b>	Hydropic villi, circumferential and diffuse trophoblastic proliferation	Only some villi are hydropic, focal/minimal trophoblastic proliferation
<b>FETAL PARTS</b>	No	Yes ( <b>partial</b> = fetal <b>parts</b> )
<b>STAINING FOR P57 PROTEIN</b>	⊖ (paternally imprinted)	⊕ (maternally expressed) <b>Partial mole is P57 positive</b>
<b>UTERINE SIZE</b>	↑	—
<b>hCG</b>	↑↑↑↑	↑
<b>IMAGING</b>	“Honeycombed” uterus or “clusters of grapes” <b>A</b> , “snowstorm” <b>B</b> on ultrasound	Fetal parts
<b>RISK OF INVASIVE MOLE</b>	15–20%	< 5%
<b>RISK OF CHORIOCARCINOMA</b>	2%	Rare

**Choriocarcinoma**

Rare; can develop during or after pregnancy in parent or baby. Malignancy of trophoblastic tissue **A** (cytotrophoblasts, syncytiotrophoblasts); no chorionic villi present. ↑ frequency of bilateral/multiple theca-lutein cysts. Presents with abnormal ↑ hCG, shortness of breath, hemoptysis. Hematogenous spread to lungs → “cannonball” metastases **B**.

Treatment: methotrexate.



**Hypertension in pregnancy**

<b>Gestational hypertension</b>	BP > 140/90 mm Hg after 20 weeks of gestation. No preexisting hypertension. No proteinuria or end-organ damage. Hypertension prior to 20 weeks of gestation suggests chronic hypertension. Treatment: antihypertensives ( <b>H</b> ydralazine, $\alpha$ - <b>M</b> ethyldopa, <b>L</b> abetalol, <b>n</b> ifedipine), deliver at 37–39 weeks. <b>H</b> ypertensive <b>m</b> oms <b>l</b> ove <b>n</b> ifedipine.
<b>Preeclampsia</b>	New-onset hypertension with either proteinuria or end-organ dysfunction after 20 weeks' gestation (onset of preeclampsia < 20 weeks of gestation may suggest molar pregnancy). Caused by abnormal placental spiral arteries → endothelial dysfunction, vasoconstriction, ischemia. ↑ incidence in patients with history of preeclampsia, chronic hypertension, diabetes, chronic kidney disease, autoimmune disorders (eg, antiphospholipid syndrome), age > 35 years. Complications: placental abruption, coagulopathy, renal failure, pulmonary edema, uteroplacental insufficiency; may lead to eclampsia and/or HELLP syndrome. Treatment: antihypertensives, IV magnesium sulfate (to prevent seizure); definitive is delivery.
<b>Eclampsia</b>	Preeclampsia with seizures. Death due to stroke, intracranial hemorrhage, ARDS. Treatment: IV magnesium sulfate, antihypertensives, immediate delivery.
<b>HELLP syndrome</b>	Preeclampsia with thrombotic microangiopathy of the liver. <b>H</b> emolysis, <b>E</b> levated <b>L</b> iver enzymes, <b>L</b> ow <b>P</b> latelets. May occur in the absence of hypertension and proteinuria. Blood smear shows schistocytes. Can lead to hepatic subcapsular hematomas (rupture → severe hypotension) and DIC (due to release of tissue factor from injured placenta). Treatment: immediate delivery.

**Supine hypotensive syndrome**

Also called aortocaval compression syndrome. Seen at > 20 weeks of gestation. Supine position → compression of patient's abdominal aorta and IVC by gravid uterus → ↓ placental perfusion (can lead to pregnancy loss) and ↓ venous return (hypotension).

**Gynecologic tumor epidemiology**

Incidence (US)—endometrial > ovarian > cervical; cervical cancer is more common worldwide due to lack of screening or HPV vaccination.  
Prognosis: **C**ervical (**b**est prognosis, diagnosed < 45 years old) > **E**ndometrial (middle-aged, about 55 years old) > **O**varian (**w**orst prognosis, > 65 years).

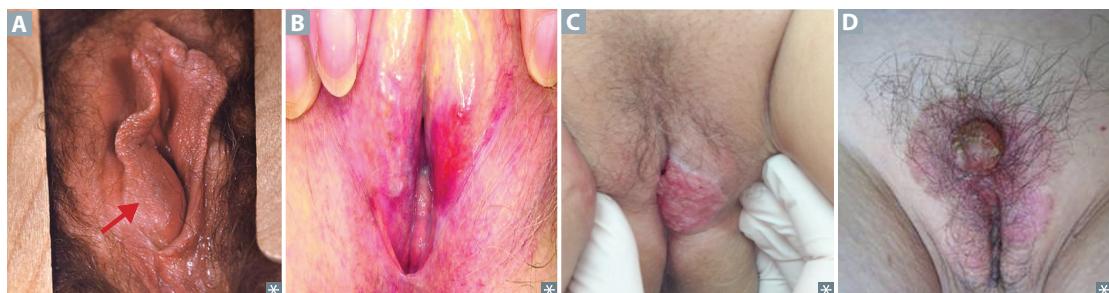
**CEOs** often go from **best** to **worst** as they get older.

**Vulvar pathology****Non-neoplastic**

<b>Bartholin cyst and abscess</b>	Due to blockage of Bartholin gland duct causing accumulation of gland fluid. May lead to abscess 2° to obstruction and inflammation <b>A</b> . Usually in reproductive-age females.
<b>Lichen sclerosus</b>	Thinning of epidermis with fibrosis/sclerosis of dermis. Presents with porcelain-white plaques with a red or violet border. Skin fragility with erosions can be observed <b>B</b> . Most common in postmenopausal females. Benign, but slightly increased risk for SCC.
<b>Lichen simplex chronicus</b>	Hyperplasia of vulvar squamous epithelium. Presents with leathery, thick vulvar skin with enhanced skin markings due to chronic rubbing or scratching. Benign, no risk of SCC.

**Neoplastic**

<b>Vulvar carcinoma</b>	Carcinoma from squamous epithelial lining of vulva <b>C</b> . Rare. Presents with leukoplakia, biopsy often required to distinguish carcinoma from other causes. HPV-related vulvar carcinoma—associated with high-risk HPV types 16, 18. Risk factors: multiple partners, early coitache. Usually in reproductive-age females. Non-HPV vulvar carcinoma—usually from long-standing lichen sclerosus. Females > 70 years old.
<b>Extramammary Paget disease</b>	Intraepithelial adenocarcinoma. Carcinoma in situ, low risk of underlying carcinoma (vs Paget disease of the breast, which is always associated with underlying carcinoma). Presents with pruritus, erythema, crusting, ulcers <b>D</b> .

**Imperforate hymen**

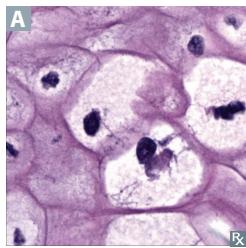
Incomplete degeneration of the central portion of the hymen. Accumulation of vaginal mucus at birth → self-resolving bulge in introitus. If untreated, leads to 1° amenorrhea, cyclic abdominal pain, hematocolpos (accumulation of menstrual blood in vagina → bulging and bluish hymenal membrane).

**Vaginal tumors**

<b>Squamous cell carcinoma</b>	Usually 2° to cervical SCC; 1° vaginal carcinoma rare.
<b>Clear cell adenocarcinoma</b>	Arises from vaginal adenosis (persistence of glandular columnar epithelium in upper 2/3 of vagina), found in females who had exposure to diethylstilbestrol in utero.
<b>Sarcoma botryoides</b>	Embryonal rhabdomyosarcoma variant. Affects females < 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, irreversible dysplasia or carcinoma in situ), depending on extent of dysplasia. Associated with HPV-16 and HPV-18, which produce both the E6 gene product (inhibits TP53) and E7 gene product (inhibits pRb) (6 before 7; P before R). Koilocytes (cells with wrinkled “raisinoid” nucleus and perinuclear halo **A**) are pathognomonic of HPV infection. May progress slowly to invasive carcinoma if left untreated. Typically asymptomatic (detected with Pap smear) or presents as abnormal vaginal bleeding (often postcoital).

Risk factors: multiple sexual partners, HPV, smoking, early coitarche, DES exposure, immunocompromise (eg, HIV, transplant).

### Invasive carcinoma

Often squamous cell carcinoma. Pap smear can detect cervical dysplasia before it progresses to invasive carcinoma. Diagnose via colposcopy and biopsy. Lateral invasion can block ureters → hydronephrosis → renal failure.

### Primary ovarian insufficiency

Also called premature ovarian failure.

Premature atresia of ovarian follicles in females of reproductive age. Most often idiopathic; associated with chromosomal abnormalities (especially in females < 30 years), autoimmunity. Need karyotype screening. Patients present with signs of menopause after puberty but before age 40. ↓ estrogen, ↑ LH, ↑ FSH.

### Most common causes of anovulation

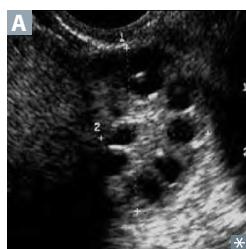
Pregnancy, polycystic ovarian syndrome, obesity, HPO axis abnormalities/immaturity, premature ovarian failure, hyperprolactinemia, thyroid disorders, eating disorders, competitive athletics, Cushing syndrome, adrenal insufficiency, chromosomal abnormalities (eg, Turner syndrome).

### Functional hypothalamic amenorrhea

Also called exercise-induced amenorrhea. Severe caloric restriction, ↑ energy expenditure, and/or stress → functional disruption of pulsatile GnRH secretion → ↓ LH, FSH, estrogen. Pathogenesis includes ↓ leptin (due to ↓ fat) and ↑ cortisol (stress, excessive exercise).

Associated with eating disorders and “female athlete triad” (↓ calorie availability/excessive exercise, ↓ bone mineral density, menstrual dysfunction).

### Polycystic ovarian syndrome



Hyperinsulinemia and/or insulin resistance hypothesized to alter hypothalamic hormonal feedback response → ↑ LH:FSH, ↑ androgens (eg, testosterone) from theca interna cells, ↓ rate of follicular maturation → unruptured follicles (cysts) + anovulation. Common cause of ↓ fertility in females.

Enlarged, bilateral cystic ovaries **A**; presents with amenorrhea/oligomenorrhea, hirsutism, acne, ↓ fertility. Associated with obesity, acanthosis nigricans. ↑ risk of endometrial cancer 2° to unopposed estrogen from repeated anovulatory cycles.

Treatment: cycle regulation via weight reduction (↓ peripheral estrone formation), OCPs (prevent endometrial hyperplasia due to unopposed estrogen); clomiphene (ovulation induction); spironolactone, finasteride, flutamide to treat hirsutism.

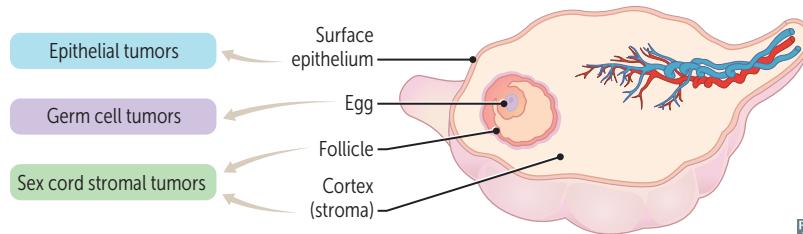
**Primary dysmenorrhea** Painful menses, caused by uterine contractions to ↓ blood loss → ischemic pain. Mediated by prostaglandins. Treatment: NSAIDs.

### Ovarian cysts

<b>Follicular cyst</b>	Distention of unruptured Graafian follicle. May be associated with hyperestrogenism, endometrial hyperplasia. Most common ovarian mass in young females.
<b>Theca lutein cyst</b>	Also called hyperreactio luteinalis. Often bilateral/multiple. Due to hCG overstimulation. Associated with choriocarcinoma and hydatidiform moles.

### Ovarian tumors

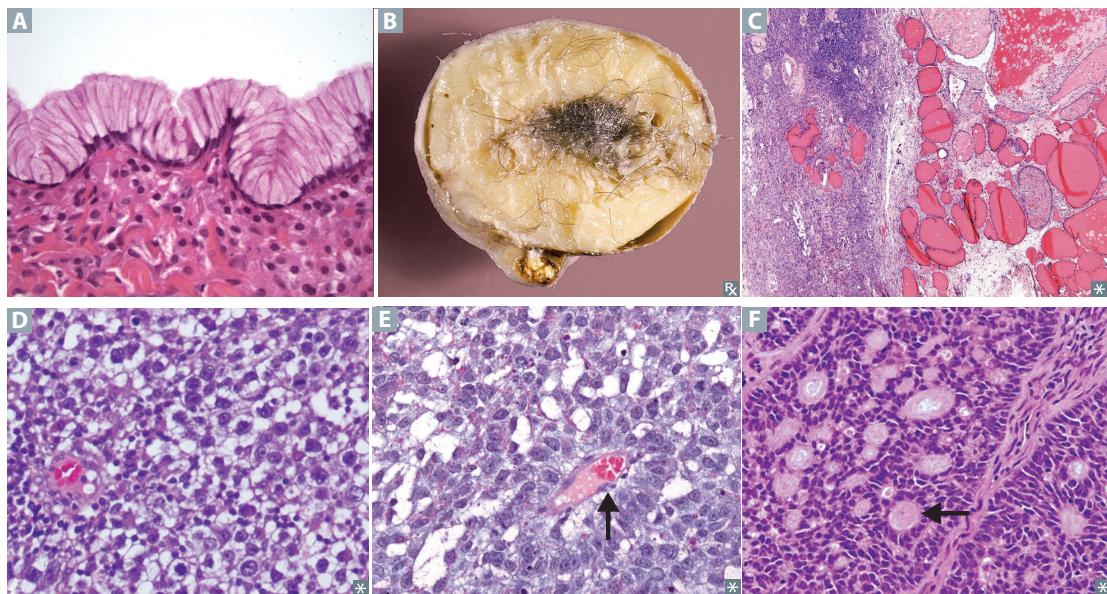
Most common adnexal mass in females > 55 years old. Present with abdominal distention, bowel obstruction, pleural effusion.  
 Risk ↑ with advanced age, infertility, endometriosis, PCOS, genetic predisposition (eg, *BRCA1* or *BRCA2* mutations, Lynch syndrome, strong family history).  
 Risk ↓ with previous pregnancy, history of breastfeeding, OCPs, tubal ligation.  
 Epithelial tumors are typically serous (lined by serous epithelium natively found in fallopian tubes, and often bilateral) or mucinous (lined by mucinous epithelium natively found in cervix). Monitor response to therapy/relapse by measuring CA 125 levels (not good for screening).  
 Germ cell tumors can differentiate into somatic structures (eg, teratomas), or extra-embryonic structures (eg, yolk sac tumors), or can remain undifferentiated (eg, dysgerminoma).  
 Sex cord stromal tumors develop from embryonic sex cord (develops into theca and granulosa cells of follicle, Sertoli and Leydig cells of seminiferous tubules) and stromal (ovarian cortex) derivatives.



TYPE	CHARACTERISTICS
<b>Epithelial tumors</b>	
<b>Serous cystadenoma</b>	Benign. Most common ovarian neoplasm.
<b>Mucinous cystadenoma</b>	Benign. Multiloculated, large. Lined by mucus-secreting epithelium <b>A</b> . Can result in pseudomyxoma peritonei intraperitoneal accumulation of mucinous material.
<b>Brenner tumor</b>	Usually benign. Solid, pale yellow-tan tumor that appears encapsulated. “Coffee <b>b</b> ean” nuclei on H&E stain.
<b>Serous carcinoma</b>	Most common malignant ovarian neoplasm. Psammoma bodies.
<b>Mucinous carcinoma</b>	Malignant. Rare. May be metastatic from appendiceal or other GI tumors.

**Ovarian tumors (continued)**

TYPE	CHARACTERISTICS
<b>Germ cell tumors</b>	
<b>Mature cystic teratoma</b>	Also called dermoid cyst. Benign. Most common ovarian tumor in young females. Cystic mass with elements from all 3 germ layers (eg, teeth, hair, sebum) <b>B</b> . May be painful 2° to ovarian enlargement or torsion. Monodermal form with thyroid tissue (struma ovarii <b>C</b> ) may present with hyperthyroidism. Malignant transformation rare (usually to squamous cell carcinoma).
<b>Immature teratoma</b>	Malignant, aggressive. Contains fetal tissue, neuroectoderm. Commonly diagnosed before age 20. Typically represented by immature/embryonic-like neural tissue.
<b>Dysgerminoma</b>	Malignant. Most common in adolescents. Equivalent to male seminoma but rarer. Sheets of uniform “fried egg” cells <b>D</b> . Tumor markers: ↑ hCG, ↑ LDH.
<b>Yolk sac tumor</b>	Also called endodermal sinus tumor. Malignant, aggressive. Yellow, friable (hemorrhagic) mass. 50% have Schiller-Duval bodies (resemble glomeruli, arrow in <b>E</b> ). Tumor marker: ↑ AFP. Occurs in <b>c</b> children and young adult females.
<b>Sex cord stromal tumors</b>	
<b>Fibroma</b>	Benign. Bundle of spindle-shaped fibroblasts.
	<b>Meigs syndrome</b> —triad of ovarian fibroma, ascites, pleural effusion. “Pulling” sensation in groin.
<b>Thecoma</b>	Benign. May produce estrogen. Usually presents as abnormal uterine bleeding in a postmenopausal female.
<b>Sertoli-Leydig cell tumor</b>	Benign. Small, grey to yellow-brown mass. Resembles testicular histology with tubules/cords lined by pink Sertoli cells. May produce androgens → virilization (eg, hirsutism, male pattern baldness, clitoral enlargement).
<b>Granulosa cell tumor</b>	Most common malignant sex cord stromal tumor. Predominantly occurs in females in their 50s. Often produces estrogen and/or progesterone. Presents with postmenopausal bleeding, endometrial hyperplasia, sexual precocity (in preadolescents), breast tenderness. Histology shows <b>Call-Exner bodies</b> (granulosa cells arranged haphazardly around collections of eosinophilic fluid, resembling primordial follicles; arrow in <b>F</b> ). Tumor marker: ↑ inhibin. “Give <b>Granny</b> a <b>Call</b> .”

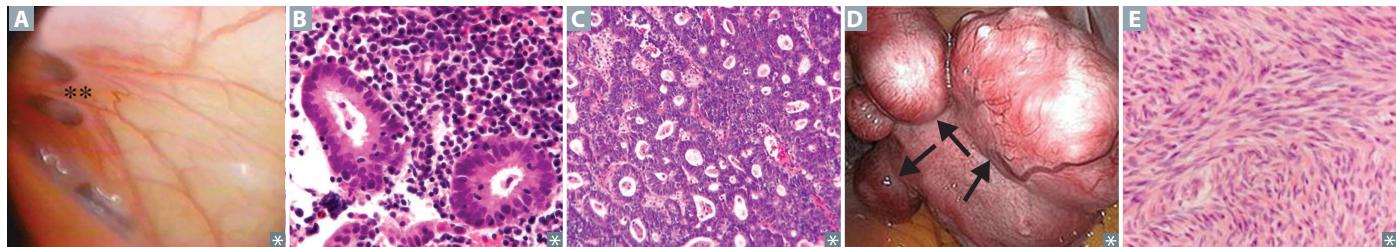


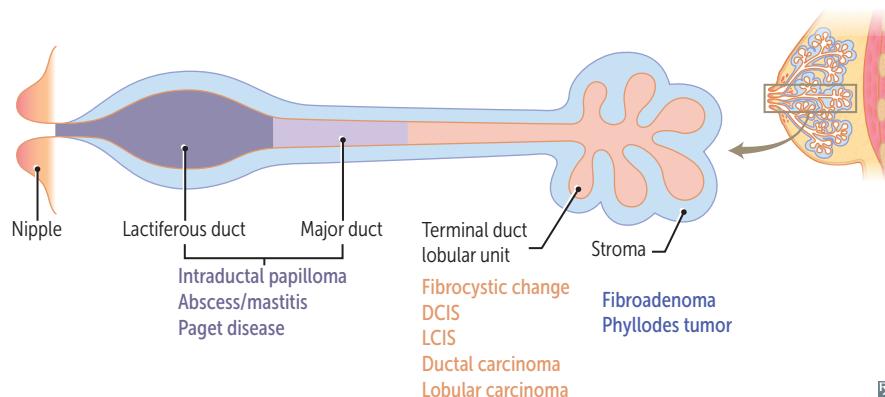
**Uterine conditions**

TYPE	CHARACTERISTICS
<b>Non-neoplastic uterine conditions</b>	
<b>Adenomyosis</b>	Extension of endometrial tissue (glandular) into uterine myometrium. Caused by hyperplasia of basal layer of endometrium. Presents with dysmenorrhea, AUB/HMB, and uniformly enlarged, soft, globular uterus. Treatment: GnRH agonists, hysterectomy, excision of an organized adenomyoma.
<b>Asherman syndrome</b>	Adhesions and/or fibrosis of the endometrium. Presents with ↓ fertility, recurrent pregnancy loss, AUB, pelvic pain. Often associated with dilation and curettage of intrauterine pregnancy.
<b>Endometrial hyperplasia</b>	Abnormal endometrial gland proliferation usually stimulated by excess estrogen. ↑ risk for endometrial carcinoma (especially with nuclear atypia). Presents as postmenopausal vaginal bleeding. ↑ risk with anovulatory cycles, hormone replacement therapy, PCOS, granulosa cell tumors.
<b>Endometriosis</b>	Endometrium-like glands/stroma outside endometrial cavity, most commonly in the ovary (frequently bilateral), pelvis, peritoneum (yellow-brown “powder burn” lesions). In ovary, appears as endometrioma (blood-filled “chocolate cysts”) [oval structures above and below asterisks in <b>A</b> ]. 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.
<b>Endometritis</b>	Inflammation of endometrium <b>B</b> associated with retained products of conception following delivery, miscarriage, abortion, or with foreign body (eg, IUD). Retained material is nidus for bacteria from vagina or GI tract. Chronic endometritis shows plasma cells on histology. Treatment: gentamicin + clindamycin +/- ampicillin.

**Uterine neoplasms**

<b>Endometrial carcinoma</b>	Most common gynecologic malignancy. Presents with irregular vaginal bleeding. Two types: <b>Endometrioid</b> <b>C</b> —most cases caused by unopposed estrogen exposure due to obesity, but also associated with early menarche, late menopause, nulliparity. Histology shows abnormally arranged endometrial glands. Early pathogenic events include loss of PTEN or mismatch repair proteins. <b>Serous</b> —associated with endometrial atrophy in postmenopausal females. Aggressive. Psammoma bodies often seen on histology. Characterized by formation of papillae and tufts.
<b>Leiomyoma (fibroid)</b>	Most common tumor in females. Often presents with multiple discrete tumors <b>D</b> . ↑ incidence in Black patients. Benign smooth muscle tumor; malignant transformation to leiomyosarcoma is rare. Estrogen sensitive; tumor size ↑ with pregnancy and ↓ with menopause. Peak occurrence at 20-40 years of age. May be asymptomatic, cause AUB, or result in miscarriage. Severe bleeding may lead to iron deficiency anemia. Whorled pattern of smooth muscle bundles with well-demarcated borders on histology <b>E</b> .
<b>Leiomyosarcoma</b>	Malignant proliferation of smooth muscle arising from myometrium; arises de novo (not from leiomyomas), usually in postmenopausal females. Exam shows single lesion with areas of necrosis.



**Breast pathology**

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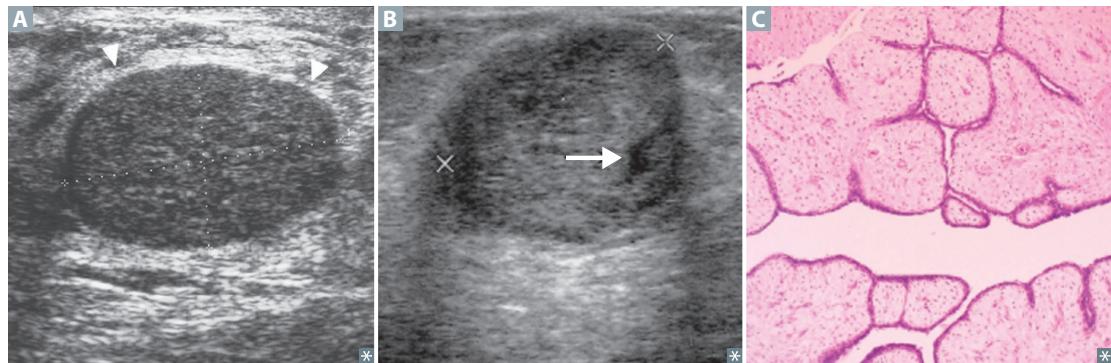
**Benign breast diseases**

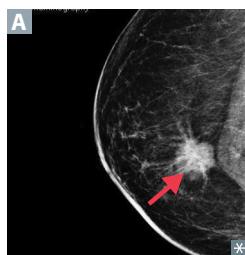
<b>Fibrocystic changes</b>	Most common in premenopausal females 20-50 years old. Present with premenstrual breast pain or lumps; often bilateral and multifocal. Nonproliferative lesions include simple cysts (fluid-filled duct dilation, blue dome), papillary apocrine change/metaplasia, stromal fibrosis. Risk of cancer is usually not increased. Subtypes include: <ul style="list-style-type: none"> <li><b>Sclerosing adenosis</b>—acini and stromal fibrosis, associated with calcifications. Slight ↑ risk for cancer.</li> <li><b>Epithelial hyperplasia</b>—cells in terminal ductal or lobular epithelium. ↑ risk of carcinoma with atypical cells.</li> </ul>
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<b>Inflammatory processes</b>	<b>Fat necrosis</b> —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. <b>Lactational mastitis</b> —occurs during breastfeeding, ↑ risk of bacterial infection through cracks in nipple. <i>S. aureus</i> is most common pathogen. Treat with antibiotics and continue breastfeeding.
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<b>Benign tumors</b>	<b>Fibroadenoma</b> —most common in females < 35 years old. Small, well-defined, mobile mass <b>A</b> . Tumor composed of fibrous tissue and glands. ↑ size and tenderness with ↑ estrogen (eg, pregnancy, prior to menstruation). Risk of cancer is usually not increased. <b>Intraductal papilloma</b> —small fibroepithelial tumor within lactiferous ducts, typically beneath areola. Most common cause of nipple discharge (serous or bloody). Slight ↑ risk for cancer. <b>Phyllodes tumor</b> —large mass <b>B</b> of connective tissue and cysts with “leaf-like” lobulations <b>C</b> . Most common in 5th decade. Some may become malignant.
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<b>Gynecomastia</b>	Breast enlargement in males due to ↑ estrogen compared with androgen activity. Physiologic in newborn, pubertal, and elderly males, but may persist after puberty. Other causes include cirrhosis, hypogonadism (eg, Klinefelter syndrome), testicular tumors, and drugs (spironolactone, hormones, cimetidine, finasteride, ketoconazole).
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**Breast cancer**

Commonly postmenopausal. Often presents as a palpable hard mass **A** most often in the upper outer quadrant. Invasive cancer can become fixed to pectoral muscles, deep fascia, Cooper ligaments, and overlying skin → nipple retraction/skin dimpling.

Usually arises from terminal duct lobular unit. Amplification/overexpression of estrogen/progesterone receptors or *c-erbB2* (HER2, an EGF receptor) is common; triple negative (ER  $\ominus$ , PR  $\ominus$ , and HER2/neu  $\ominus$ ) form more aggressive.

Risk factors in females: ↑ age; history of atypical hyperplasia; family history of breast cancer; race (White patients at highest risk, Black patients at ↑ risk for triple  $\ominus$  breast cancer); *BRCA1/BRCA2* mutations; ↑ estrogen exposure (eg, nulliparity); postmenopausal obesity (adipose tissue converts androstenedione to estrone); ↑ total number of menstrual cycles; absence of breastfeeding; later age of first pregnancy; alcohol intake. In males: *BRCA2* mutation, Klinefelter syndrome.

Axillary lymph node metastasis most important prognostic factor in early-stage disease.

TYPE	CHARACTERISTICS	NOTES
<b>Noninvasive carcinomas</b>		
<b>Ductal carcinoma in situ</b>	Fills ductal lumen (black arrow in <b>B</b> indicates neoplastic cells in duct; blue arrow shows engorged blood vessel). Arises from ductal atypia. Often seen early as microcalcifications on mammography.	Early malignancy without basement membrane penetration. Usually does not produce a mass. <b>Comedocarcinoma</b> —Subtype of DCIS. Cells have high-grade nuclei with extensive central necrosis <b>C</b> and dystrophic calcification.
<b>Paget disease</b>	Extension of underlying DCIS/invasive breast cancer up the lactiferous ducts and into the contiguous skin of nipple → eczematous patches over nipple and areolar skin <b>D</b> .	Paget cells = intraepithelial adenocarcinoma cells.
<b>Lobular carcinoma in situ</b>	↓ E-cadherin expression. No mass or calcifications → incidental biopsy finding.	↑ risk of cancer in either breast (vs DCIS, same breast and quadrant).
<b>Invasive carcinomas<sup>a</sup></b>		
<b>Invasive ductal</b>	Firm, fibrous, “rock-hard” mass with sharp margins and small, glandular, duct-like cells in desmoplastic stroma.	Most common type of invasive breast cancer.
<b>Invasive lobular</b>	↓ E-cadherin expression → orderly row of cells (“single file” <b>E</b> ) and no duct formation. Often lacks desmoplastic response.	Often bilateral with multiple lesions in the same location. Lines of cells = <b>Lobular</b> .
<b>Medullary</b>	Large, anaplastic cells growing in sheets with associated lymphocytes and plasma cells.	Well-circumscribed tumor can mimic fibroadenoma.
<b>Inflammatory</b>	Dermal lymphatic space invasion → breast pain with warm, swollen, erythematous skin around exaggerated hair follicles (peau d'orange) <b>F</b> .	Poor prognosis (50% survival at 5 years). Often mistaken for mastitis or Paget disease. Usually lacks a palpable mass.



<sup>a</sup>All types of invasive breast carcinoma can be either of tubular subtype (well-differentiated tubules that lack myoepithelium) or mucinous subtype (abundant extracellular mucin, seen in older females).

## Penile pathology

### Peyronie disease



Abnormal curvature of penis **A** due to fibrous plaque within tunica albuginea. Associated with repeated minor trauma during intercourse. Can cause pain, anxiety, erectile dysfunction. Consider surgical repair or treatment with collagenase injections once curvature stabilizes. Distinct from penile fracture (rupture of corpora cavernosa due to forced bending).

### Ischemic priapism

Painful sustained erection lasting > 4 hours. Associated with sickle cell disease (sickled RBCs block venous drainage of corpus cavernosum vascular channels), medications (eg, sildenafil, trazodone). Treat immediately with corporal aspiration, intracavernosal phenylephrine, or surgical decompression to prevent ischemia.

### Squamous cell carcinoma



Seen in the US, but more common in Asia, Africa, South America. Precursor in situ lesions: Bowen disease (in penile shaft, presents as leukoplakia “white plaque”), erythroplasia of Queyrat (carcinoma in situ of the glans **B**, presents as erythroplakia “red plaque”), Bowenoid papulosis (carcinoma in situ of unclear malignant potential, presenting as reddish papules). Associated with uncircumcised males and HPV.

## Cryptorchidism

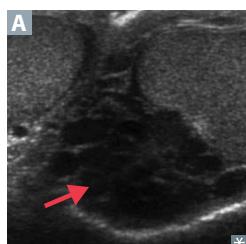


Descent failure of one **A** or both testes; impaired spermatogenesis (since sperm develop best at temperatures < 37°C); can have normal testosterone levels (Leydig cells are mostly unaffected by temperature); associated with ↑ risk of germ cell tumors. Prematurity ↑ risk of cryptorchidism. ↓ inhibin B, ↑ FSH, ↑ LH; testosterone ↓ in bilateral cryptorchidism, normal in unilateral. Most cases resolve spontaneously; otherwise, orchiopexy performed before 2 years of age.

## Testicular torsion

Rotation of testicle around spermatic cord and vascular pedicle. Commonly presents in males 12–18 years old. Associated with congenital horizontal positioning of testes (“bell clapper” deformity). May occur after an inciting event (eg, trauma) or spontaneously. Characterized by acute, severe pain, high-riding testis, and absent cremasteric reflex. ⊖ Prehn sign. Treatment: surgical correction (orchiopexy) within 6 hours, manual detorsion if surgical option unavailable in timeframe. If testis is not viable, orchiectomy. Orchiopexy, when performed, should be bilateral because the contralateral testis is at risk for subsequent torsion.

## Varicocele



Dilated veins in pampiniform plexus due to ↑ venous pressure; most common cause of scrotal enlargement in adult males; most often on left side because of ↑ resistance to flow from left gonadal vein drainage into left renal vein; can cause infertility because of ↑ temperature; diagnosed by standing clinical exam/Valsalva maneuver (distension on inspection and “bag of worms” on palpation; augmented by Valsalva) or ultrasound **A**; does not transilluminate. Treatment: consider surgical ligation or embolization if associated with pain or infertility.

**Extragonadal 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.

**Benign scrotal lesions** Testicular masses that can be transilluminated (vs solid testicular tumors).

**Congenital hydrocele**



Common cause of scrotal swelling **A** in infants, due to incomplete obliteration of processus vaginalis. Most spontaneously resolve within 1 year.

**Acquired hydrocele**

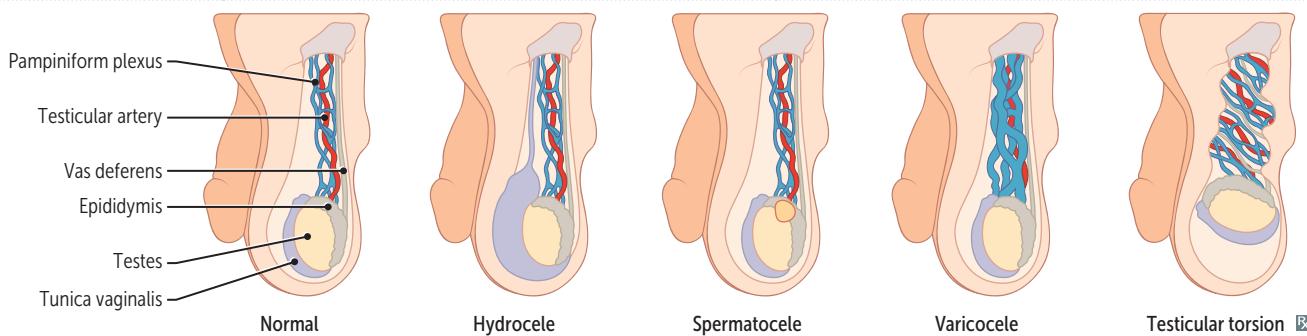
Scrotal fluid collection usually 2° to infection, trauma, tumor. If bloody → hematocoele.

Noncommunicating hydrocele.

**Spermatocele**

Cyst due to dilated epididymal duct or rete testis.

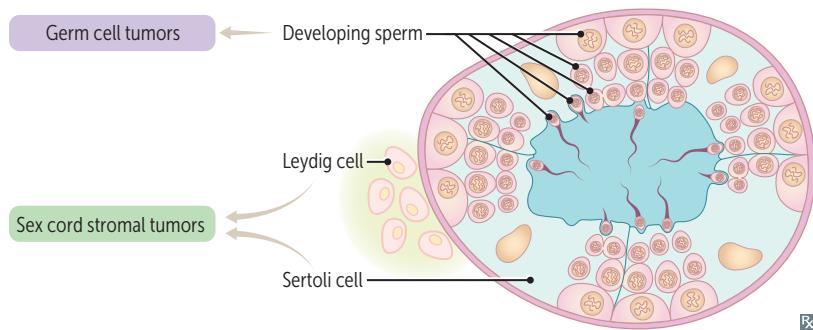
Paratesticular fluctuant nodule.



**Testicular tumors**

Germ cell tumors account for ~ 95% of all testicular tumors. Arise from germ cells that produce sperm. Most often occur in young males. Risk factors: cryptorchidism, Klinefelter syndrome. Can present as a mixed germ cell tumor. Do not transilluminate. Usually not biopsied (risk of seeding scrotum), removed via radical orchietomy.

Sex cord stromal tumors develop from embryonic sex cord (develops into Sertoli and Leydig cells of seminiferous tubules, theca and granulosa cells of follicle) derivatives. 5% of all testicular tumors. Mostly benign.



**Testicular tumors (continued)**

TYPE	CHARACTERISTICS
<b>Germ cell tumors</b>	
<b>Seminoma</b>	Malignant. Painless, homogenous testicular enlargement. Most common testicular tumor. Analogous to ovarian dysgerminoma. Does not occur in infancy. Large cells in lobules with watery cytoplasm and “fried egg” appearance on histology, ↑ placental ALP (PALP). Highly radiosensitive. Late metastasis, excellent prognosis.
<b>Embryonal carcinoma</b>	Malignant. Painful, hemorrhagic mass with necrosis. Often glandular/papillary morphology. “Pure” embryonal carcinoma is rare; most commonly mixed with other tumor types. May present with metastases. May be associated with ↑ hCG and normal AFP levels when pure (↑ AFP when mixed). Worse prognosis than seminoma.
<b>Teratoma</b>	Mature teratoma may be malignant in adult males. Benign in children and females.
<b>Yolk sac tumor</b>	Also called endodermal sinus tumor. Malignant, aggressive. Yellow, mucinous. Analogous to ovarian yolk sac tumor. Schiller-Duval bodies resemble primitive glomeruli. ↑ AFP is highly characteristic. Most common testicular tumor in children < 3 years old.
<b>Choriocarcinoma</b>	Malignant. Disordered syncytiotrophoblastic and cytotrophoblastic elements. Hematogenous metastases to lungs and brain. ↑ hCG. May produce gynecomastia, symptoms of hyperthyroidism ( $\alpha$ -subunit of hCG is identical to $\alpha$ -subunit of LH, FSH, TSH).
<b>Non–germ cell tumors</b>	
<b>Leydig cell tumor</b>	Mostly benign. Golden brown color; contains Reinke crystals (eosinophilic cytoplasmic inclusions). Produces androgens or estrogens → precocious puberty, gynecomastia.
<b>Sertoli cell tumor</b>	Also called androblastoma (arises from sex cord stroma). Mostly benign.
<b>Primary testicular lymphoma</b>	Malignant, aggressive. Typically diffuse large B-cell lymphoma. Most common testicular cancer in older males.

**Hormone levels in germ cell tumors**

	SEMINOMA	YOLK SACTUMOR	CHORIOCARCINOMA	TERATOMA	EMBRYONAL CARCINOMA
<b>PALP</b>	↑	—	—	—	—
<b>AFP</b>	—	↑↑	—	—/↑	—/↑ (when mixed)
<b>β-hCG</b>	—/↑	—/↑	↑↑	—	↑

**Epididymitis and orchitis**

Most common causes:

- *C trachomatis* and *N gonorrhoeae* (young males)
- *E coli* and *Pseudomonas* (older males, associated with UTI and BPH)
- Autoimmune (eg, granulomas involving seminiferous tubules)

**Epididymitis**

Inflammation of epididymis. Presents with localized pain and tenderness over posterior testis.

⊕ Prehn sign (pain relief with scrotal elevation). May progress to involve testis.

**Orchitis**

Inflammation of testis. Presents with testicular pain and swelling. Mumps orchitis ↑ infertility risk.

Rare in males < 10 years old.

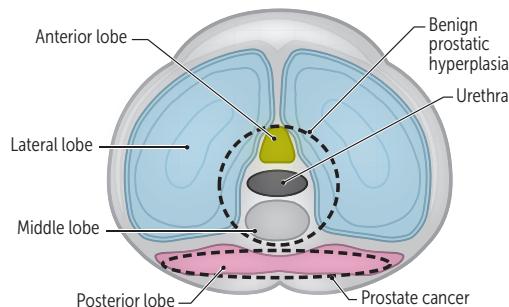
**Benign prostatic hyperplasia**

Common in males > 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. ↑ total PSA, with ↑ fraction of free PSA. PSA is made by prostatic epithelium stimulated by androgens.

Treatment:  $\alpha_1$ -antagonists (terazosin, tamsulosin), which cause relaxation of smooth muscle; 5 $\alpha$ -reductase inhibitors (eg, finasteride); PDE-5 inhibitors (eg, tadalafil); surgical resection (eg, TURP, ablation).

**Prostatitis**

Characterized by dysuria, frequency, urgency, low back pain. Warm, tender, enlarged prostate.

Acute bacterial prostatitis—in older males most common bacterium is *E coli*; in young males consider *C trachomatis*, *N gonorrhoeae*.

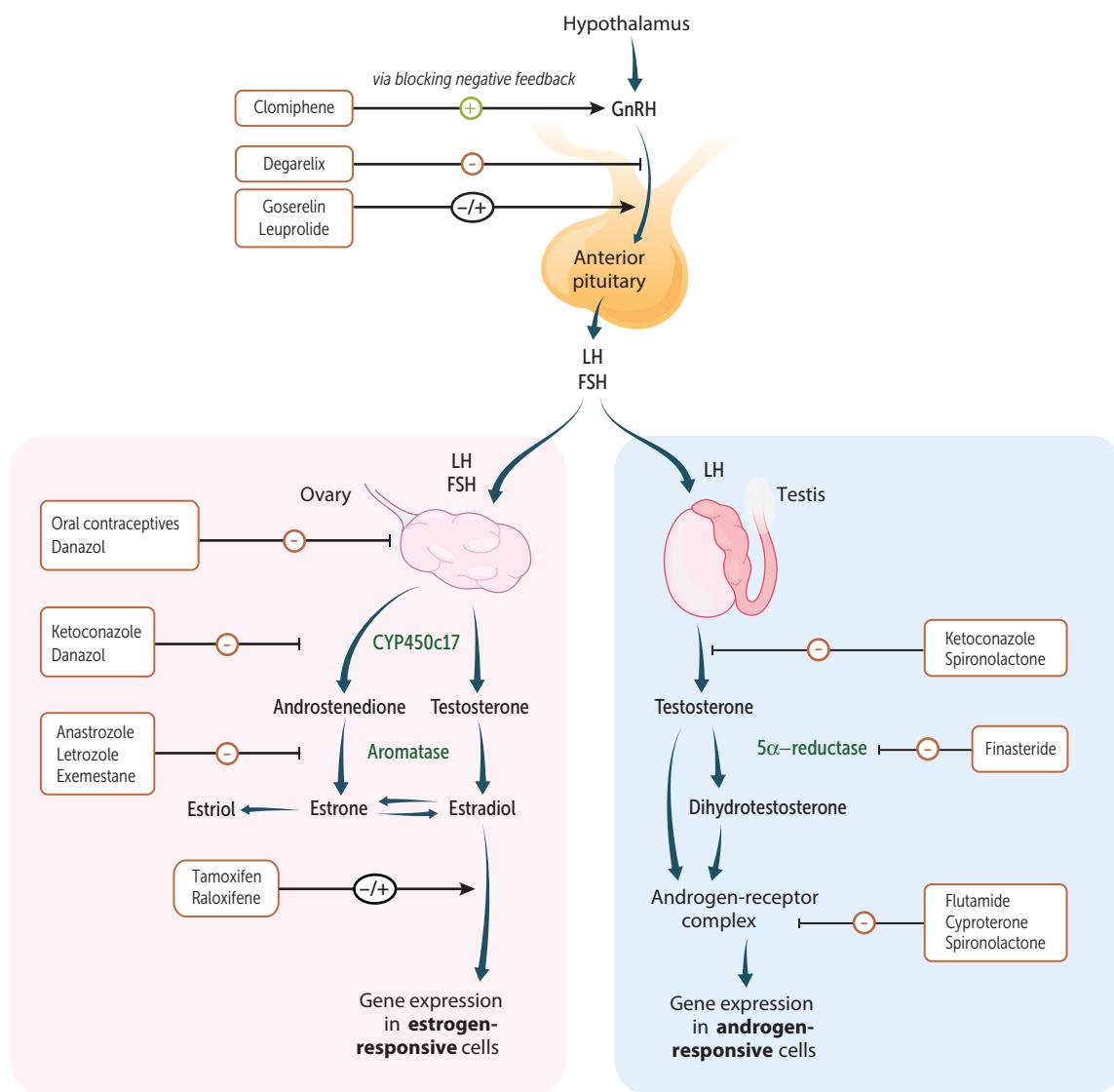
Chronic prostatitis—either bacterial or nonbacterial (eg, 2° to previous infection, nerve problems, chemical irritation).

**Prostatic adenocarcinoma**

Common in males > 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 (transrectal, ultrasound-guided). Histologically graded using Gleason grade, which is based on glandular architecture and correlates closely with metastatic potential. Prostatic acid phosphatase (PAP) and PSA are useful tumor markers (↑ total PSA, with ↓ fraction of free PSA). Osteoblastic metastases in bone may develop in late stages, as indicated by lower back pain and ↑ serum ALP and PSA. Metastasis to the spine often occurs via Batson (vertebral) venous plexus.

## ► REPRODUCTIVE—PHARMACOLOGY

## Control of reproductive hormones



**Gonadotropin-releasing hormone analogs**

**Leu**prolide, goserelin, nafarelin, histrelin.

**MECHANISM**

Act as GnRH agonists when used in pulsatile fashion.

When used in continuous fashion, first transiently act as GnRH agonists (tumor flare), but subsequently act as GnRH antagonists (downregulate GnRH receptor in pituitary → ↓ FSH and ↓ LH).

Can be used in **lieu** of GnRH.

**CLINICAL USE**

Uterine fibroids, endometriosis, precocious puberty, prostate cancer, infertility. **Pulsatile** for pregnancy, **continuous** for cancer.

**ADVERSE EFFECTS**

Hypogonadism, ↓ libido, erectile dysfunction, nausea, vomiting.

**Degarelix****MECHANISM**

GnRH antagonist. No start-up flare.

**CLINICAL USE**

Prostate cancer.

**ADVERSE EFFECTS**

Hot flashes, liver toxicity.

**Estrogens**

Ethinyl estradiol, DES, mestranol.

**MECHANISM**

Bind estrogen receptors.

**CLINICAL USE**

Hypogonadism or ovarian failure, menstrual abnormalities (combined OCPs), hormone replacement therapy in postmenopausal females.

**ADVERSE EFFECTS**

↑ risk of endometrial cancer (when given without progesterone), bleeding in postmenopausal patients, clear cell adenocarcinoma of vagina in females exposed to DES in utero, ↑ risk of thrombi. Contraindications—ER + breast cancer, history of DVTs, tobacco use in females > 35 years old.

**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, partial agonist at uterus, bone. Hot flashes, ↑ risk of thromboembolic events (especially with tobacco smoking), and endometrial cancer. Used to treat and prevent recurrence of ER/PR + breast cancer and to prevent gynecomastia in patients undergoing prostate cancer therapy.

**Raloxifene**

Antagonist at breast, uterus; agonist at bone; hot flashes, ↑ risk of thromboembolic events (especially with tobacco smoking), but no increased risk of endometrial cancer (vs tamoxifen, so you can “**relax**”); 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 females.

<b>Hormone replacement therapy</b>	Used for relief or prevention of menopausal symptoms (eg, hot flashes, vaginal atrophy), osteoporosis ( $\uparrow$ estrogen, $\downarrow$ osteoclast activity). Unopposed estrogen replacement therapy $\uparrow$ risk of endometrial cancer, progesterone/progestin is added. Possible increased cardiovascular risk.
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<b>Progestins</b>	Levonorgestrel, medroxyprogesterone, etonogestrel, norethindrone, megestrol.
MECHANISM	Bind progesterone receptors, $\downarrow$ growth and $\uparrow$ 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 bleeding upon withdrawal of progestins excludes anatomic defects (eg, Asherman syndrome) and chronic anovulation without estrogen.

<b>Antiprogestins</b>	Mifepristone, ulipristal.
MECHANISM	Competitive inhibitors of progestins at progesterone receptors.
CLINICAL USE	Termination of pregnancy (mifepristone with misoprostol); emergency contraception (ulipristal).

<b>Combined contraception</b>	Progestins and ethinyl estradiol; forms include pill, patch, vaginal ring. Estrogen and progestins inhibit LH/FSH and thus prevent estrogen surge. No estrogen surge $\rightarrow$ no LH surge $\rightarrow$ no ovulation. Progestins cause thickening of cervical mucus, thereby limiting access of sperm to uterus. Progestins also inhibit endometrial proliferation $\rightarrow$ endometrium is less suitable to the implantation of an embryo. Adverse effects: breakthrough menstrual bleeding, breast tenderness, VTE, hepatic adenomas. Contraindications: people $>$ 35 years old who smoke tobacco ( $\uparrow$ risk of cardiovascular events), patients with $\uparrow$ risk of cardiovascular disease (including history of venous thromboembolism, coronary artery disease, stroke), migraine (especially with aura), breast cancer, liver disease.
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<b>Copper intrauterine device</b>	
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. Insertion contraindicated in active PID (IUD may impede PID resolution).

<b>Tocolytics</b>	Medications that relax the uterus; include terbutaline ( $\beta_2$ -agonist action), nifedipine ( $\text{Ca}^{2+}$ channel blocker), indomethacin (NSAID). Used to $\downarrow$ contraction frequency in preterm labor and allow time for administration of steroids (to promote fetal lung maturity) or transfer to appropriate medical center with obstetrical care.
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**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, idiopathic intracranial hypertension.

**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	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**

DRUG	MECHANISM	CLINICAL USE	ADVERSE EFFECTS
<b>Abiraterone</b>	17α-hydroxylase/17,20-lyase inhibitor (↓ steroid synthesis)	Prostate cancer	Hypertension, hypokalemia (↑ mineralocorticoids)
<b>Finasteride</b>	5α-reductase inhibitor (↓ conversion of testosterone to DHT)	BPH, male-pattern baldness	Gynecomastia, sexual dysfunction
<b>Flutamide, bicalutamide</b>	Nonsteroidal competitive inhibitors at androgen receptor (↓ steroid binding)	Prostate cancer	Gynecomastia, sexual dysfunction
<b>Ketoconazole</b>	17α-hydroxylase/17,20-lyase inhibitor	Prostate cancer	Gynecomastia
<b>Spironolactone</b>	Androgen receptor and 17α-hydroxylase/17,20-lyase inhibitor	PCOS	Amenorrhea

**Tamsulosin**

$\alpha_1$ -antagonist used to treat BPH by inhibiting smooth muscle contraction. Selective for  $\alpha_{1A/D}$  receptors (found on prostate) vs vascular  $\alpha_{1B}$  receptors.

**Minoxidil**

MECHANISM	Direct arteriolar vasodilator.
CLINICAL USE	Androgenetic alopecia (pattern baldness), 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

*“Freedom is the oxygen of the soul.”*

—Moshe Dayan

*“Whenever I feel blue, I start breathing again.”*

—L. Frank Baum

*“Life is not the amount of breaths you take; it’s the moments that take your breath away.”*

—Will Smith, *Hitch*

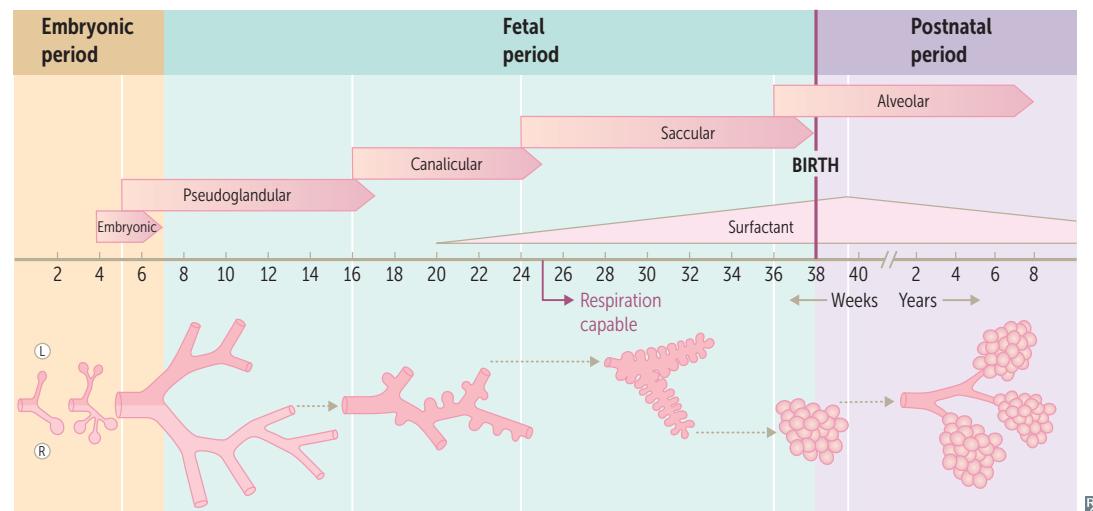
Group key respiratory, cardiovascular, and renal concepts together for study whenever possible. Respiratory physiology is challenging but high yield, especially as it relates to the pathophysiology of respiratory diseases. Develop a thorough understanding of normal respiratory function. Know obstructive vs restrictive lung disorders,  $\dot{V}/\dot{Q}$  mismatch, lung volumes, mechanics of respiration, and hemoglobin physiology. Lung cancers and other causes of lung masses are also high yield. Be comfortable reading basic chest x-rays, CT scans, and PFTs.

► Embryology	684
► Anatomy	686
► Physiology	688
► Pathology	695
► Pharmacology	710

## ► RESPIRATORY—EMBRYOLOGY

**Lung development** Occurs in five stages. Begins with the formation of lung bud from distal end of respiratory diverticulum during week 4 of development. Every pulmonologist can see alveoli.

STAGE	STRUCTURAL DEVELOPMENT	NOTES
<b>Embryonic (weeks 4–7)</b>	Lung bud → trachea → bronchial buds → mainstem bronchi → secondary (lobar) bronchi → tertiary (segmental) bronchi.	Errors at this stage can lead to tracheoesophageal fistula.
<b>Pseudoglandular (weeks 5–17)</b>	Endodermal tubules → terminal bronchioles. Surrounded by modest capillary network.	Respiration impossible, incompatible with life.
<b>Canalicular (weeks 16–25)</b>	Terminal bronchioles → respiratory bronchioles → alveolar ducts. Surrounded by prominent capillary network.	Airways increase in diameter. Pneumocytes develop starting at week 20 of development. Respiration capable at ~ week 25.
<b>Saccular (week 24–birth)</b>	Alveolar ducts → terminal sacs. Terminal sacs separated by 1° septae.	
<b>Alveolar (week 36–8 years)</b>	Terminal sacs → adult alveoli (due to 2° septation). In utero, “breathing” occurs via aspiration and expulsion of amniotic fluid → ↑ pulmonary vascular resistance through gestation. At birth, air replaces fluid → ↓ pulmonary vascular resistance.	

**Congenital lung malformations**

**Pulmonary hypoplasia** Poorly developed bronchial tree with abnormal histology. Associated with congenital diaphragmatic hernia (usually left-sided), bilateral renal agenesis (Potter sequence).

**Bronchogenic cysts** Caused by abnormal budding of the foregut and dilation of terminal or large bronchi. Discrete, round, sharply defined, fluid-filled densities on CXR (air-filled if infected). Generally asymptomatic but can drain poorly → airway compression, recurrent respiratory infections.

**Club cells**

Nonciliated; low columnar/cuboidal with secretory granules. Located in bronchioles. Degrade toxins via cytochrome P-450; secrete component of surfactant; progenitor cells for club and ciliated cells.

**Alveolar cell types****Type I pneumocytes**

Squamous. 97% of alveolar surfaces. Thinly line the alveoli (two black arrows in **A**) for optimal gas exchange.

**Type II pneumocytes**

Cuboidal and clustered **A**.

**2** functions:

1. Serve as stem cell precursors for **2** cell types (type I and type II cells); proliferate during lung damage.
2. Secrete surfactant from lamellar bodies (arrowheads in **B**).

**Surfactant**— $\downarrow$  alveolar surface tension,  $\downarrow$  alveolar collapse,  $\downarrow$  lung recoil, and  $\uparrow$  compliance.

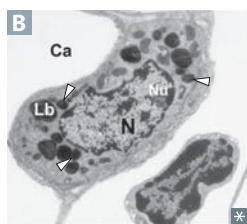
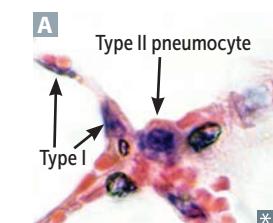
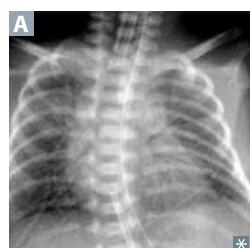
Composed of multiple lecithins, mainly dipalmitoylphosphatidylcholine (DPPC). Synthesis begins ~20 weeks' gestation and achieves mature levels ~35 weeks of gestation. Corticosteroids important for fetal surfactant synthesis and lung development.

**Alveolar macrophages**

Phagocytose foreign materials; release cytokines and alveolar proteases. Hemosiderin-laden macrophages (heart failure cells) may be found in the setting of pulmonary edema or alveolar hemorrhage.

$$\text{Collapsing pressure } (P) = \frac{2 \text{ (surface tension)}}{\text{radius}}$$

**Law of Laplace**—Alveoli have  $\uparrow$  tendency to collapse on expiration as radius  $\downarrow$ .

**Neonatal respiratory distress syndrome**

Surfactant deficiency  $\rightarrow$   $\uparrow$  surface tension  $\rightarrow$  alveolar collapse ("ground-glass" appearance of lung fields) **A**.

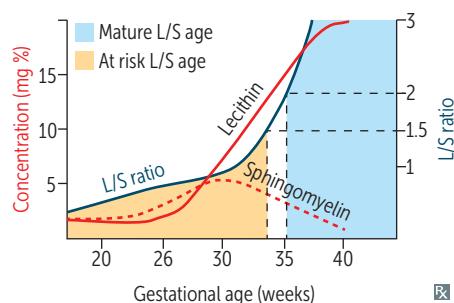
Risk factors: prematurity, diabetes during pregnancy (due to  $\uparrow$  fetal insulin), C-section delivery ( $\downarrow$  release of fetal glucocorticoids; less stressful than vaginal delivery).

Treatment: maternal steroids before birth; exogenous surfactant for infant.

Therapeutic supplemental O<sub>2</sub> can result in **Retinopathy of prematurity**, **Intraventricular hemorrhage**, **Bronchopulmonary dysplasia (RIB)**.

Screening tests for fetal lung maturity: lecithin-sphingomyelin (L/S) ratio in amniotic fluid ( $\geq 2$  is healthy;  $< 1.5$  predictive of NRDS), foam stability index, surfactant-albumin ratio.

Persistently low O<sub>2</sub> tension  $\rightarrow$  risk of PDA.



## ► RESPIRATORY—ANATOMY

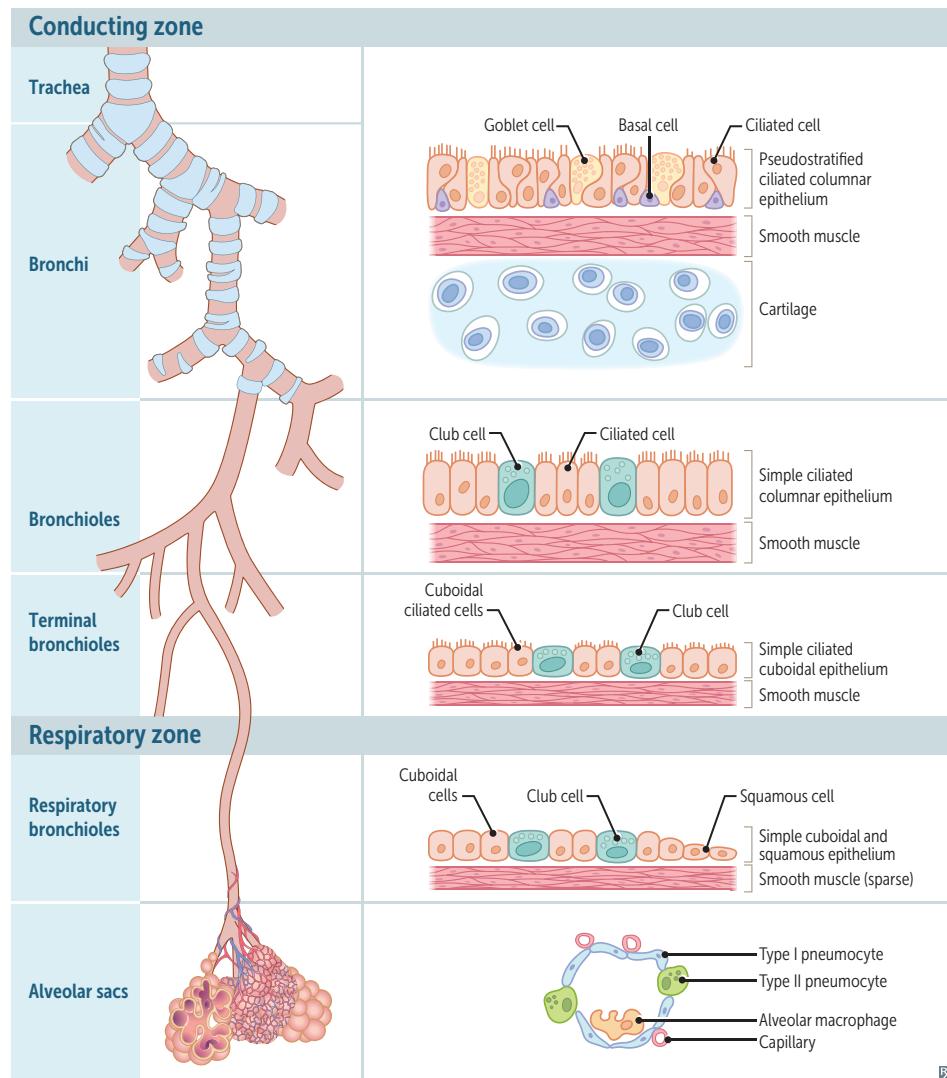
## Respiratory tree

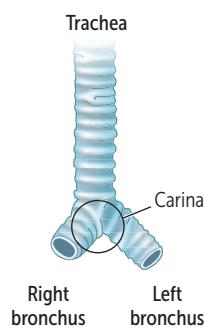
## Conducting zone

Large airways consist of nose, pharynx, larynx, trachea, and bronchi. Airway resistance highest in the large- to medium-sized bronchi. Small airways consist of bronchioles that further divide into terminal bronchioles (large numbers in parallel → least airway resistance). Warms, humidifies, and filters air but does not participate in gas exchange → “anatomic dead space.” Cartilage and goblet cells extend to the end of bronchi. Pseudostratified ciliated columnar cells primarily make up epithelium of bronchus and extend to beginning of terminal bronchioles, then transition to cuboidal cells. Clear mucus and debris from lungs (mucociliary escalator). Airway smooth muscle cells extend to end of terminal bronchioles (sparse beyond this point).

## Respiratory zone

Lung parenchyma; consists of respiratory bronchioles, alveolar ducts, and alveoli. Participates in gas exchange. Mostly cuboidal cells in respiratory bronchioles, then simple squamous cells up to alveoli. Cilia terminate in respiratory bronchioles. Alveolar macrophages clear debris and participate in immune response.



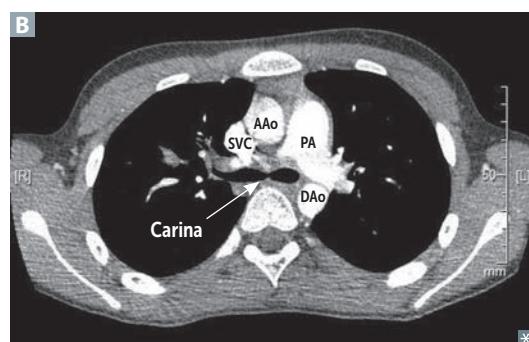
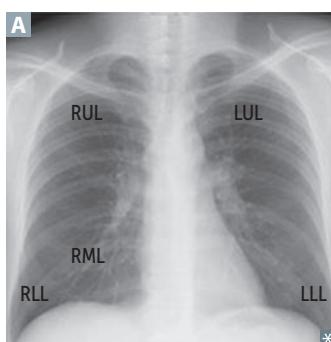
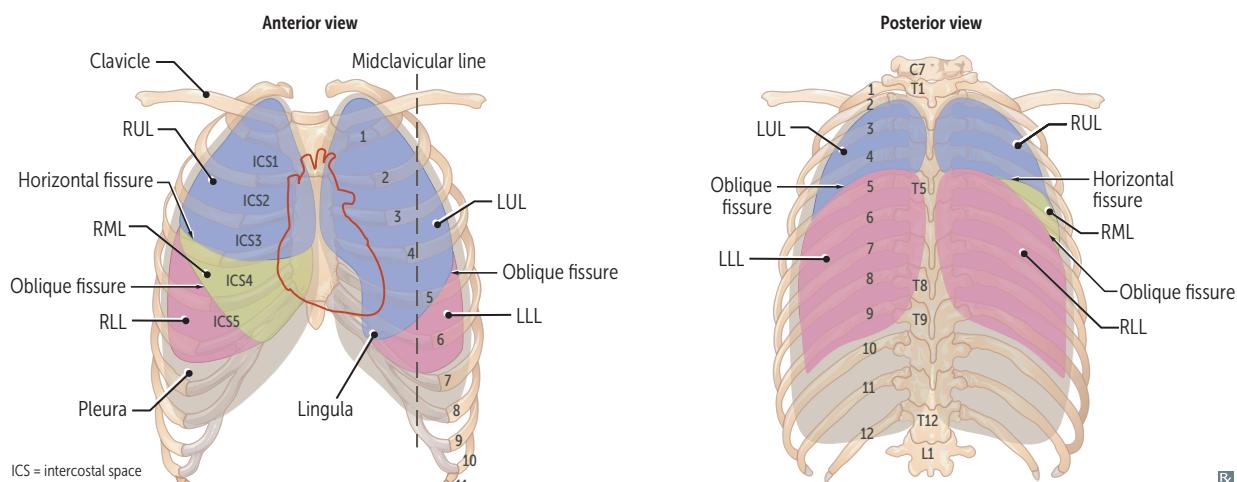
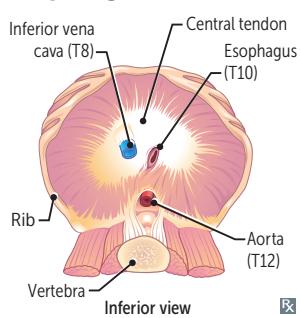
**Lung anatomy**

Right lung has 3 lobes; Left has less lobes (2) and lingula (homolog of right middle lobe). Instead of a middle lobe, left lung has a space occupied by the heart **A**.

Relation of the pulmonary artery to the bronchus at each lung hilum is described by **RALS**—Right Anterior; Left Superior. Carina is posterior to ascending aorta and anteromedial to descending aorta **B**.

Right lung is a more common site for inhaled foreign bodies because right main stem bronchus is wider, more vertical, and shorter than the left. If you aspirate a peanut:

- While supine—usually enters superior segment of right lower lobe.
- While lying on right side—usually enters right upper lobe.
- While upright—usually enters right lower lobe.

**Diaphragm structures**

Structures perforating diaphragm:

- At T8: IVC, right phrenic nerve
- At T10: esophagus, vagus (CN 10; 2 trunks)
- At T12: aorta (red), thoracic duct (white), azygos vein (blue) (“At **T-1-2** it’s the **red, white, and blue**”)

Diaphragm is innervated by C3, 4, and 5 (phrenic nerve). Pain from diaphragm irritation (eg, air, blood, or pus in peritoneal cavity) can be referred to shoulder (C5) and trapezius ridge (C3, 4).

Number of letters = T level:

**T8**: vena cava (**IVC**)

**T10**: (**O**)**esophagus**

**T12**: **aortic hiatus**

**I ate (8) ten eggs at twelve.**

**C3, 4, 5** keeps the diaphragm **alive**.

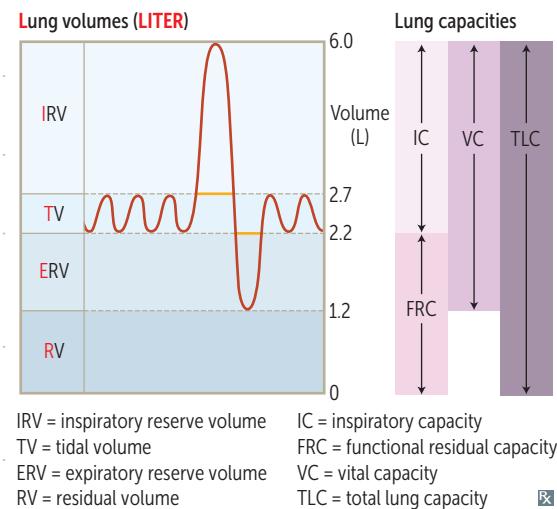
Other bifurcations:

- The **Common Carotid** bifurcates at **C4**.
- The **Trachea** bifurcates at **T4**.
- The **abdominal aorta** bifurcates at **L4**.

## ► RESPIRATORY—PHYSIOLOGY

**Lung volumes and capacities**

<b>Tidal volume</b>	Air that moves into lung with each quiet inspiration, typically 500 mL
<b>Inspiratory reserve volume</b>	Air that can still be breathed in after normal inspiration
<b>Expiratory reserve volume</b>	Air that can still be breathed out after normal expiration
<b>Residual volume</b>	Air in lung after maximal expiration; RV and any lung capacity that includes RV cannot be measured by spirometry
<b>Inspiratory capacity</b>	IRV + TV Air that can be breathed in after normal exhalation
<b>Functional residual capacity</b>	RV + ERV Volume of gas in lungs after normal expiration; outward pulling force of chest wall is balanced with inward collapsing force of lungs
<b>Vital capacity</b>	IRV + TV + ERV Maximum volume of gas that can be expired after a maximal inspiration
<b>Total lung capacity</b>	IRV + TV + ERV + RV = VC + RV Volume of gas present in lungs after a maximal inspiration

**Determination of physiologic dead space**

$$V_D = V_T \times \frac{Paco_2 - PECO_2}{Paco_2}$$

$V_D$  = 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.  
 $Paco_2$  = arterial  $Pco_2$ .  
 $PECO_2$  = expired air  $Pco_2$ .

Physiologic dead space—approximately equivalent to anatomic dead space in normal lungs. May be greater than anatomic dead space in lung diseases with  $\dot{V}/\dot{Q}$  mismatch.

**Ventilation**

<b>Minute ventilation</b>	Abbreviated as $V_E$ . Total volume of gas entering lungs per minute $V_E = V_T \times RR$
<b>Alveolar ventilation</b>	Abbreviated as $V_A$ . Volume of gas that reaches alveoli each minute $V_A = (V_T - V_D) \times RR$

Normal values:

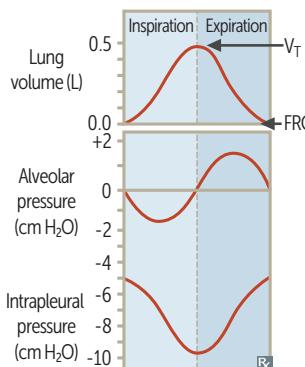
- Respiratory rate (RR) = 12–20 breaths/min
- $V_T = 500$  mL/breath
- $V_D = 150$  mL/breath

## Lung and chest wall

### Elastic recoil

Tendency for lungs to collapse inward and chest wall to spring outward.

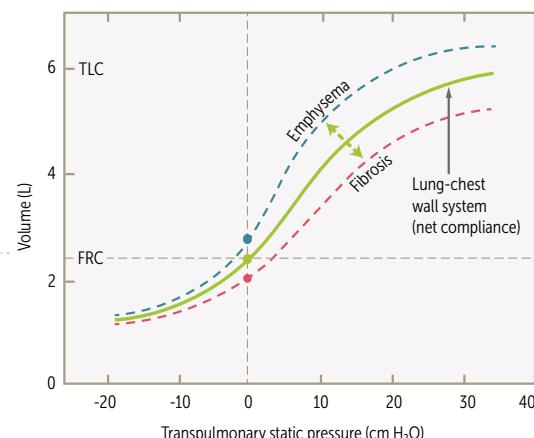
At FRC, airway and alveolar pressures equal atmospheric pressure (called zero), and intrapleural pressure is negative (preventing atelectasis). The inward pull of the lung is balanced by the outward pull of the chest wall. System pressure is atmospheric. Pulmonary vascular resistance (PVR) is at a minimum.



### Compliance

Change in lung volume for a change in pressure ( $\Delta V/\Delta P$ ). Inversely proportional to wall stiffness and increased by surfactant.

- ↑ compliance = lung easier to fill (eg, emphysema, aging)
- ↓ compliance = lung harder to fill (eg, pulmonary fibrosis, pneumonia, ARDS, pulmonary edema)



### Hysteresis

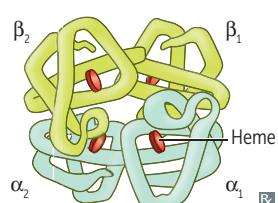
Lung inflation follows a different pressure-volume curve than lung deflation due to need to overcome surface tension forces in inflation.

## Respiratory system changes in the elderly

Aging is associated with progressive ↓ in lung function. TLC remains the same.

INCREASED	DECREASED
Lung compliance (loss of elastic recoil)	Chest wall compliance (↑ chest wall stiffness)
RV	FVC and FEV <sub>1</sub>
̄V̄Q mismatch	Respiratory muscle strength (can impair cough)
A-a gradient	Ventilatory response to hypoxia/hypercapnia

## Hemoglobin



Normal adult hemoglobin (Hb) is composed of 4 polypeptide subunits (2  $\alpha$  and 2  $\beta$ ) that each bind one  $O_2$  molecule. Hb is an allosteric protein that exhibits positive cooperativity when binding to  $O_2$ , such that:

- Oxygenated Hb has high affinity for  $O_2$  (300x).
- Deoxygenated Hb has low affinity for  $O_2 \rightarrow$  promotes release/unloading of  $O_2$ .

The protein component of hemoglobin acts as buffer for  $H^+$  ions.

Myoglobin is composed of a single polypeptide chain associated with one heme moiety. Higher affinity for oxygen than Hb.

### Oxygen content of blood

$O_2$  content =  $(1.34 \times Hb \times SaO_2) + (0.003 \times Pao_2)$ .

Hb = hemoglobin concentration;  $SaO_2$  = arterial  $O_2$  saturation.

$Pao_2$  = partial pressure of  $O_2$  in arterial blood.

Normally 1 g Hb can bind 1.34 mL  $O_2$ ; normal Hb amount in blood is 15 g/dL.

$O_2$  binding capacity  $\approx$  20 mL  $O_2$ /dL of blood.

With  $\downarrow$  Hb there is  $\downarrow$   $O_2$  content of arterial blood, but no change in  $O_2$  saturation and  $Pao_2$ .

$O_2$  delivery to tissues = cardiac output  $\times$   $O_2$  content of blood.

	Hb CONCENTRATION	% $O_2$ SAT OF Hb	DISSOLVED $O_2$ ( $Pao_2$ )	TOTAL $O_2$ CONTENT
CO poisoning	Normal	$\downarrow$ (CO competes with $O_2$ )	Normal	$\downarrow$
Anemia	$\downarrow$	Normal	Normal	$\downarrow$
Polycythemia	$\uparrow$	Normal	Normal	$\uparrow$
Methemoglobinemia	Normal	$\downarrow$ (Fe <sup>3+</sup> poor at binding $O_2$ )	Normal	$\downarrow$
Cyanide toxicity	Normal	Normal	Normal	Normal

### Methemoglobin

Iron in Hb is normally in a reduced state (ferrous Fe<sup>2+</sup>; “just the 2 of us”). Oxidized form of Hb (ferric, Fe<sup>3+</sup>) does not bind  $O_2$  as readily as Fe<sup>2+</sup>, but has  $\uparrow$  affinity for cyanide  $\rightarrow$  tissue hypoxia from  $\downarrow$   $O_2$  saturation and  $\downarrow$   $O_2$  content.

Methemoglobinemia may present with cyanosis (does not improve with supplemental  $O_2$ ) or with chocolate-colored blood.

Dapsone, local anesthetics (eg, benzocaine), and nitrites (eg, from dietary intake or polluted/high-altitude water sources) cause poisoning by oxidizing Fe<sup>2+</sup> to Fe<sup>3+</sup>.

Methemoglobinemia can be treated with methylene blue and vitamin C.

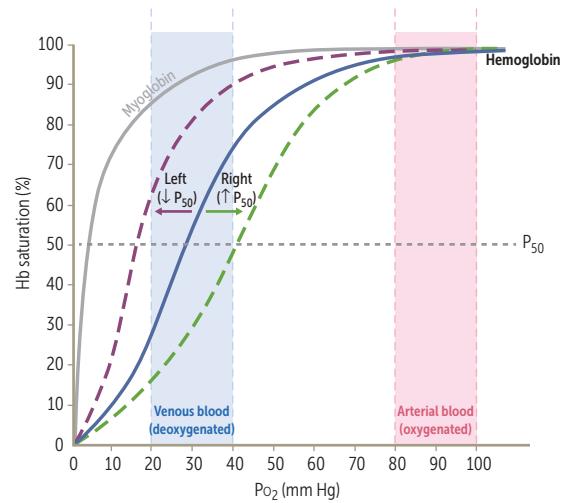
### Oxygen-hemoglobin dissociation curve

ODC has sigmoidal shape due to positive cooperativity (ie, tetrameric Hb molecule can bind 4  $O_2$  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.

Shifting ODC to the right  $\rightarrow$   $\downarrow$  Hb affinity for  $O_2$  (facilitates unloading of  $O_2$  to tissue)  $\rightarrow$   $\uparrow P_{50}$  (higher  $Po_2$  required to maintain 50% saturation). In peripheral tissue,  $\uparrow H^+$  from tissue metabolism shifts curve to right, unloading  $O_2$  (Bohr effect).

Shifting ODC to the left  $\rightarrow$   $\downarrow$   $O_2$  unloading  $\rightarrow$  renal hypoxia  $\rightarrow$   $\uparrow$  EPO synthesis  $\rightarrow$  compensatory erythrocytosis.

Fetal Hb (2  $\alpha$  and 2  $\gamma$  subunits) has higher affinity for  $O_2$  than adult Hb (due to  $\downarrow$  affinity for 2,3-BPG)  $\rightarrow$  dissociation curve is shifted left, driving diffusion of  $O_2$  across the placenta from pregnant patient to fetus.



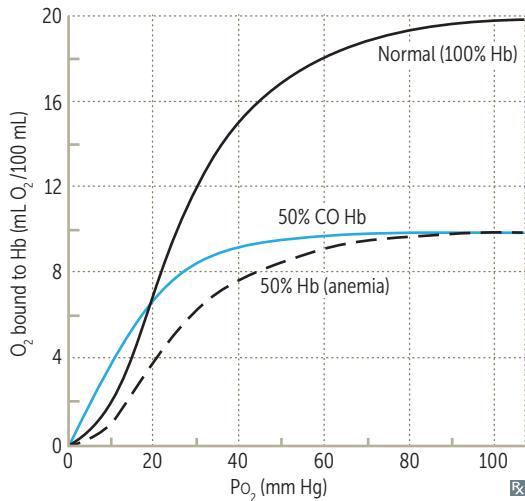
Left shift ( $\downarrow$ $O_2$ unloading to tissue) Left = lower	Right shift ( $\uparrow$ $O_2$ unloading to tissues) <b>ACE BATs right handed</b>
$\downarrow H^+$ ( $\uparrow pH$ , base) $\downarrow Pco_2$ $\downarrow$ 2,3-BPG $\downarrow$ Temperature $\uparrow CO$ $\uparrow$ MethHb $\uparrow$ Hbf	$\uparrow H^+$ ( $\downarrow pH$ , Acid) $\uparrow Pco_2$ <b>Exercise</b> $\uparrow$ 2,3-BPG <b>High Altitude</b> $\uparrow$ Temperature

Rx

### Cyanide vs carbon monoxide poisoning

Both inhibit aerobic metabolism via inhibition of complex IV of ETC (cytochrome c oxidase)  
→ hypoxia that does not fully correct with supplemental O<sub>2</sub> and ↑ anaerobic metabolism.

	Cyanide	Carbon monoxide
EXPOSURE	Synthetic product combustion, amygdalin ingestion (found in apricot seeds), cyanide ingestion (eg, in suicide attempts), fire victims.	Motor exhaust, gas heaters, fire victims.
PRESENTATION	Headache, dyspnea, drowsiness, seizure, coma. May have cherry red skin. Breath may have bitter almond odor.	Headache, vomiting, confusion, visual disturbances, coma. May have cherry-red skin with bullous skin lesions. Multiple victims may be involved (eg, family due to faulty furnace).
LABS	Normal PaO <sub>2</sub> . Elevated lactate → metabolic acidosis.	Normal PaO <sub>2</sub> . Elevated carboxyhemoglobin on co-oximetry. Classically associated with bilateral globus pallidus lesions on MRI <b>A</b> , although can rarely be seen with cyanide toxicity.
EFFECT ON OXYGEN-HEMOGLOBIN CURVE	Curve normal. Oxygen saturation may appear normal initially. Despite ample O <sub>2</sub> supply, it cannot be used due to ineffective oxidative phosphorylation.	Left shift in curve → ↑ affinity for O <sub>2</sub> → ↓ O <sub>2</sub> unloading in tissues. Binds competitively to Hb with > 200× greater affinity than O <sub>2</sub> to form carboxyhemoglobin → ↓ %O <sub>2</sub> saturation of Hb.
TREATMENT	Decontamination (eg, remove clothing). Hydroxocobalamin (binds cyanide → cyanocobalamin → renal excretion). Nitrites (oxidize Hb → methemoglobin → binds cyanide → cyanomethemoglobin → ↓ toxicity). Sodium thiosulfate (↑ cyanide conversion to thiocyanate → renal excretion).	100% O <sub>2</sub> . Hyperbaric oxygen if severe.



**Pulmonary circulation**

Normally a low-resistance, high-compliance system. A ↓ in  $\text{PAO}_2$  causes a hypoxic vasoconstriction that shifts blood away from poorly ventilated regions of lung to well-ventilated regions of lung.

Perfusion limited— $\text{O}_2$  (normal health),  $\text{CO}_2$ ,  $\text{N}_2\text{O}$ . Gas equilibrates early along the length of the capillary. Exchange can be ↑ only if blood flow ↑.

Diffusion limited— $\text{O}_2$  (emphysema, fibrosis, exercise),  $\text{CO}$ . Gas does not equilibrate by the time blood reaches the end of the capillary.  $\text{O}_2$  diffuses slowly, while  $\text{CO}_2$  diffuses very rapidly across the alveolar membrane. Disease states that lead to diffusion limitation (eg, pulmonary fibrosis) are more likely to cause early hypoxia than hypercapnia.

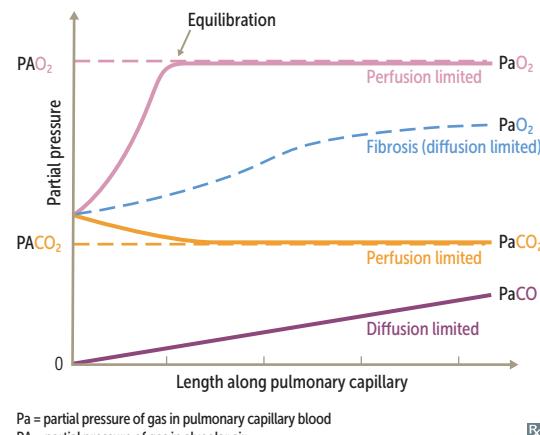
Chronic hypoxic vasoconstriction may lead to pulmonary hypertension +/- cor pulmonale.

$$\text{Diffusion: } \dot{V}_{\text{gas}} = A \times D_k \times \frac{P_1 - P_2}{\Delta_x} \text{ where}$$

$A$  = area,  $\Delta_x$  = alveolar wall thickness,  
 $D_k$  = diffusion coefficient of gas,  $P_1 - P_2$  = difference in partial pressures.  

- $A \downarrow$  in emphysema.
- $\Delta_x \uparrow$  in pulmonary fibrosis.

DLCO is the extent to which  $\text{CO}$  passes from air sacs of lungs into blood.



Pa = partial pressure of gas in pulmonary capillary blood  
PA = partial pressure of gas in alveolar air

**Pulmonary vascular resistance**

$$\text{PVR} = \frac{P_{\text{pulm artery}} - P_{\text{L atrium}}}{Q}$$

Remember:  $\Delta P = Q \times R$ , so  $R = \Delta P / Q$

$$R = \frac{8\eta l}{\pi r^4}$$

$P_{\text{pulm artery}}$  = pressure in pulmonary artery  
 $P_{\text{L atrium}}$  ≈ pulmonary artery occlusion pressure (also called pulmonary capillary wedge pressure)  
 $Q$  = cardiac output (flow)  
 $R$  = resistance  
 $\eta$  = viscosity of blood  
 $l$  = vessel length  
 $r$  = vessel radius

**Alveolar gas equation**

$$\begin{aligned} \text{PAO}_2 &= \text{PIO}_2 - \frac{\text{Paco}_2}{R} \\ &\approx 150 \text{ mm Hg}^a - \frac{\text{Paco}_2}{0.8} \end{aligned}$$

<sup>a</sup>At sea level breathing room air

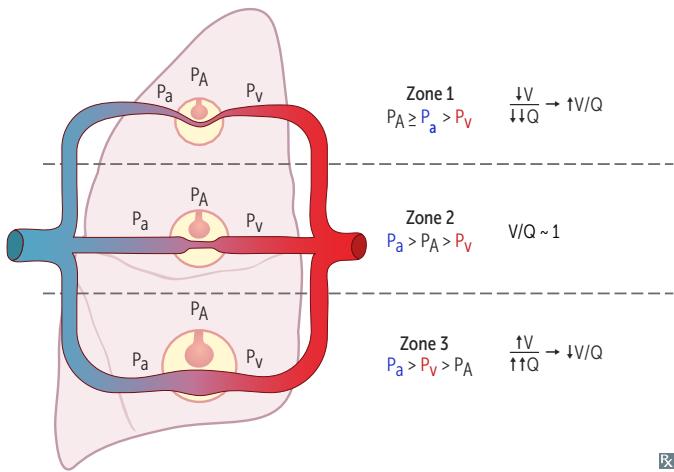
$\text{PAO}_2$  = alveolar  $\text{Po}_2$  (mm Hg)  
 $\text{PIO}_2$  =  $\text{Po}_2$  in inspired air (mm Hg)  
 $\text{Paco}_2$  = arterial  $\text{PCO}_2$  (mm Hg)  
 $R$  = respiratory quotient =  $\text{CO}_2$  produced/  
 $\text{O}_2$  consumed

A-a gradient =  $\text{PAO}_2 - \text{Pao}_2$ . Normal A-a gradient estimated as  $(\text{age}/4) + 4$  (eg, for a person <40 years old, gradient should be <14).

### Oxygen deprivation

Hypoxia ( $\downarrow O_2$ delivery to tissue)	Hypoxemia ( $\downarrow Pao_2$ )	Ischemia (loss of blood flow)
↓ cardiac output	Normal A-a gradient	Impeded arterial flow
Hypoxemia	<ul style="list-style-type: none"> <li>▪ High altitude (<math>\downarrow</math> barometric pressure)</li> </ul>	<ul style="list-style-type: none"> <li>↓ venous drainage</li> </ul>
Ischemia	<ul style="list-style-type: none"> <li>▪ Hypoventilation (eg, opioid use, obesity hypoventilation syndrome)</li> </ul>	
Anemia		
CO/cyanide poisoning	<ul style="list-style-type: none"> <li>↑ A-a gradient</li> <li>▪ <math>\dot{V}/\dot{Q}</math> mismatch</li> <li>▪ Diffusion limitation (eg, fibrosis)</li> <li>▪ Right-to-left shunt</li> </ul>	

<b>Ventilation/perfusion mismatch</b>	Ideally, ventilation is matched to perfusion (ie, $\dot{V}/\dot{Q} = 1$ ) for adequate gas exchange. Lung zones: <ul style="list-style-type: none"><li>▪ <math>\dot{V}/\dot{Q}</math> at apex of lung = 3 (wasted ventilation)</li><li>▪ <math>\dot{V}/\dot{Q}</math> at base of lung = 0.6 (wasted perfusion)</li></ul> Both ventilation and perfusion are greater at the base of the lung than at the apex of the lung. With exercise ( $\uparrow$ cardiac output), there is vasodilation of apical capillaries $\rightarrow \dot{V}/\dot{Q}$ 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).
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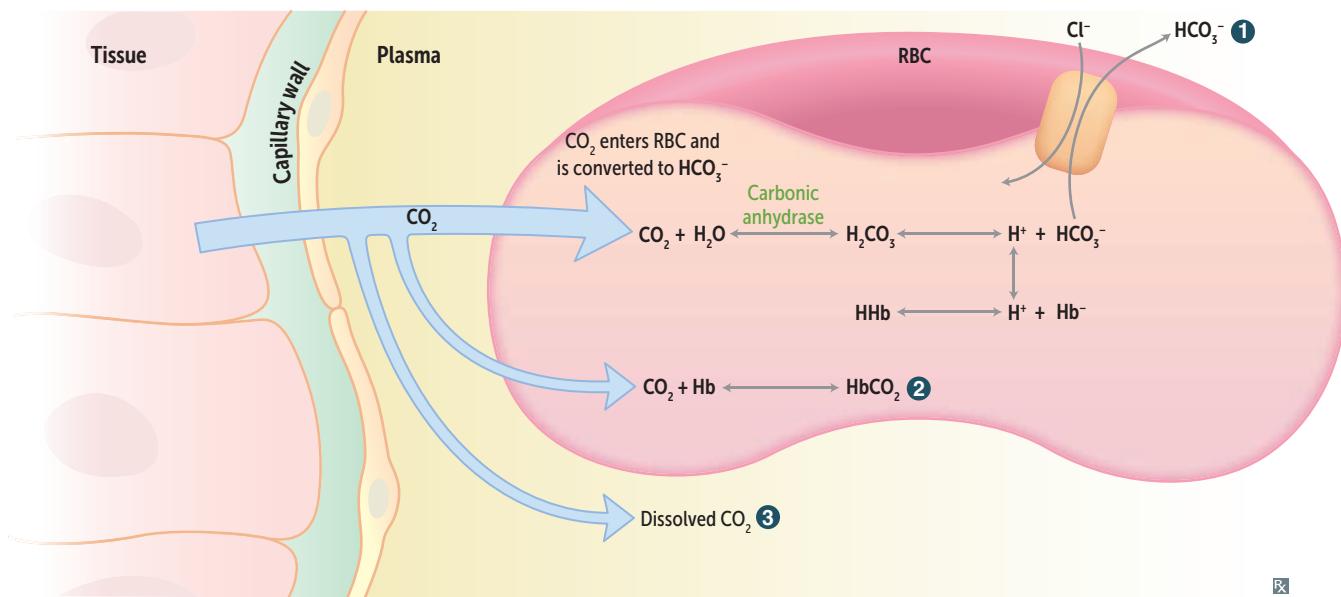


### Carbon dioxide transport

$\text{CO}_2$  is transported from tissues to lungs in 3 forms:

- ①  $\text{HCO}_3^-$  (70%).  $\text{HCO}_3^-/\text{Cl}^-$  transporter on RBC membrane allows  $\text{HCO}_3^-$  to diffuse out to plasma and  $\text{Cl}^-$  to diffuse into RBC (chloride shift).
- ② Carbaminohemoglobin or  $\text{HbCO}_2$  (21–25%).  $\text{CO}_2$  bound to Hb at N-terminus of globin (not heme).  $\text{CO}_2$  favors deoxygenated form ( $\text{O}_2$  unloaded).
- ③ Dissolved  $\text{CO}_2$  (5–9%).

In lungs, oxygenation of Hb promotes dissociation of  $\text{H}^+$  from Hb. This shifts equilibrium toward  $\text{CO}_2$  formation; therefore,  $\text{CO}_2$  is released from RBCs (Haldane effect). Majority of blood  $\text{CO}_2$  is carried as  $\text{HCO}_3^-$  in the plasma.



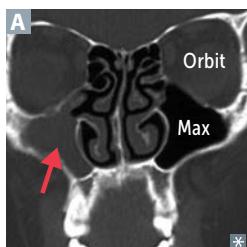
### Response to high altitude

↓ atmospheric oxygen ( $\text{PiO}_2$ ) → ↓  $\text{PaO}_2$  → ↑ ventilation → ↓  $\text{Paco}_2$  → respiratory alkalosis → altitude sickness (headaches, nausea, fatigue, lightheadedness, sleep disturbance). Chronic ↑ in ventilation.  
↑ erythropoietin → ↑ Hct and Hb (due to chronic hypoxia).  
↑ 2,3-BPG (binds to Hb → rightward shift of ODC dissociation curve → ↑  $\text{O}_2$  release).  
Cellular changes (↑ mitochondria).  
↑ renal excretion of  $\text{HCO}_3^-$  to compensate for respiratory alkalosis (can augment with acetazolamide).  
Chronic hypoxic pulmonary vasoconstriction → ↑ pulmonary vascular resistance → pulmonary hypertension, RVH.

### Response to exercise

↑  $\text{CO}_2$  production.  
↑  $\text{O}_2$  consumption.  
Right shift of ODC.  
↑ ventilation to meet  $\text{O}_2$  demand and remove excess  $\text{CO}_2$ .  
 $\dot{V}/\dot{Q}$  ratio from apex to base becomes more uniform.  
↑ pulmonary blood flow due to ↑ cardiac output.  
↓ pH during strenuous exercise ( $2^\circ$  to lactic acidosis).  
No change in  $\text{PaO}_2$  and  $\text{Paco}_2$ , but ↑ in venous  $\text{CO}_2$  content and ↓ in venous  $\text{O}_2$  content.

## ► RESPIRATORY—PATHOLOGY

**Rhinosinusitis**

Obstruction of sinus drainage into nasal cavity → inflammation and pain over affected area.

Typically affects maxillary sinuses, which drain against gravity due to ostia located superomedially (red arrow points to fluid-filled right maxillary sinus in **A**).

Superior meatus—drains sphenoid, posterior ethmoid; middle meatus—drains frontal, maxillary, and anterior ethmoid; inferior meatus—drains nasolacrimal duct.

Acute rhinosinusitis is most commonly caused by viruses (eg, rhinovirus); may lead to superimposed bacterial infection, most commonly *H influenzae*, *S pneumoniae*, *M catarrhalis*.

Paranasal sinus infections may extend to the orbits, cavernous sinus, and brain, causing complications (eg, orbital cellulitis, cavernous sinus syndrome, meningitis).

**Epistaxis**

Nose bleed. Most commonly occurs in anterior segment of nostril (**Kiesselbach plexus**). Life-threatening hemorrhages occur in posterior segment (sphenopalatine artery, a branch of maxillary artery). Common causes include foreign body, trauma, allergic rhinitis, and nasal angiofibromas (common in adolescent males).

**Kiesselbach** drives his **Lexus** with his **LEGS**: superior **L**abial artery, anterior and posterior **E**thmoidal arteries, **G**reater palatine artery, **S**phenopalatine artery.

**Head and neck cancer**

Mostly squamous cell carcinoma. Risk factors include tobacco, alcohol, HPV-16 (oropharyngeal), EBV (nasopharyngeal). Field cancerization: carcinogen damages wide mucosal area → multiple tumors that develop independently after exposure.

Nasopharyngeal carcinoma may present with unilateral nasal obstruction, discharge, epistaxis. Eustachian tube obstruction may lead to otitis media +/- effusion, hearing loss.

**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; oral contraceptive use; pregnancy)
- **E**ndothelial damage (exposed collagen triggers clotting cascade)

Most pulmonary emboli arise from proximal deep veins of lower extremity (iliac, femoral, popliteal veins).

D-dimer test may be used clinically to rule out DVT if disease probability is low or moderate (high sensitivity, low specificity).

Imaging test of choice is compression ultrasound with Doppler.

Use unfractionated heparin or low-molecular weight heparins (eg, enoxaparin) for prophylaxis and acute management.

Use direct anticoagulants (eg, rivaroxaban, apixaban) for treatment and long-term prevention.

**Pulmonary emboli**

Obstruction of the pulmonary artery or its branches by foreign material (usually thrombus) that originated elsewhere. Affected alveoli are ventilated but not perfused (V/Q mismatch). May present with sudden-onset dyspnea, pleuritic chest pain, tachypnea, tachycardia, hypoxemia, respiratory alkalosis. Large emboli or saddle embolus **A** may cause sudden death due to electromechanical dissociation (pulseless electrical activity). CT pulmonary angiography is imaging test of choice for PE (look for filling defects) **B**. ECG may show sinus tachycardia or, less commonly, SIQ3T3 abnormality. Lines of Zahn **C** are interdigitating areas of pink (platelets, fibrin) and red (RBCs) found only in thrombi formed before death; help distinguish pre- and postmortem thrombi.

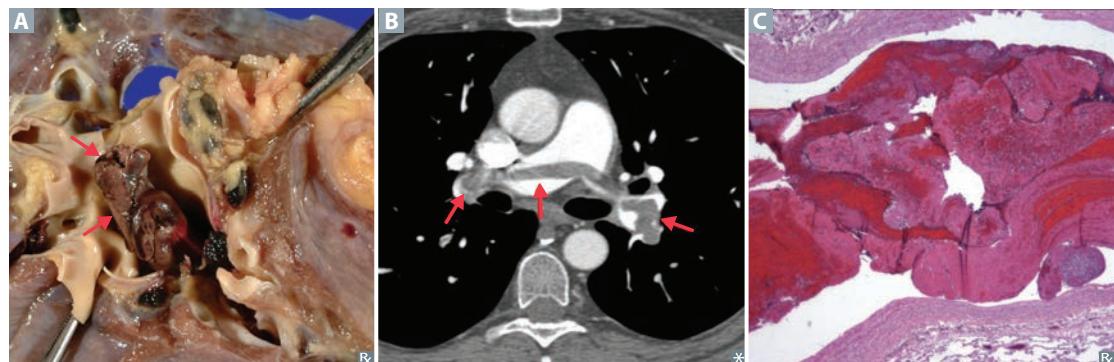
Treatment: anticoagulation (eg, heparin, direct thrombin/factor Xa inhibitors), IVC filter (if anticoagulation is contraindicated).

Types: **Fat, Air, Thrombus, Bacteria, Amniotic fluid, Tumor**. An embolus moves like a **FAT BAT**.

**Fat emboli**—associated with long bone fractures and liposuction; classic triad of hypoxemia, neurologic abnormalities, petechial rash.

**Air emboli**—nitrogen bubbles precipitate in ascending divers (caisson disease/decompression sickness); treat with hyperbaric O<sub>2</sub>; or, can be iatrogenic 2° to invasive procedures (eg, central line placement).

**Amniotic fluid emboli**—typically occurs during labor or postpartum, but can be due to uterine trauma. Can lead to DIC. Rare, but high mortality.

**Mediastinal pathology**

Normal mediastinum contains heart, thymus, lymph nodes, esophagus, and aorta.

**Mediastinal masses**

Some pathologies (eg, lymphoma, lung cancer, abscess) can occur in any compartment, but there are common associations:

- Anterior—**4 T's**: thyroid (substernal goiter), thymic neoplasm, teratoma, “terrible” lymphoma.
- Middle—esophageal carcinoma, metastases, hiatal hernia, bronchogenic cysts.
- Posterior—neurogenic tumor (eg, neurofibroma), multiple myeloma.

**Mediastinitis**

Inflammation of mediastinal tissues. Commonly due to postoperative complications of cardiothoracic procedures ( $\leq 14$  days), esophageal perforation, or contiguous spread of odontogenic/retropharyngeal infection.

Chronic mediastinitis—also known as fibrosing mediastinitis; due to ↑ proliferation of connective tissue in mediastinum. *Histoplasma capsulatum* is common cause.

Clinical features: fever, tachycardia, leukocytosis, chest pain, and sternal wound drainage.

**Pneumomediastinum**

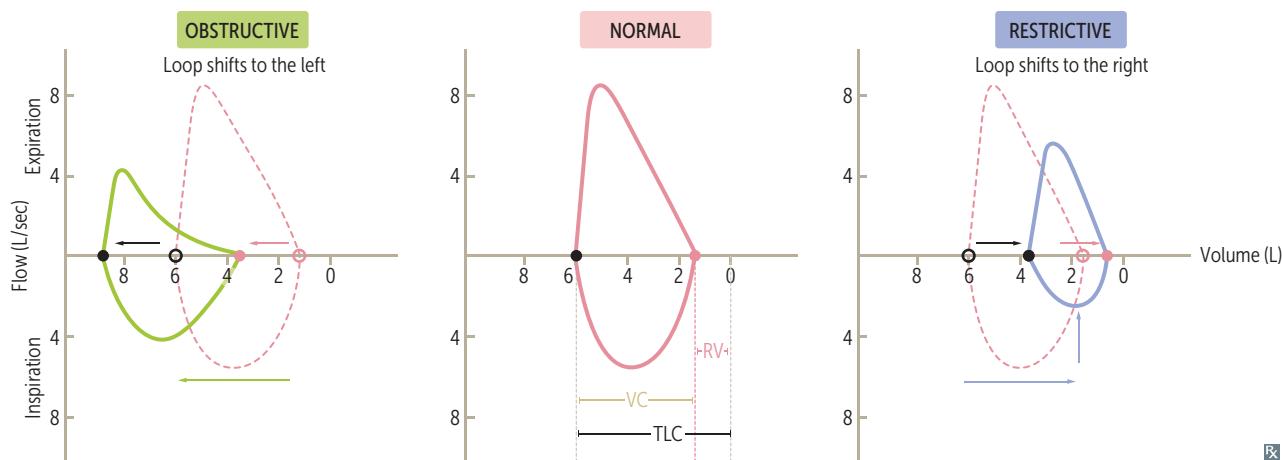
Presence of gas (usually air) in the mediastinum. Can either be spontaneous (due to rupture of pulmonary bleb) or 2° (eg, trauma, iatrogenic, Boerhaave syndrome).

Ruptured alveoli allow tracking of air into the mediastinum via peribronchial and perivascular sheaths.

Clinical features: chest pain, dyspnea, voice change, subcutaneous emphysema,  $\oplus$  Hamman sign (crepitus on cardiac auscultation).

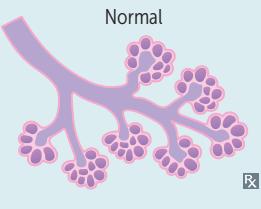
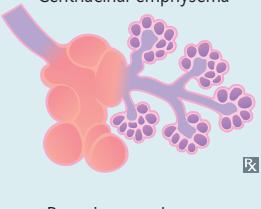
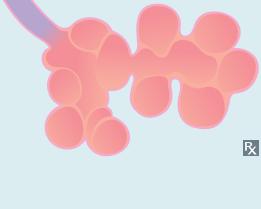
**Flow-volume loops**

FLOW-VOLUME PARAMETER	Obstructive lung disease	Restrictive lung disease
RV	↑	↓
FRC	↑	↓
TLC	↑	↓
FEV <sub>1</sub>	↓↓	↓
FVC	↓	↓
FEV <sub>1</sub> /FVC	↓ FEV <sub>1</sub> decreased more than FVC	Normal or ↑ FEV <sub>1</sub> decreased proportionately to FVC



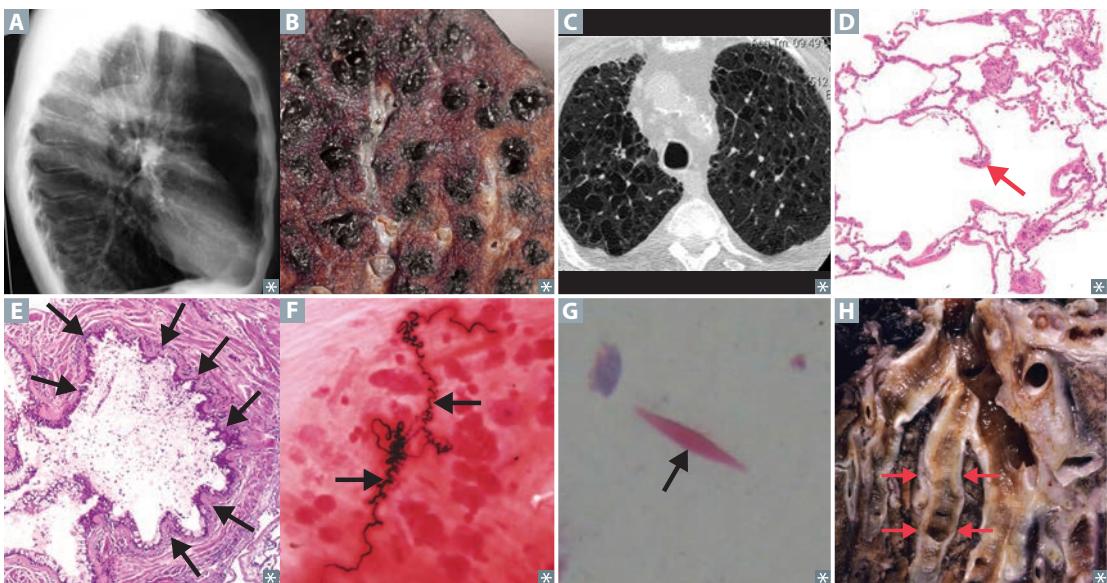
**Obstructive lung diseases**

Obstruction of air flow ( $\uparrow$  FRC,  $\uparrow$  RV,  $\uparrow$  TLC)  $\rightarrow$  air trapping in lungs with premature airway closure at high lung volumes ( $\downarrow\downarrow$  FEV<sub>1</sub>,  $\downarrow$  FVC  $\downarrow$  FEV<sub>1</sub>/FVC ratio). Leads to  $\dot{V}/\dot{Q}$  mismatch.

TYPE	PRESENTATION	PATHOLOGY	OTHER
<b>Chronic bronchitis</b>	Wheezing, crackles, cyanosis (hypoxemia due to shunting), dyspnea, CO <sub>2</sub> retention, 2° polycythemia.	Hypertrophy and hyperplasia of mucus-secreting glands in bronchi $\rightarrow$ Reid index (thickness of mucosal gland layer to thickness of wall between epithelium and cartilage) $> 50\%$ . DLCO may be normal.	Diagnostic criteria: productive cough for $\geq 3$ months in a year for $> 2$ consecutive years.
<b>Emphysema</b>	<p>Barrel-shaped chest <b>A</b>, expiration is prolonged and/or through pursed lips (increases airway pressure and prevents airway collapse).</p>   	<p>Centriacinar—affects respiratory bronchioles while sparing distal alveoli, associated with tobacco <b>smoking B C</b>. Frequently in upper lobes (<b>smoke rises up</b>).</p> <p>Panacinar—affects respiratory bronchioles and alveoli, associated with <math>\alpha_1</math>-antitrypsin deficiency. Frequently in lower lobes.</p> <p>Enlargement of air spaces <math>\downarrow</math> recoil, <math>\uparrow</math> compliance, <math>\downarrow</math> DLCO from destruction of alveolar walls (arrow in <b>D</b>) and <math>\downarrow</math> blood volume in pulmonary capillaries.</p> <p>Imbalance of proteases and antiproteases <math>\rightarrow</math> <math>\uparrow</math> elastase activity <math>\rightarrow</math> <math>\uparrow</math> loss of elastic fibers <math>\rightarrow</math> <math>\uparrow</math> lung compliance.</p>	CXR: $\uparrow$ AP diameter, flattened diaphragm, $\uparrow$ lung field lucency. Chronic inflammation is mediated by CD8 <sup>+</sup> T cells, neutrophils, and macrophages.
<b>Asthma</b>	<p>Asymptomatic baseline with intermittent episodes of coughing, wheezing, tachypnea, dyspnea, hypoxemia, <math>\downarrow</math> inspiratory/expiratory ratio, mucus plugging <b>E</b>. Severe attacks may lead to pulsus paradoxus.</p> <p>Triggers: viral URIs, allergens, stress.</p>	<p>Hyperresponsive bronchi <math>\rightarrow</math> reversible bronchoconstriction.</p> <p>Smooth muscle hypertrophy and hyperplasia, Curschmann spirals <b>F</b> (shed epithelium forms whorled mucous plugs), and Charcot-Leyden crystals <b>G</b> (eosinophilic, hexagonal, double-pointed crystals formed from breakdown of eosinophils in sputum). DLCO normal or <math>\uparrow</math>.</p>	<p>Type I hypersensitivity reaction.</p> <p>Diagnosis supported by spirometry +/- methacholine challenge.</p> <p>NSAID-exacerbated respiratory disease is a combination of COX inhibition (leukotriene overproduction <math>\rightarrow</math> airway constriction), chronic sinusitis with nasal polyps, and asthma symptoms.</p>

**Obstructive lung diseases (continued)**

TYPE	PRESENTATION	PATHOLOGY	OTHER
<b>Bronchiectasis</b>	Daily purulent sputum, recurrent infections (most often <i>P aeruginosa</i> ), hemoptysis, digital clubbing.	Chronic necrotizing infection of bronchi or obstruction → permanently dilated airways.	Associated with bronchial obstruction, poor ciliary motility (eg, tobacco smoking, Kartagener syndrome), cystic fibrosis (arrows in H show dilated airway with mucus plug), allergic bronchopulmonary aspergillosis.

**Restrictive lung diseases**

May lead to ↓ lung volumes (↓ FVC and TLC). PFTs: normal or ↑ FEV<sub>1</sub>/FVC ratio. Patient presents with short, shallow breaths.

Types:

- Altered respiratory mechanics (extrapulmonary, normal D<sub>LCO</sub>, normal A-a gradient):
  - Respiratory muscle weakness—polio, myasthenia gravis, Guillain-Barré syndrome, ALS
  - Chest wall abnormalities—scoliosis, severe obesity
- Diffuse parenchymal lung diseases, also known as interstitial lung diseases (pulmonary, ↓ D<sub>LCO</sub>, ↑ A-a gradient):
  - Pneumoconioses (eg, coal workers' pneumoconiosis, silicosis, asbestosis)
  - Sarcoidosis: bilateral hilar lymphadenopathy, noncaseating granulomas; ↑ ACE and Ca<sup>2+</sup>
  - Idiopathic pulmonary fibrosis
  - Granulomatosis with polyangiitis
  - Pulmonary Langerhans cell histiocytosis (eosinophilic granuloma)
  - Hypersensitivity pneumonitis
  - Drug toxicity (eg, bleomycin, busulfan, amiodarone, methotrexate)
  - Acute respiratory distress syndrome
  - **Radiation-induced lung injury**—Associated with proinflammatory cytokine release (eg, TNF-α, IL-1, IL-6). May be asymptomatic but most common symptoms are dry cough and dyspnea ± low-grade fever. Acute radiation pneumonitis develops within 3–12 weeks (exudative phase); radiation fibrosis may develop after 6–12 months.

**Idiopathic pulmonary fibrosis**

Progressive fibrotic lung disease of unknown etiology. May involve multiple cycles of lung injury, inflammation, and fibrosis. Associated with cigarette smoking, environmental pollutants, genetic defects.

Findings: progressive dyspnea, fatigue, nonproductive cough, crackles, clubbing. Imaging shows peripheral reticular opacities with traction bronchiectasis +/- “honeycomb” appearance of lung (advanced disease). Histologic pattern: usual interstitial pneumonia.

Complications: pulmonary hypertension, respiratory failure, lung cancer, arrhythmias.

**Hypersensitivity pneumonitis**

Mixed type III/IV hypersensitivity reaction to environmental antigens. Often seen in farmers and bird-fanciers. Acutely, causes dyspnea, cough, chest tightness, fever, headache. Often self-limiting if stimulus is removed. Chronically, leads to irreversible fibrosis with noncaseating granuloma, alveolar septal thickening, traction bronchiectasis.

**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 Black females. Often asymptomatic except for enlarged lymph nodes. CXR shows bilateral adenopathy and coarse reticular opacities **B**; CT of the chest better demonstrates the extensive hilar and mediastinal adenopathy **C**.

Associated with Bell palsy, uveitis, granulomas (noncaseating epithelioid, containing microscopic Schaumann and asteroid bodies), lupus pernio (skin lesions on face resembling lupus), interstitial fibrosis (restrictive lung disease), erythema nodosum, rheumatoid arthritis-like arthropathy, hypercalcemia (due to ↑ 1 $\alpha$ -hydroxylase-mediated vitamin D activation in macrophages).

Treatment: steroids (if symptomatic).

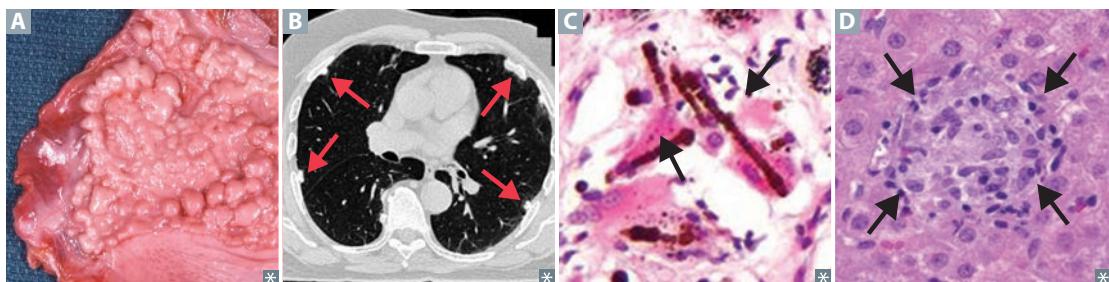
**Inhalation injury and sequelae**

Complication of inhalation of noxious stimuli (eg, smoke). Caused by heat, particulates (< 1  $\mu\text{m}$  diameter), or irritants (eg,  $\text{NH}_3$ ) → chemical tracheobronchitis, edema, pneumonia, ARDS. Many patients present 2° to burns, CO inhalation, cyanide poisoning, or arsenic poisoning. Singed nasal hairs or soot in oropharynx common on exam.

Bronchoscopy shows severe edema, congestion of bronchus, and soot deposition (**A**, 18 hours after inhalation injury; **B**, resolution at 11 days after injury).



<b>Pneumoconioses</b>	<b>Asbestos</b> is from the <b>roof</b> (was common in insulation), but affects the <b>base</b> (lower lobes). <b>Silica, coal, and berries</b> are from the <b>base</b> (earth), but affect the <b>roof</b> (upper lobes).
<b>Asbestos-related disease</b>	Asbestos causes asbestosis (pulmonary fibrosis), pleural disease, malignancies. Associated with shipbuilding, roofing, plumbing. “Ivory white,” calcified, supradiaphragmatic <b>A</b> and pleural <b>B</b> plaques are pathognomonic. Risk of bronchogenic carcinoma > risk of mesothelioma. ↑ risk of Caplan syndrome (rheumatoid arthritis and pneumoconioses with intrapulmonary nodules).
<b>Berylliosis</b>	Associated with exposure to beryllium in aerospace and manufacturing industries. Granulomatous (noncaseating) <b>D</b> on histology and therefore occasionally responsive to steroids. ↑ risk of cancer and cor pulmonale.
<b>Coal workers' pneumoconiosis</b>	Prolonged coal dust exposure → macrophages laden with <b>carbon</b> → inflammation and fibrosis. Also known as black lung disease. ↑ risk of <b>Caplan syndrome</b> .
<b>Silicosis</b>	Associated with <b>sandblasting</b> , <b>foundries</b> , <b>mines</b> . Macrophages respond to silica and release fibrogenic factors, leading to fibrosis. It is thought that silica may disrupt phagolysosomes and impair macrophages, increasing susceptibility to TB. ↑ risk of cancer, cor pulmonale, and Caplan syndrome.



**Mesothelioma**

Malignancy of the pleura associated with asbestos. May result in hemorrhagic pleural effusion (exudative), pleural thickening **A**.

Histology may show psammoma bodies. EM may show polygonal tumor cells with microvilli, desmosomes, tonofilaments.

Calretinin and cytokeratin 5/6  $\oplus$  in almost all mesotheliomas,  $\ominus$  in most carcinomas. Tobacco smoking is not a risk factor.

**Acute respiratory distress syndrome**

## PATHOPHYSIOLOGY

Alveolar insult  $\rightarrow$  release of pro-inflammatory cytokines  $\rightarrow$  neutrophil recruitment, activation, and release of toxic mediators (eg, reactive oxygen species, proteases, etc)  $\rightarrow$  capillary endothelial damage and  $\uparrow$  vessel permeability  $\rightarrow$  leakage of protein-rich fluid into alveoli  $\rightarrow$  formation of intra-alveolar hyaline membranes (arrows in **A**) and noncardiogenic pulmonary edema (normal PCWP).

Loss of surfactant also contributes to alveolar collapse.

## CAUSES

Sepsis (most common), aspiration, pneumonia, trauma, pancreatitis.

## DIAGNOSIS

Diagnosis of exclusion with the following criteria (**ARDS**):

- **A**bnormal chest X-ray (bilateral lung opacities) **B**
- **R**espiratory failure within 1 week of alveolar insult
- **D**ecreased  $\text{PaO}_2/\text{FiO}_2$  (ratio  $< 300$ , hypoxemia due to  $\uparrow$  intrapulmonary shunting and diffusion abnormalities)
- **S**ymptoms of respiratory failure are not due to HF/fluid overload

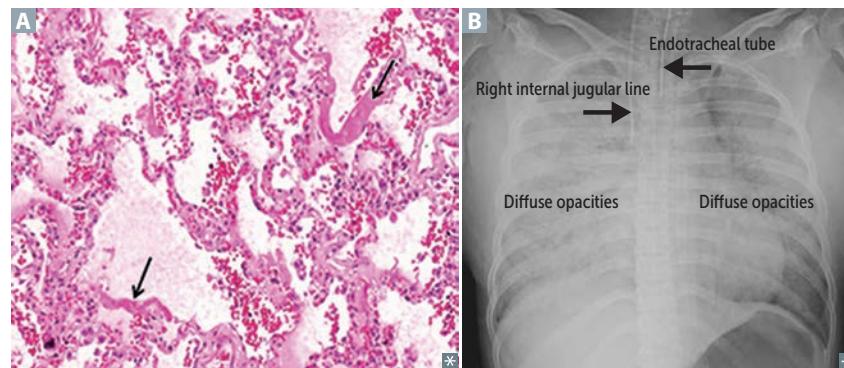
## CONSEQUENCES

Impaired gas exchange,  $\downarrow$  lung compliance; pulmonary hypertension.

## MANAGEMENT

Treat the underlying cause.

Mechanical ventilation:  $\downarrow$  tidal volume,  $\uparrow$  PEEP (keeps alveoli open during expiration).



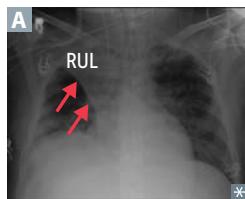
<b>Sleep apnea</b>	Repeated cessation of breathing > 10 seconds during sleep → disrupted sleep → daytime somnolence. Diagnosis confirmed by sleep study. Nocturnal hypoxia → systemic and pulmonary hypertension, arrhythmias (atrial fibrillation/flutter), sudden death. Hypoxia → ↑ EPO release → ↑ erythropoiesis.
<b>Obstructive sleep apnea</b>	Respiratory effort against airway obstruction. $\text{Pao}_2$ is usually normal during the day. Associated with obesity, loud snoring, daytime sleepiness. Usually caused by excess parapharyngeal/oropharyngeal tissue in adults, adenotonsillar hypertrophy in children. Treatment: weight loss, CPAP, dental devices, hypoglossal nerve stimulation, upper airway surgery.
<b>Central sleep apnea</b>	Impaired respiratory effort due to <b>CNS</b> injury/toxicity, <b>Congestive HF</b> , opioids. May be associated with <b>Cheyne-Stokes</b> respirations (oscillations between apnea and hyperpnea). Treatment: positive airway pressure.
<b>Obesity hypoventilation syndrome</b>	Also called Pickwickian syndrome. Obesity ( $\text{BMI} \geq 30 \text{ kg/m}^2$ ) → hypoventilation → ↑ $\text{Paco}_2$ during waking hours (retention); ↓ $\text{Pao}_2$ and ↑ $\text{Paco}_2$ during sleep. Treatment: weight loss, positive airway pressure.
<b>Pulmonary hypertension</b>	Elevated mean pulmonary artery pressure (> 20 mm Hg) at rest. Results in arteriosclerosis, medial hypertrophy, intimal fibrosis of pulmonary arteries, plexiform lesions. ↑ pulmonary vascular resistance → ↑ RV pressure → RVH, RV failure.
<hr/> <b>ETIOLOGIES</b>	
<b>Pulmonary arterial hypertension</b>	Often idiopathic. Females > males. Heritable PAH can be due to an inactivating mutation in <i>BMPR2</i> gene (normally inhibits vascular smooth muscle proliferation); poor prognosis. Pulmonary vasculature endothelial dysfunction results in ↑ vasoconstrictors (eg, endothelin) and ↓ vasodilators (eg, NO and prostacyclins). Other causes include drugs (eg, amphetamines, cocaine), connective tissue disease, HIV infection, portal hypertension, congenital heart disease, schistosomiasis.
<b>Left heart disease</b>	Causes include systolic/diastolic dysfunction and valvular disease.
<b>Lung diseases or hypoxia</b>	Destruction of lung parenchyma (eg, COPD), lung inflammation/fibrosis (eg, interstitial lung diseases), hypoxicemic vasoconstriction (eg, obstructive sleep apnea, living in high altitude).
<b>Chronic thromboembolic</b>	Recurrent microthrombi → ↓ cross-sectional area of pulmonary vascular bed.
<b>Multifactorial</b>	Causes include hematologic, systemic, and metabolic disorders, along with compression of the pulmonary vasculature by a tumor.

**Physical findings in select lung diseases**

ABNORMALITY	BREATH SOUNDS	PERCUSSION	FREMITUS	TRACHEAL DEVIATION
<b>Pleural effusion</b>	↓	Dull	↓	None if small Away from side of lesion if large
<b>Atelectasis</b>	↓	Dull	↓	Toward side of lesion
<b>Simple pneumothorax</b>	↓	Hyperresonant	↓	None
<b>Tension pneumothorax</b>	↓	Hyperresonant	↓	Away from side of lesion
<b>Consolidation (lobar pneumonia, pulmonary edema)</b>	Bronchial breath sounds; late inspiratory crackles, egophony, whispered pectoriloquy	Dull	↑	None

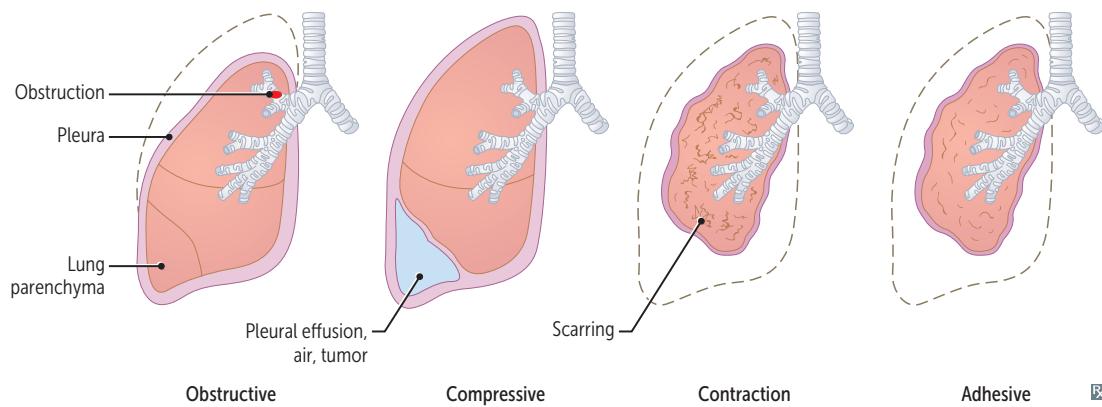
**Digital clubbing**

Increased angle between nail bed and nail plate ( $> 180^\circ$ ) **A**. Pathophysiology not well understood; in patients with intrapulmonary shunt, platelets and megakaryocytes become lodged in digital vasculature → local release of PDGF and VEGF. Can be hereditary or acquired. Causes include respiratory diseases (eg, idiopathic pulmonary fibrosis, cystic fibrosis, bronchiectasis, lung cancer), cardiovascular diseases (eg, cyanotic congenital heart disease), infections (eg, lung abscess, TB), and others (eg, IBD). Not typically associated with COPD or asthma.

**Atelectasis**

Alveolar collapse (right upper lobe collapse against mediastinum in **A**). Multiple causes:

- Obstructive—airway obstruction prevents new air from reaching distal airways, old air is resorbed (eg, foreign body, mucous plug, tumor)
- Compressive—external compression on lung decreases lung volumes (eg, space-occupying lesion, pleural effusion)
- Contraction (cicatrization)—scarring of lung parenchyma that distorts alveoli (eg, sarcoidosis)
- Adhesive—due to lack of surfactant (eg, NRDS in premature babies)



**Pleural effusions**

Excess accumulation of fluid **A** between pleural layers → restricted lung expansion during inspiration. Can be treated with thoracentesis to remove/reduce fluid **B**. Based on the Light criteria, fluid is exudate if pleural fluid protein/serum protein  $> 0.5$ , pleural fluid LDH/serum LDH  $> 0.6$ , or pleural fluid LDH  $> 2/3$  upper limit of normal serum LDH.

**Exudate**

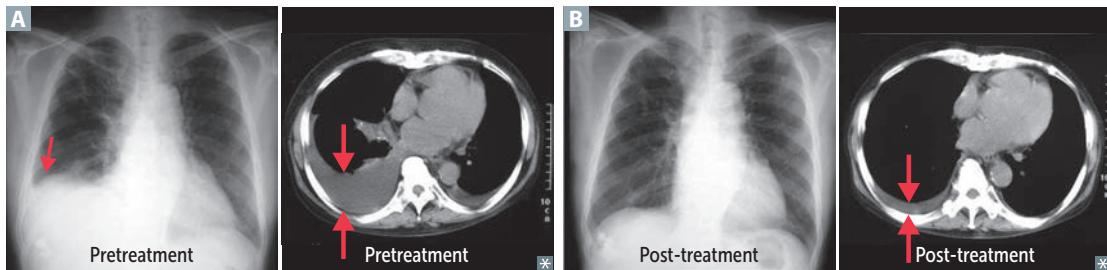
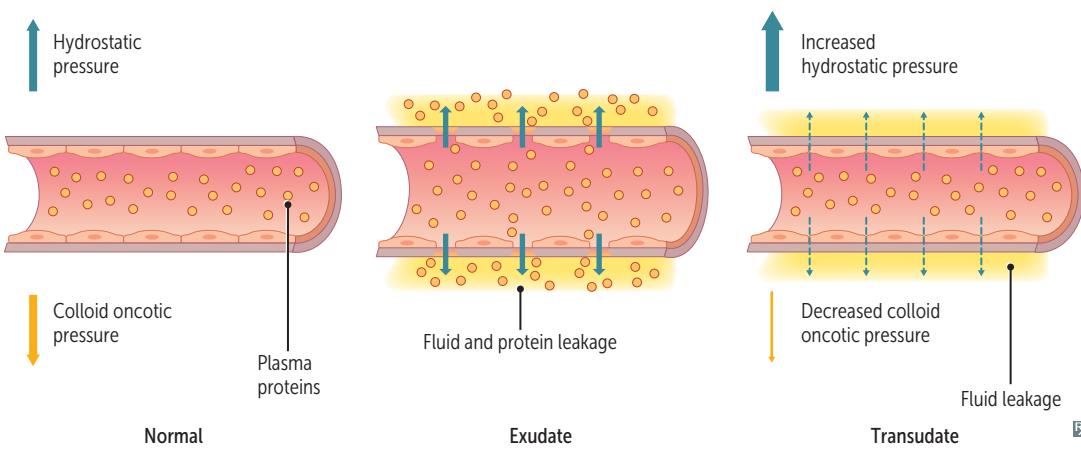
Cloudy fluid (cellular). Due to malignancy, inflammation/infection (eg, pneumonia, collagen vascular disease), trauma (occurs in states of ↑ vascular permeability). Often needs to be drained due to risk of infection.

**Transudate**

Clear fluid (hypocellular). Due to ↑ hydrostatic pressure (eg, HF,  $\text{Na}^+$  retention) and/or ↓ oncotic pressure (eg, nephrotic syndrome, cirrhosis).

**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**. Dyspnea, uneven chest expansion. Chest pain, ↓ tactile fremitus, hyperresonance, and diminished breath sounds, all on the affected side.

**Primary spontaneous pneumothorax**

Due to rupture of apical subpleural bleb or cysts. Occurs most frequently in tall, thin, young males. Associated with tobacco smoking.

**Secondary spontaneous pneumothorax**

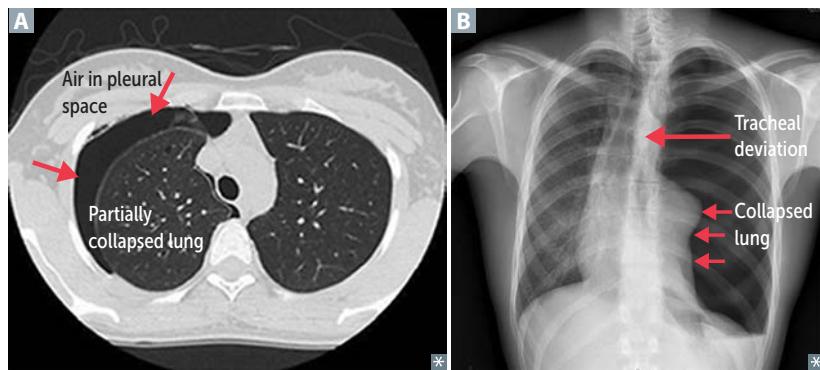
Due to diseased lung (eg, bullae in emphysema, Marfan syndrome, infections), mechanical ventilation with use of high pressures → barotrauma.

**Traumatic pneumothorax**

Caused by blunt (eg, rib fracture), penetrating (eg, gunshot), or iatrogenic (eg, central line placement, lung biopsy, barotrauma due to mechanical ventilation) trauma.

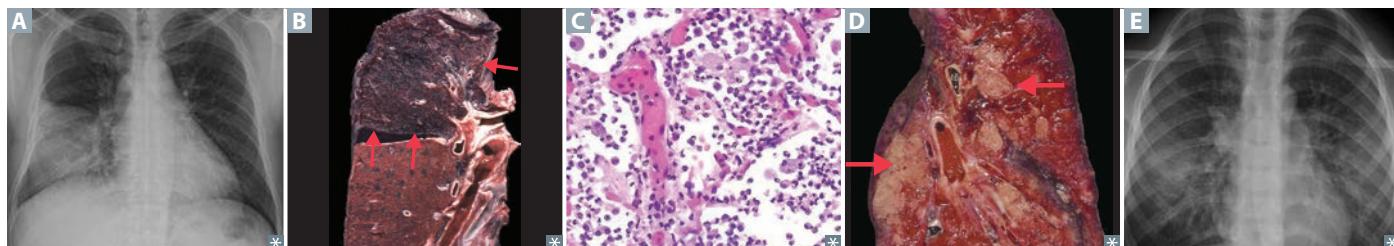
**Tension pneumothorax**

Can be from any of the above. Air enters pleural space but cannot exit. Increasing trapped air → tension pneumothorax. Trachea deviates away from affected lung **B**. May lead to increased intrathoracic pressure → mediastinal displacement → kinking of IVC → ↓ venous return → ↓ cardiac output, obstructive shock (hypotension, tachycardia), jugular venous distention. Needs immediate needle decompression and chest tube placement.

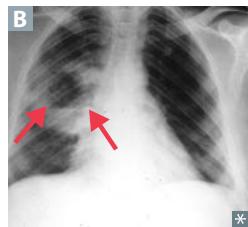


**Pneumonia**

TYPE	TYPICAL ORGANISMS	CHARACTERISTICS
<b>Lobar pneumonia</b>	<i>S pneumoniae</i> (most common), <i>Legionella</i> , <i>Klebsiella</i>	Intra-alveolar exudate → consolidation <b>A</b> ; may involve entire lobe <b>B</b> or the whole lung.
<b>Bronchopneumonia</b>	<i>S pneumoniae</i> , <i>S aureus</i> , <i>H influenzae</i> , <i>Klebsiella</i>	Acute inflammatory infiltrates <b>C</b> from bronchioles into adjacent alveoli; patchy distribution involving ≥ 1 lobe <b>D</b> .
<b>Interstitial (atypical) pneumonia</b>	<i>Mycoplasma</i> , <i>Chlamydophila pneumoniae</i> , <i>Chlamydophila psittaci</i> , <i>Legionella</i> , <i>Coxiella burnetii</i> , viruses (RSV, CMV, influenza, adenovirus)	Diffuse patchy inflammation localized to interstitial areas at alveolar walls; CXR shows bilateral multifocal opacities <b>E</b> . Generally follows a more indolent course (“walking” pneumonia).
<b>Cryptogenic organizing pneumonia</b>	Etiology unknown. ⊖ sputum and blood cultures, often responds to steroids but not to antibiotics.	Formerly known as bronchiolitis obliterans organizing pneumonia (BOOP). Noninfectious pneumonia characterized by inflammation of bronchioles and surrounding structure.

**Natural history of lobar pneumonia**

	Congestion	Red hepatization	Gray hepatization	Resolution
DAYS	1–2	3–4	5–7	8+
FINDINGS	Red-purple, partial consolidation of parenchyma Exudate with mostly bacteria	Red-brown consolidation Exudate with fibrin, bacteria, RBCs, WBCs Reversible	Uniformly gray Exudate full of WBCs, lysed RBCs, and fibrin	Enzymatic digestion of exudate by macrophages
	<b>Normal</b>	<b>Congestion</b>	<b>Red hepatization</b>	<b>Gray hepatization</b>
				<b>Resolution</b>

**Lung abscess**

Localized collection of pus within parenchyma **A**. Caused by aspiration of oropharyngeal contents (especially in patients predisposed to loss of consciousness [eg, alcohol overuse, epilepsy]) or bronchial obstruction (eg, cancer).

Air-fluid levels **B** often seen on CXR; presence suggests cavitation. Due to anaerobes (eg, *Bacteroides*, *Fusobacterium*, *Peptostreptococcus*) or *S aureus*.

Treatment: antibiotics, drainage, or surgery.

Lung abscess 2° to aspiration is most often found in right lung. Location depends on patient's position during aspiration: RLL if upright, RUL or RML if recumbent.

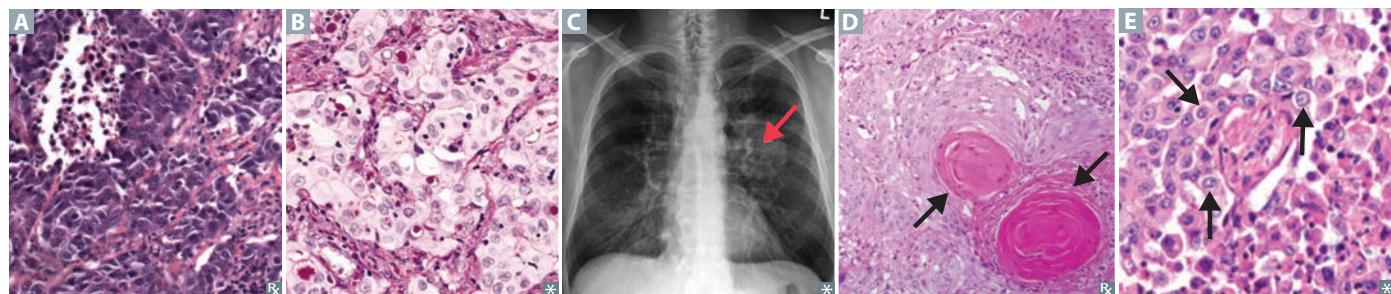
**Lung cancer**

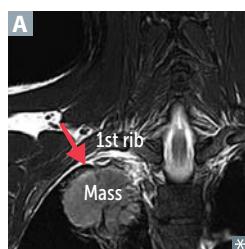
Leading cause of cancer death.  
Presentation: cough, hemoptysis, bronchial obstruction, wheezing, pneumonic “coin” lesion on CXR or noncalcified nodule on CT.  
Sites of metastases from lung cancer: liver (jaundice, hepatomegaly), adrenals, **bone** (pathologic fracture), **brain**; “Lung ‘mets’ Love affective **boneheads** and **brainiacs**.  
In the lung, metastases (usually multiple lesions) are more common than 1° neoplasms. Most often from breast, colon, prostate, and bladder cancer.

**SPHERE** of complications: Superior vena cava/thoracic outlet syndromes, **Pancoast tumor**, **Horner syndrome**, **Endocrine** (paraneoplastic), **Recurrent laryngeal nerve compression** (hoarseness), **Effusions** (pleural or pericardial).

Risk factors include tobacco smoking, secondhand smoke, radiation, environmental exposures (eg, radon, asbestos), pulmonary fibrosis, family history. **Squamous** and **small cell** carcinomas are **sentral** (central) and often caused by **smoking**.

TYPE	LOCATION	CHARACTERISTICS	HISTOLOGY
<b>Small cell</b>			
<b>Small cell (oat cell) carcinoma</b>	Central	Undifferentiated → very aggressive. May produce ACTH (Cushing syndrome), ADH (SIADH), or Antibodies against presynaptic Ca <sup>2+</sup> 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 <b>A</b> . Chromogranin A $\oplus$ , neuron-specific enolase $\oplus$ , synaptophysin $\oplus$ .
<b>Non-small cell</b>			
<b>Adenocarcinoma</b>	Peripheral	Most common 1° lung cancer. Most common subtype in people who do not smoke. More common in females than males. Activating mutations include KRAS, EGFR, and ALK. Associated with hypertrophic osteoarthropathy (clubbing). Bronchioloalveolar subtype (adenocarcinoma in situ): CXR often shows hazy infiltrates similar to pneumonia; better prognosis.	Glandular pattern, often stains mucin $\oplus$ <b>B</b> . Bronchioloalveolar subtype: grows along alveolar septa → apparent “thickening” of alveolar walls. Tall, columnar cells containing mucus.
<b>Squamous cell carcinoma</b>	Central	Hilar mass <b>C</b> arising from bronchus; cavitation; cigarettes; hypercalcemia (produces PTHrP).	Keratin pearls <b>D</b> and intercellular bridges (desmosomes).
<b>Large cell carcinoma</b>	Peripheral	Highly anaplastic undifferentiated tumor. Strong association with tobacco smoking. May produce hCG → gynecomastia. Less responsive to chemotherapy; removed surgically. Poor prognosis.	Pleomorphic <b>giant</b> cells <b>E</b> .
<b>Bronchial carcinoid tumor</b>	Central or peripheral	Excellent prognosis; metastasis rare. Symptoms due to mass effect or carcinoid syndrome (flushing, diarrhea, wheezing).	Nests of neuroendocrine cells; chromogranin A $\oplus$ .



**Pancoast tumor**

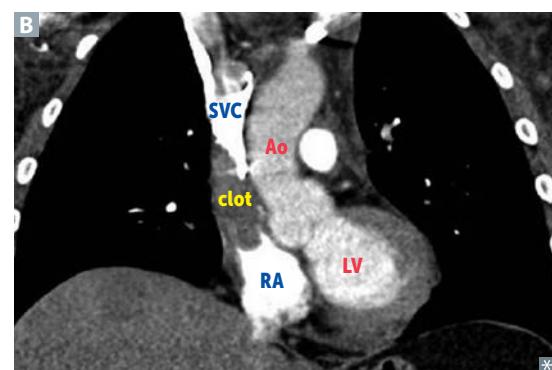
Also known as superior sulcus tumor. Carcinoma that occurs in the apex of lung **A** may cause Pancoast syndrome by invading/compressing local structures.

Compression of locoregional structures may cause array of findings:

- Recurrent laryngeal nerve → hoarseness
- Stellate ganglion → Horner syndrome (ipsilateral ptosis, miosis, anhidrosis)
- Superior vena cava → SVC syndrome
- Brachiocephalic vein → brachiocephalic syndrome (unilateral symptoms)
- Brachial plexus → shoulder pain, sensorimotor deficits (eg, atrophy of intrinsic muscles of the hand)
- Phrenic nerve → hemidiaphragm paralysis (hemidiaphragm elevation on CXR)

**Superior vena cava syndrome**

An obstruction of the SVC that impairs blood drainage from the head (“facial plethora”; note blanching after fingertip pressure in **A**), neck (jugular venous distention), and upper extremities (edema). Commonly caused by malignancy (eg, mediastinal mass, Pancoast tumor) and thrombosis from indwelling catheters **B**. Medical emergency. Can raise intracranial pressure (if obstruction is severe) → headaches, dizziness, ↑ risk of aneurysm/rupture of intracranial arteries.



## ► RESPIRATORY—PHARMACOLOGY

**H<sub>1</sub>-blockers**

Also called antihistamines. Reversible inhibitors of H<sub>1</sub> histamine receptors. May function as neutral antagonists or inverse agonists.

**First generation**

Diphenhydramine, dimenhydrinate, chlorpheniramine, doxylamine.

Names usually contain “-en/-ine” or “-en/-ate.”

**CLINICAL USE**

Allergy, motion sickness, vomiting in pregnancy, sleep aid.

**ADVERSE EFFECTS**

Sedation, antimuscarinic, anti-α-adrenergic.

**Second generation**

Loratadine, fexofenadine, desloratadine, cetirizine.

Names usually end in “-adine.” Setirizine (cetirizine) is second-generation agent.

**CLINICAL USE**

Allergy.

**ADVERSE EFFECTS**

Far less sedating than 1st generation because of ↓ entry into CNS.

**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	Activation of $\alpha$ -adrenergic receptors in nasal mucosa → local vasoconstriction.
CLINICAL USE	Reduce hyperemia, edema (used as nasal decongestants); open obstructed eustachian tubes.
ADVERSE EFFECTS	Hypertension. Rebound congestion (rhinitis medicamentosa) if used more than 4–6 days. Associated with tachyphylaxis. Can also cause CNS stimulation/anxiety (pseudoephedrine).

**Pulmonary hypertension drugs**

DRUG	MECHANISM	CLINICAL NOTES
<b>Endothelin receptor antagonists</b>	Competitively antagonizes endothelin-1 receptors → ↓ pulmonary vascular resistance.	Hepatotoxic (monitor LFTs). Example: bosentan.
<b>PDE-5 inhibitors</b>	Inhibits PDE-5 → ↑ cGMP → prolonged vasodilatory effect of NO.	Also used to treat erectile dysfunction. Contraindicated when taking nitroglycerin or other nitrates (due to risk of severe hypotension). Example: sildenafil.
<b>Prostacyclin analogs</b>	PGI <sub>2</sub> (prostacyclin) with direct vasodilatory effects on pulmonary and systemic arterial vascular beds. Inhibits platelet aggregation.	Side effects: flushing, jaw pain. Examples: epoprostenol, iloprost.

**Asthma drugs****Inhaled  $\beta_2$ -agonists**

Bronchoconstriction is mediated by (1) inflammatory processes and (2) parasympathetic tone; therapy is directed at these 2 pathways.

**Albuterol**—relaxes bronchial smooth muscle (short acting  $\beta_2$ -agonist). For acute exacerbations. Can cause tremor, arrhythmia.

**Salmeterol, formoterol**—long-acting agents for prophylaxis. Can cause tremor, arrhythmia.

**Inhaled corticosteroids**

**Fluticasone, budesonide**—inhibit the synthesis of virtually all cytokines. Inactivate NF- $\kappa$ B, the transcription factor that induces production of TNF- $\alpha$  and other inflammatory agents. 1st-line therapy for chronic asthma. Use a spacer or rinse mouth after use to prevent oral thrush.

**Muscarinic antagonists**

**Tiotropium, ipratropium**—competitively block muscarinic receptors, preventing bronchoconstriction. Also used for COPD. Tiotropium is long acting.

**Antileukotrienes**

**Montelukast, zafirlukast**—block leukotriene receptors (CysLT1). Especially good for aspirin-induced and exercise-induced asthma.

**Zileuton**—5-lipoxygenase pathway inhibitor. Blocks conversion of arachidonic acid to leukotrienes. Hepatotoxic.

**Anti-IgE monoclonal therapy**

**Omalizumab**—binds mostly unbound serum IgE and blocks binding to Fc $\epsilon$ RI. Used in allergic asthma with  $\uparrow$  IgE levels resistant to inhaled steroids and long-acting  $\beta_2$ -agonists.

**Methylxanthines**

**Theophylline**—likely causes bronchodilation by inhibiting phosphodiesterase  $\rightarrow \uparrow$  cAMP levels due to  $\downarrow$  cAMP hydrolysis. Limited use due to narrow therapeutic index (cardiotoxicity, neurotoxicity); metabolized by cytochrome P-450. Blocks actions of adenosine.

**Chromones**

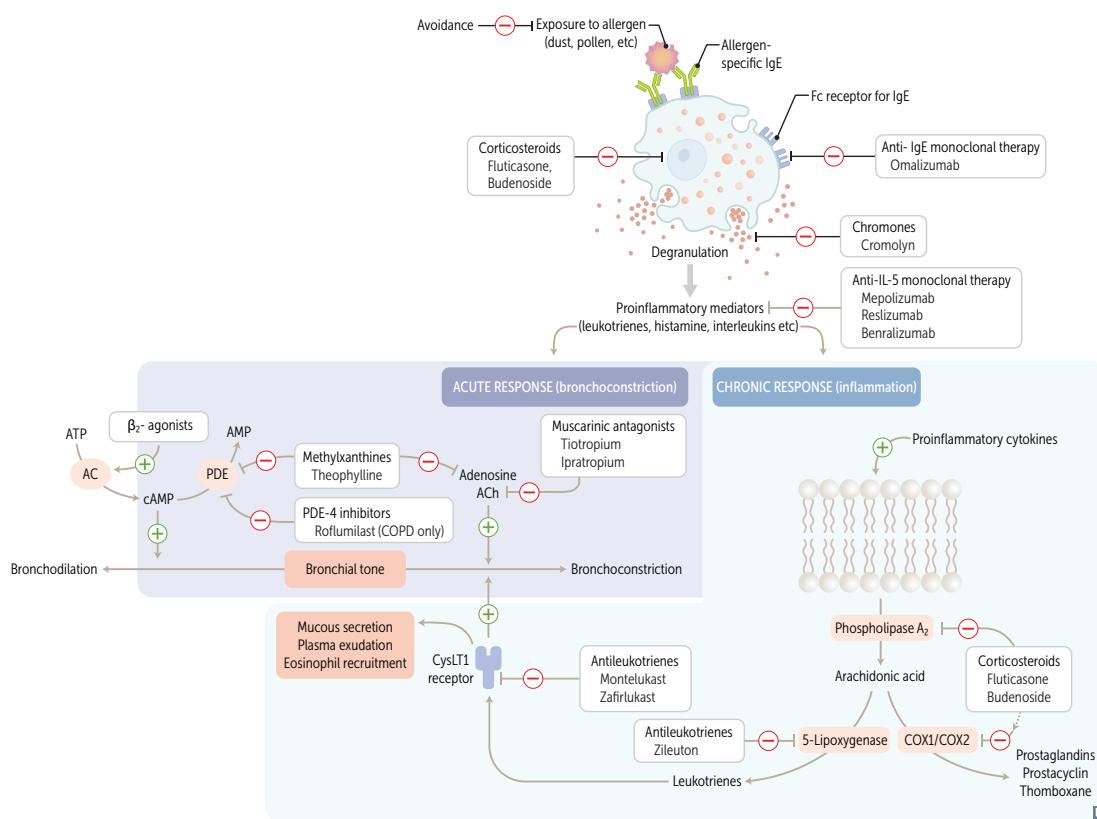
**Cromolyn**—prevents mast cell degranulation. Prevents acute asthma symptoms. Rarely used.

**Anti-IL-5 monoclonal therapy**

Prevents eosinophil differentiation, maturation, activation, and survival mediated by IL-5 stimulation. For maintenance therapy in severe eosinophilic asthma.

**Mepolizumab, reslizumab**—against IL-5.

**Benralizumab**—against IL-5 receptor  $\alpha$ .



## Rapid Review

*“Study without thought is vain: thought without study is dangerous.”*

—Confucius

*“It is better, of course, to know useless things than to know nothing.”*

—Lucius Annaeus Seneca

*“For every complex problem there is an answer that is clear, simple, and wrong.”*

—H. L. Mencken

The following tables represent a collection of high-yield associations between diseases and their clinical findings, treatments, and key associations. They can be quickly reviewed in the days before the exam.

▶ Classic Presentations	714
▶ Classic Labs/Findings	720
▶ Classic/Relevant Treatments	724
▶ Key Associations	727
▶ Equation Review	732
▶ Easily Confused Medications	734

## ► CLASSIC PRESENTATIONS

CLINICAL PRESENTATION	DIAGNOSIS/DISEASE	PAGE
Gout, intellectual disability, self-mutilating behavior in a boy	Lesch-Nyhan syndrome (HGPRT deficiency, X-linked recessive)	37
Situs inversus, chronic ear infections, sinusitis, bronchiectasis, infertility	Kartagener syndrome (dynein arm defect affecting cilia)	49
Blue sclera	Osteogenesis imperfecta (type I collagen defect)	51
Elastic skin, hypermobility of joints, ↑ bleeding tendency	Ehlers-Danlos syndrome (type V collagen defect, type III collagen defect seen in vascular subtype of ED)	51
Arachnodactyly, lens dislocation (upward and temporal), aortic dissection, hyperflexible joints	Marfan syndrome (fibrillin defect)	52
Arachnodactyly, pectus deformity, lens dislocation (downward)	Homocystinuria (autosomal recessive)	52
Café-au-lait spots (unilateral), polyostotic fibrous dysplasia, precocious puberty, multiple endocrine abnormalities	McCune-Albright syndrome ( $G_s$ -protein activating mutation)	57
Meconium ileus in neonate, recurrent pulmonary infections, nasal polyps, pancreatic insufficiency, infertility/subfertility	Cystic fibrosis (CFTR gene defect, chr 7, Phe508 deletion)	60
Calf pseudohypertrophy	Muscular dystrophy (most commonly Duchenne, due to X-linked recessive frameshift mutation of dystrophin gene)	61
Child uses arms to stand up from squat	Duchenne muscular dystrophy (Gowers sign)	61
Slow, progressive muscle weakness in boys	Becker muscular dystrophy (X-linked non-frameshift deletions in dystrophin; less severe than Duchenne)	61
Infant with cleft lip/palate, microcephaly or holoprosencephaly, polydactyly, cutis aplasia	Patau syndrome (trisomy 13)	63
Infant with microcephaly, rocker-bottom feet, clenched hands, and structural heart defect	Edwards syndrome (trisomy 18)	63
Single palmar crease	Down syndrome	63
Confusion, ophthalmoplegia/nystagmus, ataxia	Wernicke encephalopathy	66
Dilated cardiomyopathy/high-output heart failure, edema, alcoholism or malnutrition	Wet beriberi (thiamine [vitamin B <sub>1</sub> ] deficiency)	66
Burning feet syndrome	Vitamin B <sub>5</sub> deficiency	67
Dermatitis, dementia, diarrhea	Pellagra (niacin [vitamin B <sub>3</sub> ] deficiency)	67
Swollen gums, mucosal bleeding, poor wound healing, petechiae	Scurvy (vitamin C deficiency: can't hydroxylate proline/lysine for collagen synthesis); tea and toast diet	69
Bowlegs in children, bone pain, and muscle weakness	Rickets (children), osteomalacia (adults); vitamin D deficiency	70
Hemorrhagic disease of newborn with ↑ PT, ↑ PTT	Vitamin K deficiency	71
Bluish-black connective tissue, ear cartilage, sclerae; urine turns black on prolonged exposure to air	Alkaptonuria (homogentisate oxidase deficiency; ochronosis)	84
Chronic exercise intolerance with myalgia, fatigue, painful cramps, myoglobinuria	McArdle disease (skeletal muscle glycogen phosphorylase deficiency)	87

CLINICAL PRESENTATION	DIAGNOSIS/DISEASE	PAGE
Infant with hypoglycemia, hepatomegaly	Cori disease (debranching enzyme deficiency) or Von Gierke disease (glucose-6-phosphatase deficiency, more severe)	87
Myopathy (infantile hypertrophic cardiomyopathy), exercise intolerance	Pompe disease (lysosomal $\alpha$ -1,4-glucosidase deficiency)	87
“Cherry-red spots” on macula	Tay-Sachs (ganglioside accumulation) or Niemann-Pick (sphingomyelin accumulation), central retinal artery occlusion	88, 557
Hepatosplenomegaly, pancytopenia, osteoporosis, avascular necrosis of femoral head, bone crises	Gaucher disease (glucocerebrosidase [ $\beta$ -glucuronidase] deficiency)	88
Achilles tendon xanthoma	Familial hypercholesterolemia ( $\downarrow$ LDL receptor signaling)	94
Recurrent <i>Neisseria</i> infection	Terminal complement deficiencies (C5-C9)	107
Anaphylaxis following blood transfusion	IgA deficiency	116
Male child, recurrent infections, no mature B cells	Bruton disease (X-linked agammaglobulinemia)	116
Recurrent cold (noninflamed) abscesses, eczema, high serum IgE, $\uparrow$ eosinophils	Hyper-IgE syndrome (Job syndrome: neutrophil chemotaxis abnormality)	116
Late separation ( $>30$ days) of umbilical cord, no pus, recurrent skin and mucosal bacterial infections	Leukocyte adhesion deficiency (type 1; defective LFA-1 integrin)	117
Recurrent infections and granulomas with catalase $\oplus$ organisms	Chronic granulomatous disease (defect of NAPDH oxidase)	117
Fever, vomiting, diarrhea, desquamating rash following use of nasal pack or tampon	Staphylococcal toxic shock syndrome	135
“Strawberry tongue”	Scarlet fever Kawasaki disease	136, 314
Colon cancer diagnosed a few years after endocarditis	<i>Streptococcus bovis</i>	137
Abdominal pain, diarrhea, leukocytosis, recent antibiotic use	<i>Clostridium difficile</i> infection	138
Flaccid paralysis in newborn after ingestion of honey	<i>Clostridium botulinum</i> infection (floppy baby syndrome)	138
Tonsillar pseudomembrane with “bull’s neck” appearance	<i>Corynebacterium diphtheriae</i> infection	139
Back pain, fever, night sweats	Pott disease (vertebral TB)	140
Adrenal insufficiency, fever, DIC	Waterhouse-Friderichsen syndrome (meningococcemia)	142, 357
Red “currant jelly” sputum in patients with alcohol overuse or diabetes	<i>Klebsiella pneumoniae</i> pneumonia	145
Large rash with bull’s-eye appearance	Erythema migrans from <i>Ixodes</i> tick bite (Lyme disease: <i>Borrelia</i> )	146
Ulcerated genital lesion	Nonpainful, indurated: chancre (1° syphilis, <i>Treponema pallidum</i> ) Painful, with exudate: chancroid ( <i>Haemophilus ducreyi</i> )	147, 184
Pupil accommodates but doesn’t react to light	Neurosyphilis (Argyll Robertson pupil)	147
Smooth, moist, painless, wart-like white lesions on genitals	Condylomata lata (2° syphilis)	147
Fever, chills, headache, myalgia following antibiotic treatment for syphilis	Jarisch-Herxheimer reaction (due to host response to sudden release of bacterial antigens)	148

CLINICAL PRESENTATION	DIAGNOSIS/DISEASE	PAGE
Dog or cat bite resulting in infection (cellulitis, osteomyelitis)	<i>Pasteurella multocida</i> (cellulitis at inoculation site)	149
Atypical "walking pneumonia" with x-ray looking worse than the patient	<i>Mycoplasma pneumoniae</i> infection	150
Rash on palms and soles	Coxsackie A, 2° syphilis, Rocky Mountain spotted fever	150
Black eschar on face of patient with diabetic ketoacidosis and/or neutropenia	<i>Mucor</i> or <i>Rhizopus</i> fungal infection	153
Chorioretinitis, hydrocephalus, intracranial calcifications	Congenital toxoplasmosis	156
Pruritus, serpiginous rash after walking barefoot	Hookworm ( <i>Ancylostoma</i> spp, <i>Necator americanus</i> )	159
Child with fever later develops red rash on face that spreads to body	Erythema infectiosum/fifth disease ("slapped cheeks" appearance, caused by parvovirus B19)	164
Fever, cough, conjunctivitis, coryza, diffuse rash	Measles	170
Small, irregular red spots on buccal/lingual mucosa with blue-white centers	Koplik spots (measles [rubeola] virus)	170
Bounding pulses, wide pulse pressure, diastolic heart murmur, head bobbing	Aortic regurgitation	300
Systolic ejection murmur (crescendo-decrescendo), narrow pulse pressure, pulsus parvus et tardus	Aortic stenosis	300
Continuous "machine-like" heart murmur	PDA (close with indomethacin; keep open with PGE analogs)	300
Chest pain on exertion	Angina (stable: with moderate exertion; unstable: with minimal exertion or at rest)	312
Chest pain with ST depressions on ECG	Angina (⊖ troponins) or NSTEMI (⊕ troponins)	312
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)	317
Distant heart sounds, distended neck veins, hypotension	Beck triad of cardiac tamponade	320
Painful, raised red lesions on pads of fingers/toes	Osler nodes (infective endocarditis, immune complex deposition)	321
Painless erythematous lesions on palms and soles	Janeway lesions (infective endocarditis, septic emboli/microabscesses)	321
Splinter hemorrhages in fingernails	Bacterial endocarditis	321
Retinal hemorrhages with pale centers	Roth spots (bacterial endocarditis)	321
Telangiectasias, recurrent epistaxis, skin discoloration, arteriovenous malformations, GI bleeding, hematuria	Hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu syndrome)	324
Polyuria (water diuresis), polydipsia	Primary polydipsia, diabetes insipidus (central, nephrogenic)	346
No lactation postpartum, absent menstruation, cold intolerance	Sheehan syndrome (postpartum hemorrhage leading to pituitary infarction)	347
Heat intolerance, weight loss, palpitations	Hyperthyroidism	348
Cold intolerance, weight gain, brittle hair	Hypothyroidism	348
Cutaneous/dermal edema due to deposition of mucopolysaccharides in connective tissue	Myxedema (caused by hypothyroidism, Graves disease [pretibial])	348

CLINICAL PRESENTATION	DIAGNOSIS/DISEASE	PAGE
Facial muscle spasm upon tapping	Chvostek sign (hypocalcemia)	352
Carpal spasm upon inflation of BP cuff	Trousseau sign (hypocalcemia)	352
Deep, labored breathing/hyperventilation	Diabetic ketoacidosis (Kussmaul respirations)	355
Skin hyperpigmentation, orthostatic hypotension, fatigue, weakness, muscle aches, weight loss, GI disturbances	Chronic 1° adrenal insufficiency (Addison disease) → ↑ ACTH, ↑ α-MSH	357
Shock, altered mental status, vomiting, abdominal pain, weakness, fatigue	Acute adrenal insufficiency (adrenal crisis)	357
Pancreatic, pituitary, parathyroid tumors	MEN 1 (autosomal dominant MEN1 mutation)	360
Thyroid tumors, pheochromocytoma, ganglioneuromatosis, Marfanoid habitus	MEN 2B (autosomal dominant RET mutation)	360
Thyroid and parathyroid tumors, pheochromocytoma	MEN 2A (autosomal dominant RET mutation)	360
Cutaneous flushing, diarrhea, bronchospasm, heart murmur	Carcinoid syndrome (↑ 5-HIAA)	361
Jaundice, palpable distended non-tender gallbladder	Courvoisier sign (distal malignant obstruction of biliary tree)	378
Vomiting blood following gastroesophageal lacerations	Mallory-Weiss syndrome (alcohol use disorder, bulimia nervosa)	387
Dysphagia (esophageal webs), glossitis, iron deficiency anemia	Plummer-Vinson syndrome (may progress to esophageal squamous cell carcinoma)	387
Enlarged, hard left supraclavicular node	Virchow node (abdominal metastasis)	389
Hematemesis, melena	Upper GI bleeding (eg, peptic ulcer disease)	390
Hematochezia	Lower GI bleeding (eg, colonic diverticulosis)	390
Arthralgias, adenopathy, cardiac and neurological symptoms, diarrhea	Whipple disease ( <i>Tropheryma whipplei</i> )	391
Severe RLQ pain with palpation of LLQ	Rovsing sign (acute appendicitis)	393
Severe RLQ pain with deep tenderness	McBurney sign (acute appendicitis)	393
Hamartomatous GI polyps, hyperpigmented macules on mouth, feet, hands, genitalia	Peutz-Jeghers syndrome (inherited, benign polyposis can cause bowel obstruction; ↑ cancer risk, mainly GI)	397
Multiple colon polyps, osteomas/soft tissue tumors, impacted/supernumerary teeth	Gardner syndrome (subtype of FAP)	397
Severe jaundice in neonate	Crigler-Najjar syndrome (congenital unconjugated hyperbilirubinemia)	404
Golden brown rings around peripheral cornea	Wilson disease (Kayser-Fleischer rings due to copper accumulation)	405
Female, fat, fertile, forty	Cholelithiasis (gallstones)	406
Painless jaundice with enlarged gallbladder	Cancer of the pancreatic head obstructing bile duct	408
Bluish line on gingiva	Burton line (lead poisoning)	429
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)	431
Red/pink urine, fragile RBCs	Paroxysmal nocturnal hemoglobinuria	432
Painful blue fingers/toes, hemolytic anemia	Cold agglutinin disease (autoimmune hemolytic anemia caused by <i>Mycoplasma pneumoniae</i> , infectious mononucleosis, CLL)	433

CLINICAL PRESENTATION	DIAGNOSIS/DISEASE	PAGE
Petechiae, mucosal bleeding, prolonged bleeding time	Platelet disorders (eg, Glanzmann thrombasthenia, Bernard Soulier, HUS, TTP, ITP)	437
Fever, night sweats, weight loss	B symptoms of malignancy	438
Skin patches/plaques, Pautrier microabscesses, atypical T cells	Mycosis fungoides (cutaneous T-cell lymphoma) or Sézary syndrome (mycosis fungoides + malignant T cells in blood)	439
Neonate with arm paralysis following difficult birth, arm in “waiter’s tip” position	Erb-Duchenne palsy (superior trunk [C5–C6] brachial plexus injury)	458
Anterior drawer sign $\oplus$	Anterior cruciate ligament injury	464
Bone pain, bone enlargement, arthritis	Osteitis deformans (Paget disease of bone, $\uparrow$ osteoblastic and osteoclastic activity)	475
Swollen, hard, painful finger joints in an elderly individual, pain worse with activity	Osteoarthritis (osteophytes on PIP [Bouchard nodes], DIP [Heberden nodes])	478
Sudden swollen/painful big toe joint, tophi	Gout/podagra (hyperuricemia)	479
Dry eyes, dry mouth, arthritis	Sjögren syndrome (autoimmune destruction of exocrine glands)	480
Urethritis, conjunctivitis, arthritis in a male	Reactive arthritis associated with HLA-B27	481
“Butterfly” facial rash, arthritis, cytopenia, and fever in a young female	Systemic lupus erythematosus	482
Cervical lymphadenopathy, desquamating rash, coronary aneurysms, red conjunctivae and tongue, hand-foot changes	Kawasaki disease (mucocutaneous lymph node syndrome, treat with IVIG and aspirin)	484
Palpable purpura on buttocks/legs, joint pain, abdominal pain (child), hematuria	Immunoglobulin A vasculitis (Henoch-Schönlein purpura, affects skin and kidneys)	485
Painful fingers/toes changing color from white to blue to red with cold or stress	Raynaud phenomenon (vasospasm in extremities)	486
Dark purple skin/mouth nodules in a patient with AIDS	Kaposi sarcoma, associated with HHV-8	492
Pruritic, purple, polygonal planar papules and plaques (6 P’s)	Lichen planus	496
Ataxia, nystagmus, vertigo, dysarthria	Cerebellar lesion (lateral affects voluntary movement of extremities; medial affects axial and proximal movement)	515
Dorsiflexion of large toe with fanning of other toes upon plantar scrape	Babinski sign (UMN lesion)	527
Hyperphagia, hypersexuality, hyperorality	Klüver-Bucy syndrome (bilateral amygdala lesion)	528
Resting tremor, athetosis, chorea	Basal ganglia lesion	528
Lucid interval after traumatic brain injury	Epidural hematoma (middle meningeal artery rupture; branch of maxillary artery)	531
“Worst headache of my life”	Subarachnoid hemorrhage	531
Dysphagia, hoarseness, $\downarrow$ gag reflex, nystagmus, ipsilateral Horner syndrome	Lateral medullary syndrome (posterior inferior cerebellar artery lesion)	533
Resting tremor, rigidity, akinesia, postural instability, shuffling gait, micrographia	Parkinson disease (loss of dopaminergic neurons in substantia nigra pars compacta)	538
Chorea, dementia, caudate degeneration	Huntington disease (autosomal dominant CAG repeat expansion)	538

CLINICAL PRESENTATION	DIAGNOSIS/DISEASE	PAGE
Urinary incontinence, gait apraxia, cognitive dysfunction	Normal pressure hydrocephalus	540
Nystagmus, intention tremor, scanning speech, bilateral internuclear ophthalmoplegia	Multiple sclerosis	541
Rapidly progressive limb weakness that ascends following GI/upper respiratory infection	Guillain-Barré syndrome (acute inflammatory demyelinating polyneuropathy)	542
Café-au-lait spots, Lisch nodules (iris hamartoma), cutaneous neurofibromas, pheochromocytomas, optic gliomas	Neurofibromatosis type I	543
Vascular birthmark (port-wine stain) of the face	Nevus flammeus (benign, but associated with Sturge-Weber syndrome)	543
Renal cell carcinoma (bilateral), hemangioblastomas, angiomyomatosis, pheochromocytoma	von Hippel-Lindau disease (deletion of VHL gene on chromosome 3p)	543
Bilateral vestibular schwannomas	Neurofibromatosis type 2	543
Hyperreflexia, hypertonia, Babinski sign present	UMN damage	547
Hyporeflexia, hypotonia, atrophy, fasciculations	LMN damage	547
Flaccid limb weakness, fasciculations, atrophy, bulbar palsy	UMN and LMN deficits	548
Staggering gait, frequent falls, nystagmus, hammer toes, diabetes mellitus, hypertrophic cardiomyopathy	Friedreich ataxia	549
Unilateral facial drooping involving forehead	LMN facial nerve (CN VII) palsy; UMN lesions spare the forehead	550
Episodic vertigo, tinnitus, sensorineural hearing loss	Ménière disease	552
Ptosis, miosis, anhidrosis	Horner syndrome (sympathetic chain lesion)	559
Conjugate horizontal gaze palsy, horizontal diplopia	Internuclear ophthalmoplegia (damage to MLF; may be unilateral or bilateral)	563
“Waxing and waning” level of consciousness (acute onset), ↓ attention span, ↓ level of arousal	Delirium (usually 2° to other cause)	581
Polyuria, renal tubular acidosis type II, growth retardation, electrolyte imbalances, hypophosphatemic rickets	Fanconi syndrome (multiple combined dysfunction of the proximal convoluted tubule)	610
Periorbital and/or peripheral edema, proteinuria (> 3.5g/day), hypoalbuminemia, hypercholesterolemia	Nephrotic syndrome	619
Hereditary nephritis, sensorineural hearing loss, retinopathy, lens dislocation	Alport syndrome (mutation in type IV collagen)	620
Wilms tumor, macroglossia, organomegaly, hemihyperplasia, omphalocele	Beckwith-Wiedemann syndrome (WT2 mutation)	629
Streak ovaries, congenital heart disease, horseshoe kidney, cystic hygroma, short stature, webbed neck, lymphedema	Turner syndrome (45,XO)	661
Red, itchy, swollen rash of nipple/areola	Paget disease of the breast (sign of underlying neoplasm)	674
Ovarian fibroma, ascites, pleural effusion	Meigs syndrome	671
Fibrous plaques in tunica albuginea of penis with abnormal curvature	Peyronie disease (connective tissue disorder)	675
Hypoxemia, polycythemia, hypercapnia	Chronic bronchitis (hypertrophy and hyperplasia of mucous cells, “blue bloater”)	698

CLINICAL PRESENTATION	DIAGNOSIS/DISEASE	PAGE
Pink complexion, dyspnea, hyperventilation	Emphysema (“pink puffer,” centriacinar [smoking] or panacinar [ $\alpha_1$ -antitrypsin deficiency])	698
Bilateral hilar adenopathy, uveitis	Sarcoidosis (noncaseating granulomas)	700

## ► CLASSIC LABS/FINDINGS

LAB/DIAGNOSTIC FINDING	DIAGNOSIS/DISEASE	PAGE
Colonies of mucoid <i>Pseudomonas</i> in lungs	Cystic fibrosis (autosomal recessive mutation in CFTR gene → fat-soluble vitamin deficiency and mucous plugs)	60
↓ AFP in amniotic fluid/maternal serum	Down syndrome, Edwards syndrome	63
↑ β-hCG, ↓ PAPP-A on first trimester screening	Down syndrome	63
↑ serum homocysteine, ↑ mehtylmalonic acid, ↓ folate	Vitamin B <sub>12</sub> deficiency	69
Anti-histone antibodies	Drug-induced SLE (eg, hydralazine, isoniazid, phenytoin, TNF-α inhibitors)	115, 501
↓ T cells, ↓ PTH, ↓ Ca <sup>2+</sup> , absent thymic shadow on CXR	Thymic aplasia (DiGeorge syndrome, velocardiofacial syndrome)	116
Large granules in phagocytes, immunodeficiency	Chédiak-Higashi disease (congenital failure of phagolysosome formation)	117
Recurrent infections, eczema, thrombocytopenia	Wiskott-Aldrich syndrome	117
Optochin sensitivity	Sensitive: <i>S pneumoniae</i> ; resistant: viridans streptococci ( <i>S mutans</i> , <i>S sanguis</i> )	134
Novobiocin response	Sensitive: <i>S epidermidis</i> ; resistant: <i>S saprophyticus</i>	134
Bacitracin response	Sensitive: <i>S pyogenes</i> (group A); resistant: <i>S agalactiae</i> (group B)	134
Branching gram + rods with sulfur granules	<i>Actinomyces israelii</i>	139
Hilar lymphadenopathy, peripheral granulomatous lesion in middle or lower lung lobes (can calcify)	Ghon complex (1° TB: <i>Mycobacterium bacilli</i> )	140
“Thumb sign” on lateral neck x-ray	Epiglottitis ( <i>Haemophilus influenzae</i> )	142
Bacteria-covered vaginal epithelial cells	“Clue cells” ( <i>Gardnerella vaginalis</i> )	148
Dilated cardiomyopathy with apical atrophy	Chagas disease ( <i>Trypanosoma cruzi</i> )	158
Atypical lymphocytes, heterophile antibodies	Infectious mononucleosis (EBV infection)	165
Eosinophilic intranuclear inclusions with perinuclear halo	Cells infected by herpesviruses (eg, HSV, VZV, CMV)	165, 166
“Steeple” sign on frontal CXR	Croup (parainfluenza virus)	170
Eosinophilic inclusion bodies in cytoplasm of hippocampal and cerebellar neurons	Negri bodies of rabies	171
Ring-enhancing brain lesion on CT/MRI in AIDS	<i>Toxoplasma gondii</i> , CNS lymphoma	177
Psammoma bodies	Meningiomas, papillary thyroid carcinoma, mesothelioma, papillary serous carcinoma of the endometrium and ovary	228

LAB/DIAGNOSTIC FINDING	DIAGNOSIS/DISEASE	PAGE
“Delta wave” on ECG, short PR interval, supraventricular tachycardia	Wolff-Parkinson-White syndrome (bundle of Kent bypasses AV node)	315
“Boot-shaped” heart on x-ray	Tetralogy of Fallot (due to RVH)	306
Rib notching (inferior surface, on x-ray)	Coarctation of the aorta	307
Granuloma with giant cells after pharyngeal infection	Aschoff bodies (rheumatic fever)	322
Electrical alternans (alternating amplitude on ECG)	Cardiac tamponade	320
Enlarged thyroid cells with ground-glass nuclei with central clearing	“Orphan Annie” eyes nuclei (papillary carcinoma of the thyroid)	351
“Brown” tumor of bone	Hyperparathyroidism or osteitis fibrosa cystica (deposited hemosiderin from hemorrhage gives brown color)	353, 476
Hypertension, hypokalemia, metabolic alkalosis	1° hyperaldosteronism (eg, Conn syndrome)	358
Mucin-filled cell with peripheral nucleus	“Signet ring” (gastric carcinoma)	389
Anti-transglutaminase/anti-gliadin/anti-endomysial antibodies	Celiac disease (diarrhea, weight loss)	391
Narrowing of bowel lumen on barium x-ray	“String sign” (Crohn disease)	392
“Lead pipe” appearance of colon on abdominal imaging	Ulcerative colitis (loss of haustra)	392
Thousands of polyps on colonoscopy	Familial adenomatous polyposis (autosomal dominant, mutation of APC gene)	397
“Apple core” lesion on barium enema x-ray	Colorectal cancer (usually left-sided)	398
Eosinophilic cytoplasmic inclusion in liver cell	Mallory body (alcoholic liver disease)	401
Triglyceride accumulation in liver cell vacuoles	Fatty liver disease (alcoholic or metabolic syndrome)	401
Anti-smooth muscle antibodies (ASMA), anti-liver/kidney microsomal-1 (anti-LKM1) antibodies	Autoimmune hepatitis	401
“Nutmeg” appearance of liver	Chronic passive congestion of liver due to right heart failure or Budd-Chiari syndrome	402
Antimitochondrial antibodies (AMAs)	1° biliary cholangitis (female, cholestasis, portal hypertension)	405
Low serum ceruloplasmin	Wilson disease (hepatolenticular degeneration; Kayser-Fleischer rings due to copper accumulation)	405
Migratory thrombophlebitis (leading to migrating DVTs and vasculitis)	Trousseau syndrome (adenocarcinoma of pancreas or lung)	408
Hypersegmented neutrophils	Megaloblastic anemia ( $B_{12}$ deficiency: neurologic symptoms; folate deficiency: no neurologic symptoms)	416
Basophilic nuclear remnants in RBCs	Howell-Jolly bodies (due to splenectomy or nonfunctional spleen)	426
Basophilic stippling of RBCs	Lead poisoning or sideroblastic anemia	426
Hypochromic, microcytic anemia	Iron deficiency anemia, lead poisoning, thalassemia (fetal hemoglobin sometimes present)	427, 428
“Hair on end” (“crew cut”) appearance on x-ray	$\beta$ -thalassemia, sickle cell disease (marrow expansion)	428, 432
Anti-GpIIb/IIIa antibodies	Immune thrombocytopenia	436
High level of d-dimers	DVT, DIC	437, 695

LAB/DIAGNOSTIC FINDING	DIAGNOSIS/DISEASE	PAGE
Giant B cells with bilobed nuclei with prominent inclusions (“owl’s eye”)	Reed-Sternberg cells (Hodgkin lymphoma)	438
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)	439
Lytic (“punched-out”) bone lesions on x-ray	Multiple myeloma	440
Monoclonal spike on serum protein electrophoresis	<ul style="list-style-type: none"> <li>▪ Multiple myeloma (usually IgG or IgA)</li> <li>▪ Waldenström macroglobulinemia (IgM)</li> <li>▪ Monoclonal gammopathy of undetermined significance</li> </ul>	440
Stacks of RBCs	Rouleaux formation (high ESR, multiple myeloma)	440
Azurophilic peroxidase $\oplus$ granular inclusions in granulocytes and myeloblasts	Auer rods (APL)	442
WBCs that look “smudged”	CLL	442
“Tennis racket”-shaped cytoplasmic organelles (EM) in Langerhans cells	Birbeck granules (Langerhans cell histiocytosis)	444
“Soap bubble” in femur or tibia on x-ray	Giant cell tumor of bone (generally benign)	476
Raised periosteum (creating a “Codman triangle”)	Aggressive bone lesion (eg, osteosarcoma, Ewing sarcoma)	477
“Onion skin” periosteal reaction	Ewing sarcoma (malignant small blue cell tumor)	477
Anti-IgG antibodies	Rheumatoid arthritis (systemic inflammation, joint pannus, boutonniere and swan neck deformities)	478
Rhomboid crystals, $\oplus$ birefringent	Pseudogout (calcium pyrophosphate dihydrate crystals)	479
Needle-shaped, $\ominus$ birefringent crystals	Gout (monosodium urate crystals)	479
$\uparrow$ uric acid levels	Gout, Lesch-Nyhan syndrome, tumor lysis syndrome, loop and thiazide diuretics	479
“Bamboo spine” on x-ray	Ankylosing spondylitis (chronic inflammatory arthritis: HLA-B27)	481
Antinuclear antibodies (ANAs: anti-Smith and anti-dsDNA)	SLE (type III hypersensitivity)	482
Antineutrophil cytoplasmic antibodies (ANCAs)	Microscopic polyangiitis and eosinophilic granulomatosis with polyangiitis (MPO-ANCA/p-ANCA); granulomatosis with polyangiitis (PR3-ANCA/c-ANCA); primary sclerosing cholangitis (MPO-ANCA/p-ANCA)	485
Anticentromere antibodies	Scleroderma (CREST syndrome)	487
Anti-topoisomerase antibodies	Diffuse scleroderma	487
Anti-desmoglein (anti-desmosome) antibodies	Pemphigus vulgaris (blistering)	494
Keratin pearls on a skin biopsy	Squamous cell carcinoma	498
$\uparrow$ AFP in amniotic fluid/maternal serum	Dating error, anencephaly, spina bifida (open neural tube defects)	505
Bloody or yellow tap on lumbar puncture	Xanthochromia (due to subarachnoid hemorrhage)	531
Eosinophilic cytoplasmic inclusion in neuron	Lewy body (Parkinson disease and Lewy body dementia)	538, 539
Extracellular amyloid deposition in gray matter of brain	Senile plaques (Alzheimer disease)	538

LAB/DIAGNOSTIC FINDING	DIAGNOSIS/DISEASE	PAGE
Depigmentation of neurons in substantia nigra	Parkinson disease (basal ganglia disorder: rigidity, resting tremor, bradykinesia)	538
Protein aggregates in neurons from hyperphosphorylation of tau protein	Neurofibrillary tangles (Alzheimer disease) and Pick bodies (Pick disease)	538
Silver-staining spherical aggregation of tau proteins in neurons	Pick bodies (frontotemporal dementia: progressive dementia, changes in personality)	538
Pseudopalisading pleomorphic tumor cells on brain biopsy	Glioblastoma multiforme	544
Circular grouping of dark tumor cells surrounding pale neurofibrils	Homer-Wright rosettes (neuroblastoma, medulloblastoma)	546
“Waxy” casts with very low urine flow	Chronic end-stage renal disease	618
WBC casts in urine	Acute pyelonephritis, transplant rejection, tubulointerstitial inflammation	618
RBC casts in urine	Glomerulonephritis	618
“Tram-track” appearance of capillary loops of glomerular basement membranes on light microscopy	Membranoproliferative glomerulonephritis	620
Anti-glomerular basement membrane antibodies	Goodpasture syndrome (glomerulonephritis and hemoptysis)	620
Cellular crescents in Bowman capsule	Rapidly progressive (crescentic) glomerulonephritis	620
“Wire loop” glomerular capillary appearance on light microscopy	Diffuse proliferative glomerulonephritis (usually seen with lupus)	620
Linear appearance of IgG deposition on glomerular and alveolar basement membranes	Goodpasture syndrome	620
“Lumpy bumpy” appearance of glomeruli on immunofluorescence	Poststreptococcal glomerulonephritis (due to deposition of IgG, IgM, and C3)	620
Necrotizing vasculitis (lungs) and necrotizing glomerulonephritis	Granulomatosis with polyangiitis (PR3-ANCA/c-ANCA) and Goodpasture syndrome (anti–basement membrane antibodies)	620
Nodular hyaline deposits in glomeruli	Kimmelstiel-Wilson nodules (diabetic nephropathy)	621
Podocyte fusion or “effacement” on electron microscopy	Minimal change disease (child with nephrotic syndrome)	621
“Spikes” on basement membrane, “dome-like” subepithelial deposits	Membranous nephropathy (nephrotic syndrome)	621
Thyroid-like appearance of kidney	Chronic pyelonephritis (usually due to recurrent infections)	624
Granular casts in urine	Acute tubular necrosis (eg, ischemia or toxic injury)	626
hCG elevated	Multiple gestations, hydatidiform moles, choriocarcinomas, Down syndrome	658
Dysplastic squamous cervical cells with “raisinoid” nuclei and hyperchromasia	Koilocytes (HPV: predisposes to cervical cancer)	669
Sheets of uniform “fried egg” cells, ↑ hCG, ↑ LDH	Dysgerminoma	671
Disarrayed granulosa cells arranged around collections of eosinophilic fluid	Call-Exner bodies (granulosa cell tumor of the ovary)	671
“Chocolate cyst” of ovary	Endometriosis (frequently involves both ovaries)	672
Mammary gland (“blue domed”) cyst	Fibrocystic change of the breast	673

LAB/DIAGNOSTIC FINDING	DIAGNOSIS/DISEASE	PAGE
Glomerulus-like structure surrounding vessel in germ cells	Schiller-Duval bodies (yolk sac tumor)	671
Rectangular, crystal-like, cytoplasmic inclusions in Leydig cells	Reinke crystals (Leydig cell tumor)	677
Thrombi made of white/red layers	Lines of Zahn (arterial thrombus, layers of platelets/ RBCs)	696
Hexagonal, double-pointed, needle-like crystals in bronchial secretions	Bronchial asthma (Charcot-Leyden crystals: eosinophilic granules)	698
Desquamated epithelium casts in sputum	Curschmann spirals (bronchial asthma; can result in whorled mucous plugs)	698
“Honeycomb lung” on x-ray or CT	Idiopathic pulmonary fibrosis	700
Iron-containing nodules in alveolar septum	Ferruginous bodies (asbestosis: ↑ chance of lung cancer)	701
Bronchogenic apical lung tumor on imaging	Pancoast tumor (can compress cervical sympathetic chain and cause Horner syndrome)	709

## ▶ CLASSIC/RELEVANT TREATMENTS

CONDITION	COMMON TREATMENT(S)	PAGE
Ethylene glycol/methanol intoxication	Fomepizole (alcohol dehydrogenase inhibitor)	72
Chronic hepatitis B or C	IFN-α (HBV and HCV); ribavirin, simeprevir, sofosbuvir (HCV)	121, 204
<i>Streptococcus bovis</i>	Penicillin prophylaxis; evaluation for colon cancer if linked to endocarditis	137
<i>Clostridium botulinum</i>	Human botulinum immunoglobulin	138
<i>Clostridium tetani</i>	Antitoxin and wound debridement	138
<i>Clostridium difficile</i>	Oral metronidazole; if refractory, oral vancomycin. Refractory cases: repeat regimen or fecal microbiota transplant	138
<i>Haemophilus influenzae</i> (B)	Amoxicillin ± clavulanate (mucosal infections), ceftriaxone (meningitis), rifampin (prophylaxis)	142
<i>Neisseria gonorrhoeae</i>	Ceftriaxone (add azithromycin or doxycycline to cover likely concurrent <i>C trachomatis</i> )	142
<i>Neisseria meningitidis</i>	Penicillin/ceftriaxone, rifampin/ciprofloxacin/ceftriaxone (prophylaxis)	142
<i>Legionella pneumophila</i>	Macrolides (eg, azithromycin or fluoroquinolones)	143
<i>Pseudomonas aeruginosa</i>	Piperacillin-tazobactam, cephalosporins, monobactams, fluoroquinolones, carbapenems	143
<i>Treponema pallidum</i>	Penicillin G	147
<i>Chlamydia trachomatis</i>	Azithromycin or doxycycline (+ ceftriaxone for gonorrhea coinfection), oral erythromycin to treat chlamydial conjunctivitis in infants	148

CONDITION	COMMON TREATMENT(S)	PAGE
<i>Candida albicans</i>	Topical azoles (vaginitis); nystatin, fluconazole, caspofungin (oral); fluconazole, caspofungin, amphotericin B (esophageal or systemic)	153
<i>Cryptococcus neoformans</i>	Induction with amphotericin B and flucytosine, maintenance with fluconazole (in AIDS patients)	153
<i>Sporothrix schenckii</i>	Itraconazole, oral potassium iodide	154
<i>Pneumocystis jirovecii</i>	TMP-SMX (prophylaxis and treatment in immunosuppressed patients, CD4 < 200/mm <sup>3</sup> )	154
<i>Toxoplasma gondii</i>	Sulfadiazine + pyrimethamine	156
Malaria	Chloroquine, mefloquine, atovaquone/proguanil (for blood schizont), primaquine (for liver hypnozoite)	157
<i>Trichomonas vaginalis</i>	Metronidazole (patient and partner[s])	158
<i>Streptococcus pyogenes</i>	Penicillin prophylaxis	187
<i>Streptococcus pneumoniae</i>	Penicillin/cephalosporin (systemic infection, pneumonia), vancomycin (meningitis)	187, 190
<i>Staphylococcus aureus</i>	MSSA: nafcillin, oxacillin, dicloxacillin (antistaphylococcal penicillins); MRSA: vancomycin, daptomycin, linezolid, ceftaroline	188, 190, 198
Enterococci	Vancomycin, aminopenicillins/cephalosporins. VRE: daptomycin, linezolid, tigecycline, streptogramins	189, 198
<i>Rickettsia rickettsii</i>	Doxycycline, chloramphenicol	192
<i>Mycobacterium tuberculosis</i>	RIPE (rifampin, isoniazid, pyrazinamide, ethambutol)	196
UTI prophylaxis	TMP-SMX	198
Influenza	Oseltamivir, zanamivir	201
CMV	Ganciclovir, foscarnet, cidofovir	202
Patent ductus arteriosus	Close with indomethacin; keep open with PGE analogs	291
Stable angina	Sublingual nitroglycerin	312
Hypercholesterolemia	Statins (first-line)	328
Hypertriglyceridemia	Fibrates	328
Arrhythmia in damaged cardiac tissue	Class IB antiarrhythmic (lidocaine, mexiletine)	330
Prolactinoma	Cabergoline/bromocriptine (dopamine agonists)	338
Diabetes insipidus	Desmopressin (central); hydrochlorothiazide, indomethacin, amiloride (nephrogenic)	346
SIADH	Fluid restriction, IV hypertonic saline, conivaptan/tolvaptan, demeclocycline	346
Diabetic ketoacidosis/hyperosmolar hyperglycemic state	Fluids, insulin, K <sup>+</sup>	355
Pheochromocytoma	$\alpha$ -antagonists (eg, phenoxybenzamine)	359
Carcinoid syndrome	Octreotide, telotristat	361
Diabetes mellitus type 1	Dietary intervention (low carbohydrate) + insulin replacement	362
Diabetes mellitus type 2	Dietary intervention, oral hypoglycemics, and insulin (if refractory)	362

CONDITION	COMMON TREATMENT(S)	PAGE
Crohn disease	Corticosteroids, infliximab, azathioprine	392
Ulcerative colitis	5-ASA preparations (eg, mesalamine), 6-mercaptopurine, infliximab, colectomy	392
Sickle cell disease	Hydroxyurea ( $\uparrow$ fetal hemoglobin)	432
Chronic myelogenous leukemia	BCR-ABL tyrosine kinase inhibitors (eg, imatinib)	442
Acute promyelocytic leukemia (M3)	All- <i>trans</i> retinoic acid, arsenic trioxide	442
Drug of choice for anticoagulation in pregnancy	Low-molecular-weight heparin	445
Immediate anticoagulation	Heparin	445
Long-term anticoagulation	Warfarin, dabigatran, direct factor Xa inhibitors	446
Heparin reversal	Protamine sulfate	447
Warfarin reversal	Vitamin K (slow) +/- fresh frozen plasma or prothrombin complex concentrate (rapid)	447
Dabigatran reversal	Idarucizumab	447
Direct factor Xa inhibitor reversal	Andexanet alfa	447
HER2 $\oplus$ breast cancer	Trastuzumab	452
Hemorrhagic cystitis from cyclophosphamide/ifosfamide	Mesna	453
Nephrotoxicity from platinum compounds	Amifostine	453
Cardiotoxicity from anthracyclines	Dexrazoxane	453
Myelosuppression from methotrexate	Leucovorin	453
Osteoporosis	Calcium/vitamin D supplementation (prophylaxis); bisphosphonates, PTH analogs, SERMs, calcitonin, denosumab (treatment)	474
Osteomalacia/rickets	Vitamin D supplementation	475
Chronic gout	Xanthine oxidase inhibitors (eg, allopurinol, febuxostat); pegloticase; probenecid	479
Acute gout attack	NSAIDs, colchicine, glucocorticoids	479
Buerger disease	Smoking cessation	484
Kawasaki disease	IVIG, aspirin	484
Temporal arteritis	High-dose glucocorticoids	484
Granulomatosis with polyangiitis	Cyclophosphamide, glucocorticoids	485
Neural tube defect prevention	Prenatal folic acid	505
Migraine	Abortive therapies (eg, sumatriptan, NSAIDs); prophylaxis (eg, propranolol, topiramate, anti-CGRP antibodies, amitriptyline)	536
Multiple sclerosis	Disease-modifying therapies (eg, $\beta$ -interferon, glatiramer, natalizumab); for acute flares, use IV steroids	541
Tonic-clonic seizures	Levetiracetam, phenytoin, valproate, carbamazepine	564
Absence seizures	E ethosuximide	564
Trigeminal neuralgia (tic douloureux)	Carbamazepine	536

CONDITION	COMMON TREATMENT(S)	PAGE
Malignant hyperthermia	Dantrolene	572
Anorexia	Nutrition, psychotherapy, SSRIs	590
Bulimia nervosa	Nutrition rehabilitation, psychotherapy, SSRIs	590
Alcohol use disorder	Disulfiram, acamprosate, naltrexone, supportive care	595
ADHD	Methylphenidate, amphetamines, behavioral therapy, atomoxetine, guanfacine, clonidine	580, 596
Alcohol withdrawal	Long-acting benzodiazepines	596
Bipolar disorder	Mood stabilizers (eg, lithium, valproic acid, carbamazepine), atypical antipsychotics	596
Depression	SSRIs (first-line)	596
Generalized anxiety disorder	SSRIs, SNRIs (first line); buspirone (second line)	596
Schizophrenia	Atypical antipsychotics	583, 596
Hyperaldosteronism	Spironolactone	632
Benign prostatic hyperplasia	$\alpha_1$ -antagonists, 5 $\alpha$ -reductase inhibitors, PDE-5 inhibitors, TURP	678
Infertility	Leuprorelin, GnRH (pulsatile), clomiphene	680
Breast cancer in postmenopausal woman	Aromatase inhibitor (anastrozole)	680
ER/PR + breast cancer	Tamoxifen	680
Uterine fibroids	Leuprorelin, GnRH (continuous)	680
Medical abortion	Mifepristone	681
Prostate adenocarcinoma	Flutamide, GnRH (continuous), degarelix, ketoconazole	680, 682
Erectile dysfunction	Sildenafil	711
Pulmonary arterial hypertension (idiopathic)	Sildenafil, bosentan, epoprostenol, iloprost	711

## ▶ KEY ASSOCIATIONS

DISEASE/FINDING	MOST COMMON/IMPORTANT ASSOCIATIONS	PAGE
Mitochondrial inheritance	Disease occurs in both males and females, inherited through females only	59
Intellectual disability	Down syndrome, fragile X syndrome	62, 63
Vitamin deficiency (USA)	Folate (pregnant women are at high risk; body stores only 3- to 4-month supply; prevents neural tube defects)	68
Lysosomal storage disease	Gaucher disease	88
Bacterial meningitis (> 6 months old)	<i>S pneumoniae</i>	180
Bacterial meningitis (newborns and kids)	Group B streptococcus/ <i>E coli</i> / <i>Listeria monocytogenes</i> (newborns)	180

DISEASE/FINDING	MOST COMMON/IMPORTANT ASSOCIATIONS	PAGE
HLA-DR3	Diabetes mellitus type 1, SLE, Graves disease, Hashimoto thyroiditis (also associated with HLA-DR5), Addison disease	100
HLA-DR4	Diabetes mellitus type 1, rheumatoid arthritis, Addison disease	100
Bacteria associated with gastritis, peptic ulcer disease, and gastric malignancies (eg, adenocarcinoma, MALToma)	<i>H pylori</i>	146
Opportunistic respiratory infection in AIDS	<i>Pneumocystis jirovecii</i> pneumonia	154
Helminth infection (US)	<i>Enterobius vermicularis</i>	159
Viral encephalitis affecting temporal lobe	HSV-1	164
Infection 2° to blood transfusion	Hepatitis C	173
Food poisoning (exotoxin mediated)	<i>S aureus, B cereus</i>	178
Osteomyelitis	<i>S aureus</i> (most common overall)	180
Osteomyelitis in sickle cell disease	<i>Salmonella</i>	180
Osteomyelitis with IV drug use	<i>S aureus, Pseudomonas, Candida</i>	180
UTI	<i>E coli, Staphylococcus saprophyticus</i> (young women)	181
Sexually transmitted disease	<i>C trachomatis</i> (usually coinfected with <i>N gonorrhoeae</i> )	184
Nosocomial pneumonia	<i>S aureus, Pseudomonas, Klebsiella, Acinetobacter</i>	185
Pelvic inflammatory disease	<i>C trachomatis, N gonorrhoeae</i>	185
Metastases to bone	Prostate, breast > kidney, thyroid, lung	224
Metastases to brain	Lung > breast > melanoma, colon, kidney	224
Metastases to liver	Colon >> stomach > pancreas	224
S3 heart sound	↑ ventricular filling pressure (eg, mitral regurgitation, HF), common in dilated ventricles	296
S4 heart sound	Stiff/hypertrophic ventricle (aortic stenosis, restrictive cardiomyopathy)	296
Constrictive pericarditis	TB (developing world); idiopathic, viral illness (developed world)	296, 320
Holosystolic murmur	VSD, tricuspid regurgitation, mitral regurgitation	299
Ejection click	Aortic stenosis	300
Mitral valve stenosis	Rheumatic heart disease	300
Opening snap	Mitral stenosis	300
Heart murmur, congenital	Mitral valve prolapse	300
Chronic arrhythmia	Atrial fibrillation (associated with high risk of emboli)	316
Cyanosis (early; less common)	Tetralogy of Fallot, transposition of great vessels, truncus arteriosus, total anomalous pulmonary venous return, tricuspid atresia	306
Late cyanotic shunt (uncorrected left to right becomes right to left)	Eisenmenger syndrome (caused by ASD, VSD, PDA; results in pulmonary hypertension/polycythemia)	307
Congenital cardiac anomaly	VSD	307

DISEASE/FINDING	MOST COMMON/IMPORTANT ASSOCIATIONS	PAGE
Hypertension, 2°	Renal artery stenosis, chronic kidney disease (eg, polycystic kidney disease, diabetic nephropathy), hyperaldosteronism	308
Aortic aneurysm, thoracic	Marfan syndrome (idiopathic cystic medial degeneration)	310
Aortic aneurysm, abdominal	Atherosclerosis, smoking is major risk factor	310
Aortic aneurysm, ascending or arch	3° syphilis (syphilitic aortitis), vasa vasorum destruction	310
Sites of atherosclerosis	Abdominal aorta > coronary artery > popliteal artery > carotid artery	310
Aortic dissection	Hypertension	311
Right heart failure due to a pulmonary cause	Cor pulmonale	319
Heart valve in bacterial endocarditis	Mitral > aortic (rheumatic fever), tricuspid (IV drug abuse)	321
Endocarditis presentation associated with bacterium	<i>S aureus</i> (acute, IVDA, tricuspid valve), viridans streptococci (subacute, dental procedure), <i>S bovis</i> (colon cancer), culture negative ( <i>Coxiella</i> , <i>Bartonella</i> , HACEK)	321
Temporal arteritis	Risk of ipsilateral blindness due to occlusion of ophthalmic artery; polymyalgia rheumatica	484
Recurrent inflammation/thrombosis of small/medium vessels in extremities	Buerger disease (strongly associated with tobacco)	484
Cardiac 1° tumor (kids)	Rhabdomyoma, often seen in tuberous sclerosis	324
Cardiac tumor (adults)	Metastasis, myxoma (90% in left atrium; “ball valve”)	324
Congenital adrenal hyperplasia, hypotension	21-hydroxylase deficiency	343
Hypopituitarism	Pituitary adenoma (usually benign tumor)	347
Congenital hypothyroidism (cretinism)	Thyroid dysgenesis/dyshormonogenesis, iodine deficiency	349
Thyroid cancer	Papillary carcinoma (childhood irradiation)	351
Hypoparathyroidism	Accidental excision during thyroidectomy	352
1° hyperparathyroidism	Adenomas, hyperplasia, carcinoma	353
2° hyperparathyroidism	Hypocalcemia of chronic kidney disease	353
Cushing syndrome	<ul style="list-style-type: none"> <li>▪ Iatrogenic (from corticosteroid therapy)</li> <li>▪ Adrenocortical adenoma (secretes excess cortisol)</li> <li>▪ ACTH-secreting pituitary adenoma (Cushing disease)</li> <li>▪ Paraneoplastic (due to ACTH secretion by tumors)</li> </ul>	356
1° hyperaldosteronism	Adrenal hyperplasia or adenoma	358
Tumor of the adrenal medulla (kids)	Neuroblastoma (malignant)	358
Tumor of the adrenal medulla (adults)	Pheochromocytoma (usually benign)	359
Refractory peptic ulcers and high gastrin levels	Zollinger-Ellison syndrome (gastrinoma of duodenum or pancreas), associated with MEN1	360, 361
Esophageal cancer	Squamous cell carcinoma (worldwide); adenocarcinoma (US)	388
Acute gastric ulcer associated with CNS injury	Cushing ulcer (↑ intracranial pressure stimulates vagal gastric H <sup>+</sup> secretion)	389
Acute gastric ulcer associated with severe burns	Curling ulcer (greatly reduced plasma volume results in sloughing of gastric mucosa)	389

DISEASE/FINDING	MOST COMMON/IMPORTANT ASSOCIATIONS	PAGE
Bilateral ovarian metastases from gastric carcinoma	Krukenberg tumor (mucin-secreting signet ring cells)	389
Chronic atrophic gastritis (autoimmune)	Predisposition to gastric carcinoma (can also cause pernicious anemia)	389
Alternating areas of transmural inflammation and normal colon	Skip lesions (Crohn disease)	392
Site of diverticula	Sigmoid colon	393
Diverticulum in pharynx	Zenker diverticulum (diagnosed by barium swallow)	394
Hepatocellular carcinoma	HBV (+/- cirrhosis) or other causes of cirrhosis (eg, alcoholic liver disease, hemochromatosis), aflatoxins	402
Congenital conjugated hyperbilirubinemia (black liver)	Dubin-Johnson syndrome (inability of hepatocytes to secrete conjugated bilirubin into bile)	404
Hereditary harmless jaundice	Gilbert syndrome (benign congenital unconjugated hyperbilirubinemia)	404
Wilson disease	Hereditary ATP7B mutation (copper buildup in liver, brain, cornea, kidneys)	405
Hemochromatosis	Multiple blood transfusions or hereditary <i>HFE</i> mutation (can result in heart failure, “bronze diabetes,” and ↑ risk of hepatocellular carcinoma)	405
Pancreatitis (acute)	Gallstones, alcohol	407
Pancreatitis (chronic)	Alcohol (adults), cystic fibrosis (kids)	407
Microcytic anemia	Iron deficiency	428
Autosplenectomy (fibrosis and shrinkage)	Sickle cell disease (hemoglobin S)	432
Bleeding disorder with GpIb deficiency	Bernard-Soulier syndrome (defect in platelet adhesion to von Willebrand factor)	436
Bleeding disorder with GpIIb/IIIa deficiency	Glanzmann thrombasthenia (defect in platelet-to-platelet aggregation)	436
Hereditary bleeding disorder	von Willebrand disease	437
Hereditary thrombophilia	Factor V Leiden	437
DIC	Severe sepsis, obstetric complications, cancer, burns, trauma, major surgery, acute pancreatitis, APL	437
Malignancy associated with noninfectious fever	Hodgkin lymphoma	438
Type of Hodgkin lymphoma	Nodular sclerosis	438
t(14;18)	Follicular lymphoma ( <i>BCL-2</i> activation, anti-apoptotic oncogene)	439, 444
t(8;14)	Burkitt lymphoma ( <i>c-myc</i> fusion, transcription factor oncogene)	439, 444
Type of non-Hodgkin lymphoma	Diffuse large B-cell lymphoma	439
1° bone tumor (adults)	Multiple myeloma	440
Age ranges for patient with ALL/CLL/AML/CML	ALL: child, CLL: adult > 60, AML: adult ~ 65, CML: adult 45–85	442
Malignancy (kids)	Leukemia, brain tumors	442, 546

DISEASE/FINDING	MOST COMMON/IMPORTANT ASSOCIATIONS	PAGE
Death in CML	Blast crisis	442
t(9;22)	Philadelphia chromosome, CML (BCR-ABL oncogene, tyrosine kinase activation), more rarely associated with ALL	442, 444
Vertebral compression fracture	Osteoporosis	474
HLA-B27	Psoriatic arthritis, ankylosing spondylitis, IBD-associated arthritis, reactive arthritis	481
Death in SLE	Lupus nephropathy	482
Tumor of infancy	Strawberry hemangioma (grows rapidly and regresses spontaneously by childhood)	492
Actinic (solar) keratosis	Precursor to squamous cell carcinoma	496
Herald patch	Pityriasis rosea	496
Cerebellar tonsillar herniation	Chiari I malformation	506
Atrophy of the mammillary bodies	Wernicke encephalopathy (thiamine deficiency causing ataxia, ophthalmoplegia, and confusion)	528
Epidural hematoma	Rupture of middle meningeal artery (trauma; lentiform shaped)	531
Subdural hematoma	Rupture of bridging veins (crescent shaped)	531
Dementia	Alzheimer disease, multiple infarcts (vascular dementia)	538, 539
Demyelinating disease in young women	Multiple sclerosis	541
Brain tumor (adults)	Supratentorial: metastasis, astrocytoma (including glioblastoma multiforme), meningioma, schwannoma	544
Pituitary tumor	Prolactinoma, somatotrophic adenoma	545
Brain tumor (children)	Infratentorial: medulloblastoma (cerebellum) or supratentorial: craniopharyngioma	546
Mixed (UMN and LMN) motor neuron disease	Amyotrophic lateral sclerosis	548
Degeneration of dorsal column fibers	Tabes dorsalis (3° syphilis), subacute combined degeneration (dorsal columns, lateral corticospinal, spinocerebellar tracts affected)	548
Glomerulonephritis (adults)	Berger disease (IgA nephropathy)	620
Nephrotic syndrome (adults)	Membranous nephropathy	621
Nephrotic syndrome (children)	Minimal change disease	621
Kidney stones	<ul style="list-style-type: none"> <li>▪ Calcium = radiopaque</li> <li>▪ Struvite (ammonium) = radiopaque (formed by urease <math>\oplus</math> organisms such as <i>Proteus mirabilis</i>, <i>S saprophyticus</i>, <i>Klebsiella</i>)</li> <li>▪ Uric acid = radiolucent</li> <li>▪ Cystine = faintly radiopaque</li> </ul>	622
Renal tumor	Renal cell carcinoma: associated with von Hippel-Lindau and cigarette smoking; paraneoplastic syndromes (EPO, renin, PTHrP, ACTH)	628
1° amenorrhea	Turner syndrome (45,XO or 45,XO/46,XX mosaic)	661

DISEASE/FINDING	MOST COMMON/IMPORTANT ASSOCIATIONS	PAGE
Neuron migration failure	Kallmann syndrome (hypogonadotropic hypogonadism and anosmia)	662
Clear cell adenocarcinoma of the vagina	DES exposure in utero	668
Ovarian tumor (benign, bilateral)	Serous cystadenoma	670
Ovarian tumor (malignant)	Serous carcinoma	670
Tumor in women	Leiomyoma (estrogen dependent, not precancerous)	672
Gynecologic malignancy	Endometrial carcinoma (most common in US); cervical carcinoma (most common worldwide)	672
Breast mass	Fibrocystic change, carcinoma (in postmenopausal women)	673
Breast tumor (benign, young woman)	Fibroadenoma	673
Breast cancer	Invasive ductal carcinoma	674
Testicular tumor	Seminoma (malignant, radiosensitive), ↑ placental ALP	677
Obstruction of male urinary tract	BPH	678
Hypercoagulability, endothelial damage, blood stasis	Virchow triad (↑ risk of thrombosis)	695
Pulmonary hypertension	Idiopathic, heritable, left heart disease (eg, HF), lung disease (eg, COPD), hypoxic vasoconstriction (eg, OSA), thromboembolic (eg, PE)	703
SIADH	Small cell carcinoma of the lung	709

## ▶ EQUATION REVIEW

TOPIC	EQUATION	PAGE
Volume of distribution	$V_d = \frac{\text{amount of drug in the body}}{\text{plasma drug concentration}}$	233
Half-life	$t_{1/2} = \frac{0.7 \times V_d}{CL}$	233
Drug clearance	$CL = \frac{\text{rate of elimination of drug}}{\text{plasma drug concentration}} = V_d \times K_e$ (elimination constant)	233
Loading dose	$LD = \frac{C_p \times V_d}{F}$	233
Maintenance dose	$D = \frac{C_p \times CL \times \tau}{F}$	233
Therapeutic index	$TI = \text{median toxic dose}/\text{median effective dose} = TD_{50}/ED_{50}$	237
Odds ratio (for case-control studies)	$OR = \frac{a/c}{b/d} = \frac{ad}{bc}$	262
Relative risk	$RR = \frac{a/(a+b)}{c/(c+d)}$	262

TOPIC	EQUATION	PAGE
Attributable risk	$AR = \frac{a}{a+b} - \frac{c}{c+d}$	262
Relative risk reduction	$RRR = 1 - RR$	262
Absolute risk reduction	$ARR = \frac{c}{c+d} - \frac{a}{a+b}$	262
Number needed to treat	$NNT = 1/ARR$	262
Number needed to harm	$NNH = 1/AR$	262
Likelihood ratio +	$LR+ = \text{sensitivity}/(1 - \text{specificity}) = \text{TP rate}/\text{FP rate}$	263
Likelihood ratio -	$LR- = (1 - \text{sensitivity})/\text{specificity} = \text{FN rate}/\text{TN rate}$	263
Sensitivity	$\text{Sensitivity} = \text{TP} / (\text{TP} + \text{FN})$	264
Specificity	$\text{Specificity} = \text{TN} / (\text{TN} + \text{FP})$	264
Positive predictive value	$PPV = \text{TP} / (\text{TP} + \text{FP})$	264
Negative predictive value	$NPV = \text{TN} / (\text{FN} + \text{TN})$	264
Cardiac output	$CO = \frac{\text{rate of O}_2 \text{ consumption}}{(\text{arterial O}_2 \text{ content} - \text{venous O}_2 \text{ content})}$  $CO = \text{stroke volume} \times \text{heart rate}$	294 294
Mean arterial pressure	$MAP = \text{cardiac output} \times \text{total peripheral resistance}$  $MAP = \frac{2}{3} \text{ diastolic} + \frac{1}{3} \text{ systolic}$	294 294
Stroke volume	$SV = EDV - ESV$	294
Ejection fraction	$EF = \frac{SV}{EDV} = \frac{EDV - ESV}{EDV}$	294
Resistance	$\text{Resistance} = \frac{\text{driving pressure } (\Delta P)}{\text{flow } (Q)} = \frac{8\eta \text{ (viscosity)} \times \text{length}}{\pi r^4}$	295
Capillary fluid exchange	$J_v = \text{net fluid flow} = K_f[(P_c - P_i) - \sigma(\pi_c - \pi_i)]$	305
Reticulocyte production index	$RPI = \frac{\text{reticulocyte \%} \times \text{actual Hct}}{\text{normal Hct } (\approx 45\%)}$	427
Renal clearance	$C_x = (U_x V)/P_x$	606
Glomerular filtration rate	$C_{\text{inulin}} = GFR = U_{\text{inulin}} \times V/P_{\text{inulin}}$  $= K_f [(P_{GC} - P_{BS}) - (\pi_{GC} - \pi_{BS})]$	606
Effective renal plasma flow	$eRPF = U_{PAH} \times \frac{V}{P_{PAH}} = C_{PAH}$	606
Renal blood flow	$RBF = \frac{RPF}{1 - Hct}$	606
Filtration fraction	$FF = \frac{GFR}{RPF}$	607
Henderson-Hasselbalch equation (for extracellular pH)	$pH = 6.1 + \log \frac{[\text{HCO}_3^-]}{0.03 \text{ Pco}_2}$	616
Winters formula	$\text{Pco}_2 = 1.5 [\text{HCO}_3^-] + 8 \pm 2$	616

TOPIC	EQUATION	PAGE
Anion gap	$\text{Na}^+ - (\text{Cl}^- + \text{HCO}_3^-)$	616
Physiologic dead space	$V_D = V_T \times \frac{\text{PaCO}_2 - \text{PECO}_2}{\text{PaCO}_2}$	688
Pulmonary vascular resistance	$\text{PVR} = \frac{P_{\text{pulm artery}} - P_{\text{L atrium}}}{\text{cardiac output}}$	692
Alveolar gas equation	$\text{PAO}_2 = \text{PIO}_2 - \frac{\text{PaCO}_2}{R}$	692

## ► EASILY CONFUSED MEDICATIONS

DRUG	CLINICAL USE/MECHANISM OF ACTION
Amiloride	K <sup>+</sup> -sparing diuretic
Amiodarone	Class III antiarrhythmic
Amlodipine	Dihydropyridine Ca <sup>2+</sup> channel blocker
Benztropine	Cholinergic antagonist
Bromocriptine	Dopamine agonist
Buspirone	Generalized anxiety disorder (5-HT <sub>1A</sub> -receptor agonist)
Bupropion	Depression, smoking cessation (NE-DA reuptake inhibitor)
Cimetidine	H <sub>2</sub> -receptor antagonist
Cetirizine	2nd-generation antihistamine
Chloramphenicol	Antibiotic (blocks 50S subunit)
Chlordiazepoxide	Long-acting benzodiazepine
Chlorpromazine	Typical antipsychotic
Chlorpropamide	1st-generation sulfonylurea
Chlorpheniramine	1st-generation antihistamine
Chlorthalidone	Thiazide diuretic
Clozapine	Atypical antipsychotic
Clomipramine	Tricyclic antidepressant
Clomiphene	Selective estrogen receptor modulator
Clonidine	α <sub>2</sub> -agonist
Doxepin	Tricyclic antidepressant
Doxazosin	α <sub>1</sub> -antagonist
Eplerenone	K <sup>+</sup> -sparing diuretic
Propafenone	Class IC antiarrhythmic
Fluoxetine	Selective serotonin reuptake inhibitor
Fluphenazine	Typical antipsychotic
Duloxetine	Serotonin-norepinephrine reuptake inhibitor
Mifepristone	Progesterone receptor antagonist

DRUG	CLINICAL USE/MECHANISM OF ACTION
Misoprostol	PGE <sub>1</sub> synthetic analog
Naloxone	Opioid receptor antagonist (treats toxicity)
Naltrexone	Opioid receptor antagonist (prevents relapse)
Nitroprusside	Hypertensive emergency ( $\uparrow$ cGMP/NO)
Nitroglycerin	Antianginal ( $\uparrow$ cGMP/NO)
Omeprazole	Proton pump inhibitor
Ketoconazole	Antifungal (inhibits fungal sterol synthesis)
Aripiprazole	Atypical antipsychotic
Anastrozole	Aromatase inhibitor
Rifaximin	Hepatic encephalopathy ( $\downarrow$ ammoniagenic bacteria)
Rifampin	Antimicrobial (inhibits DNA-dependent RNA polymerase)
Sertraline	Selective serotonin reuptake inhibitor
Selegiline	MAO-B inhibitor
Trazodone	Insomnia (blocks 5-HT <sub>2</sub> , $\alpha_1$ -adrenergic, and H <sub>1</sub> receptors)
Tramadol	Chronic pain (weak opioid agonist)
Varenicline	Smoking cessation (nicotinic ACh receptor partial agonist)
Venlafaxine	Serotonin-norepinephrine reuptake inhibitor

▶ NOTES

## SECTION IV

# Top-Rated Review Resources

*“Some books are to be tasted, others to be swallowed, and some few to be chewed and digested.”*

—Sir Francis Bacon

*“Always read something that will make you look good if you die in the middle of it.”*

—P.J. O’Rourke

*“So many books, so little time.”*

—Frank Zappa

*“If one cannot enjoy reading a book over and over again, there is no use in reading it at all.”*

—Oscar Wilde

*“Start where you are. Use what you have. Do what you can.”*

—Arthur Ashe

▶ How to Use the Database	738
▶ Question Banks	740
▶ Web and Mobile Apps	740
▶ Comprehensive	741
▶ Anatomy, Embryology, and Neuroscience	741
▶ Behavioral Science	742
▶ Biochemistry	742
▶ Cell Biology and Histology	743
▶ Microbiology and Immunology	743
▶ Pathology	743
▶ Pharmacology	744
▶ Physiology	744

## ► HOW TO USE THE DATABASE

This section is a database of top-rated basic science review books, sample examination books, websites, apps, and commercial review courses that have been marketed to medical students studying for the USMLE Step 1. For each recommended resource, we list (where applicable) the **Title**, the **First Author** (or editor), the **Series Name** (where applicable), the **Current Publisher**, the **Copyright Year**, the **Number of Pages**, the **ISBN**, the **Approximate List Price**, the **Format** of the resource, and the **Number of Test Questions**. We also include **Summary Comments** that describe their style and overall utility for studying. Finally, each recommended resource receives a **Rating**. Within each section, resources are arranged first by Rating and then alphabetically by the first author within each Rating group.

A letter rating scale with six different grades reflects the detailed student evaluations for **Rated Resources**. Each rated resource receives a rating as follows:

A+	Excellent for boards review.
A	Very good for boards review; choose among the group.
A-	
B+	Good, but use only after exhausting better resources.
B	
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 importance of the discipline for the USMLE Step 1
- The appropriateness and accuracy of the material
- The readability of the text
- The quality and number of sample questions
- The quality of written answers to sample questions
- The cost
- The quality of the user interface and learning experience, for web and mobile apps
- The quality and appropriateness of the images and illustrations
- The length of the text (longer is not necessarily better)
- The quality and number of other resources available in the same discipline

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 for the basic sciences.

Evaluations are based on the cumulative results of formal and informal surveys of thousands of medical students at many medical schools across the country. The summary comments and overall ratings represent a consensus opinion, but there may have been a broad range of opinion or limited student feedback on any particular resource.

Please note that the data listed are subject to change in that:

- Publisher and app store prices change frequently.
- Retail and online bookstores may set their own prices.
- New editions and app versions come out frequently, and the quality of updating varies.
- The same book may be reissued through another publisher.

We actively encourage medical students and faculty to submit their opinions and ratings of these basic science review materials so that we may update our database. In addition, we ask that publishers and authors submit for evaluation review copies of basic science review books, including new editions and books not included in our database. We also solicit reviews of new books, mobile apps, websites, flash cards, and commercial review courses.

#### **Disclaimer/Conflict of Interest Statement**

None of the ratings reflects the opinion or influence of the publisher. All errors and omissions will gladly be corrected if brought to the attention of the authors through our blog at [firstaidteam.com](http://firstaidteam.com). Please note that USMLE-Rx, ScholarRx, and the entire *First Aid for the USMLE* series are publications by certain authors of *First Aid for the USMLE Step 1*; the following ratings are based solely on recommendations from the student authors of *First Aid for the USMLE Step 1* as well as data from the student survey and feedback forms.

## ► TOP-RATED REVIEW RESOURCES

**Question Banks**

		AUTHOR	PUBLISHER	TYPE	PRICE
<b>A<sup>+</sup></b>	<b><i>UWorld Qbank</i></b>	UWorld	uworld.com	Test/3000+ q	\$269–\$799
<b>A</b>	<b><i>NBME Practice Exams</i></b>	National Board of Medical Examiners	nbme.org/students/sas/Comprehensive.html	Test/200 q	\$60
<b>A<sup>-</sup></b>	<b><i>AMBOSS</i></b>	Amboss	amboss.com	Test/3500 q	\$59–\$286
<b>A<sup>-</sup></b>	<b><i>USMLE-Rx Qmax</i></b>	USMLE-Rx	usmle-rx.com	Test/2300+ q	\$79–\$349
<b>B<sup>+</sup></b>	<b><i>Kaplan Qbank</i></b>	Kaplan	kaptest.com	Test/3300 q	\$99–\$599
<b>B<sup>+</sup></b>	<b><i>TrueLearn Review</i></b>		truelearn.com	Test/2200 q	\$160–\$400
<b>B</b>	<b><i>BoardVitals</i></b>		boardvitals.com	Test/3150 q	Free–\$189
<b>B</b>	<b><i>Pastest</i></b>		pastest.com	Test/2100 q	\$79–\$249

**Web and Mobile Apps**

		AUTHOR	PUBLISHER	TYPE	PRICE
<b>A</b>	<b><i>Anki</i></b>		ankisrs.net	Flash cards	Free
<b>A</b>	<b><i>Boards and Beyond</i></b>		boardsbeyond.com	Review/Test/2300 q	\$19–\$299
<b>A</b>	<b><i>SketchyMedical</i></b>		sketchnymedical.com	Review	\$100–\$550
<b>A</b>	<b><i>Rx Bricks</i></b>		usmle-rx.scholarrx.com/rx-bricks	Study plan	\$15–\$199
<b>A<sup>-</sup></b>	<b><i>Physeo</i></b>		physeo.com	Review	\$30–\$150
<b>A<sup>-</sup></b>	<b><i>USMLE-Rx Step 1 Express</i></b>		usmle-rx.com	Review/Test	\$49–\$199
<b>A<sup>-</sup></b>	<b><i>USMLE-Rx Step 1 Flash Facts</i></b>		usmle-rx.com	Flash cards	\$29–\$149
<b>A<sup>-</sup></b>	<b><i>Dirty Medicine</i></b>		youtube.com/c/DirtyMedicine		Free
<b>B<sup>+</sup></b>	<b><i>USMLE Step 1 Mastery</i></b>		builtbyhlt.com/medical/usmle-step-1-mastery	Test/1400 q	\$10–\$30
<b>B<sup>+</sup></b>	<b><i>Cram Fighter</i></b>		cramfighter.com	Study plan	\$29–\$159
<b>B<sup>+</sup></b>	<b><i>Medical School Pathology</i></b>		medicalschoolpathology.com	Review	Free
<b>B<sup>+</sup></b>	<b><i>OnlineMedEd</i></b>		onlinemeded.org	Review	Free
<b>B<sup>+</sup></b>	<b><i>Osmosis</i></b>		osmosis.org	Test	\$299–\$399
<b>B<sup>+</sup></b>	<b><i>Medbullets</i></b>		step1.medbullets.com	Review/Test/1000 q	Free–\$250
<b>B<sup>+</sup></b>	<b><i>Ninja Nerd Medicine</i></b>		youtube.com/c/NinjaNerdMedicine		Free
<b>B<sup>+</sup></b>	<b><i>WebPath: The Internet Pathology Laboratory</i></b>		webpath.med.utah.edu	Review/Test/1300 q	Free
<b>B</b>	<b><i>Digital Anatomist Project: Interactive Atlases</i></b>		da.si.washington.edu/da.html	Review	Free

<b>B</b>	<i>Dr. Najeeb Lectures</i>	drnajeeblectures.com	Review	\$199
<b>B</b>	<i>Firecracker</i>	firecracker.lww.com	Review/Test/2800 q	\$99–\$499
<b>B</b>	<i>KISSPrep</i>	kissprep.com	Review	\$30–\$150
<b>B</b>	<i>Memorang</i>	memorangapp.com	Flash cards	\$19–\$239
<b>B</b>	<i>Picmonic</i>	picmonic.com	Review	\$25–\$480
<b>B</b>	<i>Radiopaedia.org</i>	radiopaedia.org	Cases/Test	Free
<b>B-</b>	<i>Innerbody Research</i>	innerbody.com/htm/body.html	Review	Free
<b>B-</b>	<i>Lecturio</i>	lecturio.com/usmle-step-1	Review/Test/2150 q	\$105–\$720

## Comprehensive

		AUTHOR	PUBLISHER	TYPE	PRICE
<b>A</b>	<i>First Aid for the Basic Sciences: General Principles</i>	Le	McGraw-Hill, 2017, 528 pages, ISBN 9781259587016	Review	\$75
<b>A</b>	<i>First Aid Cases for the USMLE Step 1</i>	Le	McGraw-Hill, 2018, 496 pages, ISBN 9781260143133	Cases	\$50
<b>A-</b>	<i>First Aid for the Basic Sciences: Organ Systems</i>	Le	McGraw-Hill, 2017, 912 pages, ISBN 9781259587030	Review	\$72
<b>A-</b>	<i>Cracking the USMLE Step 1</i>	Princeton Review	Princeton Review, 2013, 832 pages, ISBN 9780307945068	Review	\$45
<b>B+</b>	<i>USMLE Step 1 Secrets in Color</i>	Brown	Elsevier, 2016, 800 pages, ISBN 9780323396790	Review	\$43
<b>B+</b>	<i>USMLE Step 1 Lecture Notes 2020</i>	Kaplan	Kaplan Medical, 2019, 2624 pages, ISBN 9781506254944	Review	\$330
<b>B+</b>	<i>Crush Step 1: The Ultimate USMLE Step 1 Review</i>	O'Connell	Elsevier, 2017, 704 pages, ISBN 9780323481632	Review	\$45
<b>B</b>	<i>Kaplan USMLE Step 1 Qbook</i>	Kaplan	Kaplan Medical, 2017, 468 pages, ISBN 9781506223544	Test/850 q	\$50
<b>B</b>	<i>medEssentials for the USMLE Step 1</i>	Kaplan	Kaplan Medical, 2019, 528 pages, ISBN 9781506223599	Review	\$55
<b>B</b>	<i>Step-Up to USMLE Step 1 2015</i>	McInnis	Lippincott Williams & Wilkins, 2015, 528 pages, ISBN 9781469894690	Review	\$60
<b>B-</b>	<i>USMLE Step 1 Made Ridiculously Simple</i>	Carl	MedMaster, 2017, 416 pages, ISBN 9781935660224	Review/Test 1000 q	\$30

## Anatomy, Embryology, and Neuroscience

		AUTHOR	PUBLISHER	TYPE	PRICE
<b>A-</b>	<i>High-Yield Gross Anatomy</i>	Dudek	Lippincott Williams & Wilkins, 2015, 320 pages, ISBN 9781451190236	Review	\$45
<b>A-</b>	<i>Clinical Anatomy Made Ridiculously Simple</i>	Goldberg	MedMaster, 2016, 175 pages, ISBN 9780940780972	Review	\$30

**Anatomy, Embryology, and Neuroscience (continued)**

		AUTHOR	PUBLISHER	TYPE	PRICE
B+	<i>BRS Embryology</i>	Dudek	Lippincott Williams & Wilkins, 2014, 336 pages, ISBN 9781451190380	Review/Test/220 q	\$56
B+	<i>High-Yield Embryology</i>	Dudek	Lippincott Williams & Wilkins, 2013, 176 pages, ISBN 9781451176100	Review	\$43
B+	<i>Clinical Neuroanatomy Made Ridiculously Simple</i>	Goldberg	MedMaster, 2014, 99 pages, ISBN 9781935660194	Review/Test/Few q	\$26
B+	<i>High-Yield Neuroanatomy</i>	Gould	Lippincott Williams & Wilkins, 2015, 208 pages, ISBN 9781451193435	Review/Test/50 q	\$42
B+	<i>Crash Course: Anatomy and Physiology</i>	Stephens	Elsevier, 2019, 350 pages, ISBN 9780702073755	Review	\$40
B	<i>Anatomy—An Essential Textbook</i>	Gilroy	Thieme, 2017, 528 pages, ISBN 9781626234390	Text/Test/400 q	\$50
B	<i>Netter's Anatomy Flash Cards</i>	Hansen	Elsevier, 2018, 688 flash cards, ISBN 9780323530507	Flash cards	\$40
B	<i>Case Files: Anatomy</i>	Toy	McGraw-Hill, 2014, 416 pages, ISBN 9780071794862	Cases	\$35
B-	<i>Case Files: Neuroscience</i>	Toy	McGraw-Hill, 2014, 432 pages, ISBN 9780071790253	Cases	\$35

**Behavioral Science**

		AUTHOR	PUBLISHER	TYPE	PRICE
A-	<i>BRS Behavioral Science</i>	Fadem	Lippincott Williams & Wilkins, 2020, 384 pages, ISBN 9781975118365	Review/Test/600 q	\$55
B	<i>Biostatistics and Epidemiology: A Primer for Health and Biomedical Professionals</i>	Wassertheil-Smoller	Springer, 2015, 4th edition, 280 pages, ISBN 9781493921331	Review	\$75

**Biochemistry**

		AUTHOR	PUBLISHER	TYPE	PRICE
A-	<i>Pixorize</i>		pixorize.com	Review	\$130–\$200
B+	<i>Lippincott Illustrated Reviews: Biochemistry</i>	Ferrier	Lippincott Williams & Wilkins, 2017, 560 pages, ISBN 9781496344496	Review/Test/200 q	\$78
B+	<i>BRS Biochemistry, Molecular Biology, and Genetics</i>	Lieberman	Lippincott Williams & Wilkins, 2019, 448 pages, ISBN 9781496399236	Review/Test/500 q	\$55
B+	<i>PreTest Biochemistry and Genetics</i>	Wilson	McGraw-Hill, 2013, 592 pages, ISBN 9780071791441	Test/500 q	\$38
B	<i>Lange Flash Cards Biochemistry and Genetics</i>	Baron	McGraw-Hill, 2017, 184 flash cards, ISBN 9781259837210	Flash cards	\$40
B	<i>Case Files: Biochemistry</i>	Toy	McGraw-Hill, 2014, 480 pages, ISBN 9780071794886	Cases	\$35

## Cell Biology and Histology

	AUTHOR	PUBLISHER	TYPE	PRICE	
B+	<i>Blue Histology</i>	www.lab.anhb.uwa.edu.au/mb140	Text	Free	
B+	<i>Crash Course: Cell Biology and Genetics</i>	Stubbs	Mosby, 2015, 216 pages, ISBN 9780723438762	Review/Print + online	\$47
B	<i>BRS Cell Biology and Histology</i>	Gartner	Lippincott Williams & Wilkins, 2018, 448 pages, ISBN 9781496396358	Review/Test/320 q	\$54

## Microbiology and Immunology

	AUTHOR	PUBLISHER	TYPE	PRICE	
A-	<i>Medical Microbiology and Immunology Flash Cards</i>	Rosenthal	Elsevier, 2016, 192 flash cards, ISBN 9780323462242	Flash cards	\$40
B+	<i>Basic Immunology</i>	Abbas	Elsevier, 2019, 336 pages, ISBN 9780323549431	Review	\$70
B+	<i>Clinical Microbiology Made Ridiculously Simple</i>	Gladwin	MedMaster, 2019, 418 pages, ISBN 9781935660330	Review	\$38
B+	<i>Microcards: Microbiology Flash Cards</i>	Harpavat	Lippincott Williams & Wilkins, 2015, 312 flash cards, ISBN 9781451192353	Flash cards	\$53
B+	<i>Review of Medical Microbiology and Immunology</i>	Levinson	McGraw-Hill, 2020, 864 pages, ISBN 9781260116717	Review/Test/650 q	\$77
B+	<i>Lange Microbiology and Infectious Diseases Flash Cards, 3e</i>	Somers	McGraw-Hill, 2017, ISBN 9781259859823	Flash cards	\$55
B	<i>Case Studies in Immunology: Clinical Companion</i>	Geha	W. W. Norton & Company, 2016, 384 pages, ISBN 9780815345121	Cases	\$62
B	<i>How the Immune System Works</i>	Sompayrac	Wiley-Blackwell, 2019, 168 pages, ISBN 9781119542124	Review	\$50
B	<i>Case Files: Microbiology</i>	Toy	McGraw-Hill, 2014, 416 pages, ISBN 9780071820233	Cases	\$36
B-	<i>Lippincott Illustrated Reviews: Microbiology</i>	Cornelissen	Lippincott Williams & Wilkins, 2019, 448 pages, ISBN 9781496395856	Review/Test/Few q	\$74

## Pathology

	AUTHOR	PUBLISHER	TYPE	PRICE	
A+	<i>Pathoma: Fundamentals of Pathology</i>	Sattar	Pathoma, 2021, 226 pages, ISBN 9780983224648	Review/Lecture	\$85–\$120
A-	<i>Crash Course: Pathology</i>	McKinney	Elsevier, 2019, 438 pages, ISBN 9780702073540	Review	\$40
B+	<i>Rapid Review: Pathology</i>	Goljan	Elsevier, 2018, 864 pages, ISBN 9780323476683	Review/Test/500 q	\$65
B+	<i>Robbins and Cotran Review of Pathology</i>	Klatt	Elsevier, 2014, 504 pages, ISBN 9781455751556	Test/1100 q	\$55
B	<i>BRS Pathology</i>	Gupta	Lippincott Williams & Wilkins, 2020, 496 pages, ISBN 9781975136628	Review/Test/450 q	\$55
B	<i>Pathophysiology of Disease: Introduction to Clinical Medicine</i>	Hammer	McGraw-Hill, 2018, 832 pages, ISBN 9781260026504	Text	\$90

**Pathology (continued)**

<b>B</b>	<i>Haematology at a Glance</i>	Mehta	Wiley-Blackwell, 2014, 136 pages, ISBN 9781119969228	Review	\$51
<b>B</b>	<i>Pocket Companion to Robbins and Cotran Pathologic Basis of Disease</i>	Mitchell	Elsevier, 2016, 896 pages, ISBN 9781455754168	Review	\$39

**Pharmacology**

	AUTHOR	PUBLISHER	TYPE	PRICE	
<b>B+</b>	<i>Master the Boards USMLE Step 1 Pharmacology Flashcards</i>	Fischer	Kaplan, 2015, 200 flash cards, ISBN 9781618657947	Flash cards	\$55
<b>B+</b>	<i>Crash Course: Pharmacology</i>	Page	Elsevier, 2019, 336 pages, ISBN 9780702073441	Review	\$40
<b>B+</b>	<i>Katzung &amp; Trevor's Pharmacology: Examination and Board Review</i>	Trevor	McGraw-Hill, 2018, 592 pages, ISBN 9781259641022	Review/Test/800 q	\$54
<b>B</b>	<i>Lange Pharmacology Flash Cards</i>	Baron	McGraw-Hill, 2017, 266 flash cards, ISBN 9781259837241	Flash cards	\$39
<b>B</b>	<i>Pharmacology Flash Cards</i>	Brenner	Elsevier, 2017, 230 flash cards, ISBN 9780323355643	Flash cards	\$45
<b>B</b>	<i>BRS Pharmacology</i>	Lerchenfeldt	Lippincott Williams & Wilkins, 2019, 384 pages, ISBN 9781975105495	Review/Test/200 q	\$55
<b>B-</b>	<i>Lippincott Illustrated Reviews: Pharmacology</i>	Whalen	Lippincott Williams & Wilkins, 2018, 576 pages, ISBN 9781496384133	Review/Test/380 q	\$76

**Physiology**

	AUTHOR	PUBLISHER	TYPE	PRICE	
<b>A-</b>	<i>Physiology</i>	Costanzo	Elsevier, 2017, 528 pages, ISBN 9780323478816	Text	\$60
<b>A-</b>	<i>Color Atlas of Physiology</i>	Silbernagl	Thieme, 2015, 472 pages, ISBN 978135450070	Review	\$50
<b>A-</b>	<i>Pulmonary Pathophysiology: The Essentials</i>	West	Lippincott Williams & Wilkins, 2017, 264 pages, ISBN 9781496339447	Review/Test/75 q	\$57
<b>B+</b>	<i>BRS Physiology</i>	Costanzo	Lippincott Williams & Wilkins, 2018, 304 pages, ISBN 9781496367617	Review/Test/350 q	\$55
<b>B+</b>	<i>Vander's Renal Physiology</i>	Eaton	McGraw-Hill, 2018, 224 pages, ISBN 9781260019377	Text	\$49
<b>B+</b>	<i>Pathophysiology of Heart Disease</i>	Lilly	Lippincott Williams & Williams, 2020, 480 pages, ISBN 9781975120597	Review	\$57
<b>B+</b>	<i>Acid-Base, Fluids, and Electrolytes Made Ridiculously Simple</i>	Preston	MedMaster, 2017, 166 pages, ISBN 9781935660293	Review	\$24
<b>B</b>	<i>Endocrine Physiology</i>	Molina	McGraw-Hill, 2018, 320 pages, ISBN 9781260019353	Review	\$59
<b>B</b>	<i>Netter's Physiology Flash Cards</i>	Mulroney	Saunders, 2015, 450 flash cards, ISBN 9780323359542	Flash cards	\$40

## SECTION IV

# Abbreviations and Symbols

ABBREVIATION	MEANING
1st MC*	1st metacarpal
A-a	alveolar-arterial [gradient]
AA	Alcoholics Anonymous, amyloid A
AAMC	Association of American Medical Colleges
AAo*	ascending aorta
Ab	antibody
ABPA	allergic bronchopulmonary aspergillosis
AC	adenylyl cyclase
ACA	anterior cerebral artery
Acetyl-CoA	acetyl coenzyme A
ACD	anemia of chronic disease
ACE	angiotensin-converting enzyme
ACh	acetylcholine
AChE	acetylcholinesterase
ACL	anterior cruciate ligament
ACom	anterior communicating [artery]
ACTH	adrenocorticotrophic hormone
AD	Alzheimer disease, autosomal dominant
ADA	adenosine deaminase, Americans with Disabilities Act
ADH	antidiuretic hormone
ADHD	attention-deficit hyperactivity disorder
ADP	adenosine diphosphate
ADPKD	autosomal-dominant polycystic kidney disease
AFP	$\alpha$ -fetoprotein
Ag	antigen, silver
AICA	anterior inferior cerebellar artery
AIDS	acquired immunodeficiency syndrome
AIHA	autoimmune hemolytic anemia
AKI	acute kidney injury
AKT	protein kinase B
AL	amyloid light [chain]
ALA	aminolevulinate
ALI	acute lung injury
ALL	acute lymphoblastic (lymphocytic) leukemia
ALP	alkaline phosphatase
ALS	amyotrophic lateral sclerosis
ALT	alanine transaminase
AMA	American Medical Association, antimitochondrial antibody
AML	acute myelogenous (myeloid) leukemia
AMP	adenosine monophosphate
ANA	antineuclear antibody
ANCA	antineutrophil cytoplasmic antibody
ANOVA	analysis of variance

ABBREVIATION	MEANING
ANP	atrial natriuretic peptide
ANS	autonomic nervous system
Ant*	anterior
anti-CCP	anti-cyclic citrullinated peptide
Ao*	aorta
AOA	American Osteopathic Association
AP	action potential, A & P [ribosomal binding sites]
APC	antigen-presenting cell, activated protein C
APL	Acute promyelocytic leukemia
Apo	apolipoprotein
APP	amyloid precursor protein
APRT	adenine phosphoribosyltransferase
aPTT	activated partial thromboplastin time
APUD	amine precursor uptake decarboxylase
AR	attributable risk, autosomal recessive, aortic regurgitation
ARB	angiotensin receptor blocker
ARDS	acute respiratory distress syndrome
Arg	arginine
ARPKD	autosomal-recessive polycystic kidney disease
ART	antiretroviral therapy
AS	aortic stenosis
ASA	anterior spinal artery
Asc*	ascending
Asc Ao*	ascending aorta
ASD	atrial septal defect
ASO	anti-streptolysin O
AST	aspartate transaminase
AT	angiotensin, antithrombin
ATN	acute tubular necrosis
ATP	adenosine triphosphate
ATPase	adenosine triphosphatase
ATTR	transthyretin-mediated amyloidosis
AUB	abnormal uterine bleeding
AV	atrioventricular
AZT	azidothymidine
BAL	British anti-Lewisite [dimercaprol]
BBB	blood-brain barrier
BCG	bacille Calmette-Guérin
BD*	bile duct
BH <sub>4</sub>	tetrahydrobiopterin
BM	basement membrane
BOOP	bronchiolitis obliterans organizing pneumonia
BP	bisphosphate, blood pressure
BPG	bisphosphoglycerate

\*Image abbreviation only

ABBREVIATION	MEANING
BPH	benign prostatic hyperplasia
BT	bleeding time
BUN	blood urea nitrogen
C*	caudate
Ca*	capillary
Ca <sup>2+</sup>	calcium ion
CAD	coronary artery disease
CAF	common application form
cAMP	cyclic adenosine monophosphate
CBG	corticosteroid-binding globulin
Cbm*	cerebellum
CBSE	Comprehensive Basic Science Examination
CBSSA	Comprehensive Basic Science Self-Assessment
CBT	computer-based test, cognitive behavioral therapy
CC*	corpus callosum
CCA*	common carotid artery
CCK	cholecystokinin
CCS	computer-based case simulation
CD	cluster of differentiation
CDK	cyclin-dependent kinase
cDNA	complementary deoxyribonucleic acid
CEA	carcinoembryonic antigen
CETP	cholesterol-ester transfer protein
CF	cystic fibrosis
CFTR	cystic fibrosis transmembrane conductance regulator
CGD	chronic granulomatous disease
cGMP	cyclic guanosine monophosphate
CGRP	calcitonin gene-related peptide
C <sub>H</sub> 1–C <sub>H</sub> 3	constant regions, heavy chain [antibody]
ChAT	choline acetyltransferase
CHD*	common hepatic duct
χ <sup>2</sup>	chi-squared
CI	confidence interval
CIN	candidate identification number, carcinoma in situ, cervical intraepithelial neoplasia
CIS	Communication and Interpersonal Skills
CK	clinical knowledge, creatine kinase
CKD	chronic kidney disease
CK-MB	creatinine kinase, MB fraction
C <sub>L</sub>	constant region, light chain [antibody]
CL	clearance
Cl <sup>-</sup>	chloride ion
CLL	chronic lymphocytic leukemia
CMC	carpometacarpal (joint)
CML	chronic myelogenous (myeloid) leukemia
CMV	cytomegalovirus
CN	cranial nerve
CN <sup>-</sup>	cyanide ion
CNS	central nervous system
CNV	copy number variation
CO	carbon monoxide, cardiac output
CO <sub>2</sub>	carbon dioxide
CoA	coenzyme A
Coarct*	coarctation

ABBREVIATION	MEANING
COL1A1	collagen, type I, alpha 1
COL1A2	collagen, type I, alpha 2
COMT	catechol-O-methyltransferase
COP	coat protein
COPD	chronic obstructive pulmonary disease
CoQ	coenzyme Q
COVID-19	Coronavirus disease 2019
COX	cyclooxygenase
C <sub>p</sub>	plasma concentration
CPAP	continuous positive airway pressure
CPR	cardiopulmonary resuscitation
Cr	creatinine
CRC	colorectal cancer
CREST	calcinosis, Raynaud phenomenon, esophageal dysfunction, sclerosis, and telangiectasias [syndrome]
CRH	corticotropin-releasing hormone
CRP	C-reactive protein
CS	clinical skills
C-section	cesarean section
CSF	cerebrospinal fluid
CT	computed tomography
CTP	cytidine triphosphate
CXR	chest x-ray
DA	dopamine
DAF	decay-accelerating factor
DAG	diacylglycerol
DAo*	descending aorta
dATP	deoxyadenosine triphosphate
DCIS	ductal carcinoma in situ
DCT	distal convoluted tubule
ddI	didanosine
DES	diethylstilbestrol
Desc Ao*	descending aorta
DHAP	dihydroxyacetone phosphate
DHEA	dehydroepiandrosterone
DHF	dihydrofolic acid
DHT	dihydrotestosterone
DI	diabetes insipidus
DIC	disseminated intravascular coagulation
DIP	distal interphalangeal [joint]
DKA	diabetic ketoacidosis
DLCO	diffusing capacity for carbon monoxide
DM	diabetes mellitus
DNA	deoxyribonucleic acid
DNR	do not resuscitate
dNTP	deoxynucleotide triphosphate
DO	doctor of osteopathy
DPGN	diffuse proliferative glomerulonephritis
DPM	doctor of podiatric medicine
DPP-4	dipeptidyl peptidase-4
DPPC	dipalmitoylphosphatidylcholine
DS	double stranded
dsDNA	double-stranded deoxyribonucleic acid
dsRNA	double-stranded ribonucleic acid
DRG	dorsal root ganglion

\*Image abbreviation only

ABBREVIATION	MEANING	ABBREVIATION	MEANING
d4T	didehydrodeoxythymidine [stavudine]	FBPase-2	fructose bisphosphatase-2
dTMP	deoxythymidine monophosphate	Fc	fragment, crystallizable
DTR	deep tendon reflex	FcR	Fc receptor
DTs	delirium tremens	5f-dUMP	5-fluorodeoxyuridine monophosphate
dUDP	deoxyuridine diphosphate	Fe <sup>2+</sup>	ferrous ion
dUMP	deoxyuridine monophosphate	Fe <sup>3+</sup>	ferric ion
DVT	deep venous thrombosis	Fem*	femur
E*	euthromatin, esophagus	FENa	excreted fraction of filtered sodium
EBV	Epstein-Barr virus	FEV <sub>1</sub>	forced expiratory volume in 1 second
ECA*	external carotid artery	FF	filtration fraction
ECF	extracellular fluid	FFA	free fatty acid
ECFMG	Educational Commission for Foreign Medical Graduates	FGF	fibroblast growth factor
ECG	electrocardiogram	FGFR	fibroblast growth factor receptor
ECL	enterochromaffin-like [cell]	FISH	fluorescence in situ hybridization
ECM	extracellular matrix	FIT	fecal immunochemical testing
ECT	electroconvulsive therapy	FKBP	FK506 binding protein
ED <sub>50</sub>	median effective dose	fMet	formylmethionine
EDRF	endothelium-derived relaxing factor	FMG	foreign medical graduate
EDTA	ethylenediamine tetra-acetic acid	FMN	flavin mononucleotide
EDV	end-diastolic volume	FN	false negative
EEG	electroencephalogram	FP, FP*	false positive, foot process
EF	ejection fraction	FRC	functional residual capacity
EGF	epidermal growth factor	FSH	follicle-stimulating hormone
EHEC	enterohemorrhagic <i>E coli</i>	FSMB	Federation of State Medical Boards
EIEC	enteroinvasive <i>E coli</i>	FTA-ABS	fluorescent treponemal antibody—absorbed
ELISA	enzyme-linked immunosorbent assay	FTD*	frontotemporal dementia
EM	electron micrograph/microscopy	5-FU	5-fluorouracil
EMB	eosin–methylene blue	FVC	forced vital capacity
EPEC	enteropathogenic <i>E coli</i>	GABA	γ-aminobutyric acid
Epi	epinephrine	GAG	glycosaminoglycan
EPO	erythropoietin	Gal	galactose
EPS	extrapyramidal system	GBM	glomerular basement membrane
ER	endoplasmic reticulum, estrogen receptor	GC	glomerular capillary
ERAS	Electronic Residency Application Service	G-CSF	granulocyte colony-stimulating factor
ERCP	endoscopic retrograde cholangiopancreatography	GERD	gastroesophageal reflux disease
ERP	effective refractory period	GFAP	glial fibrillary acid protein
eRPF	effective renal plasma flow	GFR	glomerular filtration rate
ERT	estrogen replacement therapy	GGT	γ-glutamyl transpeptidase
ERV	expiratory reserve volume	GH	growth hormone
ESR	erythrocyte sedimentation rate	GHB	γ-hydroxybutyrate
ESRD	end-stage renal disease	GHRH	growth hormone-releasing hormone
ESV	end-systolic volume	G <sub>i</sub>	G protein, I polypeptide
ETEC	enterotoxigenic <i>E coli</i>	GI	gastrointestinal
EtOH	ethyl alcohol	GIP	gastric inhibitory peptide
EV	esophageal vein	GIST	gastrointestinal stromal tumor
F	bioavailability	GLUT	glucose transporter
FA	fatty acid	GM	granulocyte macrophage
Fab	fragment, antigen-binding	GM-CSF	granulocyte-macrophage colony stimulating factor
FAD	flavin adenine dinucleotide	GMP	guanosine monophosphate
FADH <sub>2</sub>	reduced flavin adenine dinucleotide	GnRH	gonadotropin-releasing hormone
FAP	familial adenomatous polyposis	Gp	glycoprotein
F1,6BP	fructose-1,6-bisphosphate	G6P	glucose-6-phosphate
F2,6BP	fructose-2,6-bisphosphate	G6PD	glucose-6-phosphate dehydrogenase
FBPase	fructose bisphosphatase	GPe	globus pallidus externa

\*Image abbreviation only

ABBREVIATION	MEANING
GPI	globus pallidus interna
GPI	glycosyl phosphatidylinositol
GRP	gastrin-releasing peptide
G <sub>s</sub>	G protein, S polypeptide
GSH	reduced glutathione
GSSG	oxidized glutathione
GTP	guanosine triphosphate
GTPase	guanosine triphosphatase
GU	genitourinary
H*	heterochromatin
H <sup>+</sup>	hydrogen ion
H <sub>1</sub> , H <sub>2</sub>	histamine receptors
H <sub>2</sub> S	hydrogen sulfide
HA*	hepatic artery
HAV	hepatitis A virus
HAVAb	hepatitis A antibody
Hb	hemoglobin
HBcAb/HBcAg	hepatitis B core antibody/antigen
HBeAb/HBeAg	hepatitis B early antibody/antigen
HBsAb/HBsAg	hepatitis B surface antibody/antigen
HbCO <sub>2</sub>	carbaminohemoglobin
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
hCG	human chorionic gonadotropin
HCO <sub>3</sub> <sup>-</sup>	bicarbonate
Hct	hematocrit
HCTZ	hydrochlorothiazide
HCV	hepatitis C virus
HDL	high-density lipoprotein
HDN	hemolytic disease of the newborn
HDV	hepatitis D virus
H&E	hematoxylin and eosin
HEV	hepatitis E virus
HF	heart failure
Hfr	high-frequency recombination [cell]
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
HPGRT	hypoxanthine-guanine phosphoribosyltransferase
HHb	deoxygenated hemoglobin
HHS	hyperosmolar hyperglycemic state
HHV	human herpesvirus
5-HIAA	5-hydroxyindoleacetic acid
HIT	heparin-induced thrombocytopenia
HIV	human immunodeficiency virus
HL	hepatic lipase
HLA	human leukocyte antigen
HMG-CoA	hydroxymethylglutaryl-coenzyme A
HMP	hexose monophosphate
HMWK	high-molecular-weight kininogen
HNPCC	hereditary nonpolyposis colorectal cancer
hnRNA	heterogeneous nuclear ribonucleic acid
H <sub>2</sub> O <sub>2</sub>	hydrogen peroxide
HOCM	hypertrophic obstructive cardiomyopathy
HPA	hypothalamic-pituitary-adrenal [axis]

ABBREVIATION	MEANING
HPO	hypothalamic-pituitary-ovarian [axis]
HPV	human papillomavirus
HR	heart rate
HSP	Henoch-Schönlein purpura
HSV	herpes simplex virus
5-HT	5-hydroxytryptamine (serotonin)
HTLV	human T-cell leukemia virus
HTN	hypertension
HUS	hemolytic-uremic syndrome
HVA	homovanillic acid
IBD	inflammatory bowel disease
IBS	irritable bowel syndrome
IC	inspiratory capacity, immune complex
I <sub>Ca</sub>	calcium current [heart]
I <sub>f</sub>	funny current [heart]
ICA	internal carotid artery
ICAM	intercellular adhesion molecule
ICD	implantable cardioverter defibrillator
ICE	Integrated Clinical Encounter
ICF	intracellular fluid
ICP	intracranial pressure
ID	identification
ID <sub>50</sub>	median infective dose
IDL	intermediate-density lipoprotein
IF	immunofluorescence, initiation factor
IFN	interferon
Ig	immunoglobulin
IGF	insulin-like growth factor
I <sub>K</sub>	potassium current [heart]
IL	interleukin
IM	intramuscular
IMA	inferior mesenteric artery
IMG	international medical graduate
IMP	inosine monophosphate
IMV	inferior mesenteric vein
I <sub>Na</sub>	sodium current [heart]
INH	isoniazid
INO	internuclear ophthalmoplegia
INR	International Normalized Ratio
IO	inferior oblique [muscle]
IOP	intraocular pressure
IP <sub>3</sub>	inositol triphosphate
IPV	inactivated polio vaccine
IR	current $\times$ 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]

\*Image abbreviation only

ABBREVIATION	MEANING	ABBREVIATION	MEANING
JGA	juxtaglomerular apparatus	MC	midsystolic click, metacarpal
JVD	jugular venous distention	MCA	middle cerebral artery
JVP	jugular venous pulse	MCAT	Medical College Admissions Test
K <sup>+</sup>	potassium ion	MCHC	mean corpuscular hemoglobin concentration
KatG	catalase-peroxidase produced by <i>M tuberculosis</i>	MCL	medial collateral ligament
K <sub>e</sub>	elimination constant	MCP	metacarpophalangeal [joint]
K <sub>f</sub>	filtration constant	MCV	mean corpuscular volume
KG	ketoglutarate	MD	maintenance dose
Kid*	kidney	MDD	major depressive disorder
K <sub>m</sub>	Michaelis-Menten constant	Med cond*	medial condyle
KOH	potassium hydroxide	MELAS syndrome	mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes
L	left, lentiform, liver	MEN	multiple endocrine neoplasia
LA	left atrial, left atrium	MERS	Middle East respiratory syndrome
LAD	left anterior descending coronary artery	Mg <sup>2+</sup>	magnesium ion
LAP	leukocyte alkaline phosphatase	MgSO <sub>4</sub>	magnesium sulfate
Lat cond*	lateral condyle	MHC	major histocompatibility complex
Lb*	lamellar body	MI	myocardial infarction
LCA	left coronary artery	MIF	müllerian inhibiting factor
LCAT	lecithin-cholesterol acyltransferase	MIRL	membrane inhibitor of reactive lysis
LCC*	left common carotid artery	MLCK	myosin light-chain kinase
LCFA	long-chain fatty acid	MLF	medial longitudinal fasciculus
LCL	lateral collateral ligament	MMC	migrating motor complex
LCME	Liaison Committee on Medical Education	MMR	measles, mumps, rubella [vaccine]
LCMV	lymphocytic choriomeningitis virus	MODY	maturity onset diabetes of the young
LCX	left circumflex coronary artery	6-MP	6-mercaptopurine
LD	loading dose	MPGN	membranoproliferative glomerulonephritis
LD <sub>50</sub>	median lethal dose	MPO	myeloperoxidase
LDH	lactate dehydrogenase	MPO-ANCA/p-ANCA	myeloperoxidase/perinuclear antineutrophil cytoplasmic antibody
LDL	low-density lipoprotein	MR	medial rectus [muscle], mitral regurgitation
LES	lower esophageal sphincter	MRI	magnetic resonance imaging
LFA	leukocyte function-associated antigen	miRNA	micrornucleic acid
LFT	liver function test	mRNA	messenger ribonucleic acid
LH	luteinizing hormone	MRSA	methicillin-resistant <i>S aureus</i>
Liv*	liver	MS	mitral stenosis, multiple sclerosis
LLL*	left lower lobe (of lung)	MSH	melanocyte-stimulating hormone
LLQ	left lower quadrant	mtDNA	mitochondrial DNA
LM	lateral meniscus, left main coronary artery, light microscopy	mTOR	mammalian target of rapamycin
LMN	lower motor neuron	MTP	metatarsophalangeal [joint]
LOS	lipooligosaccharide	MTX	methotrexate
LPA*	left pulmonary artery	MVO <sub>2</sub>	myocardial oxygen consumption
LPL	lipoprotein lipase	MVP	mitral valve prolapse
LPS	lipopolysaccharide	N <sup>*</sup>	nucleus
LR	lateral rectus [muscle]	Na <sup>+</sup>	sodium ion
LT	labile toxin, leukotriene	NAT	nucleic acid testing
LUL*	left upper lobe (of lung)	NAD	nicotinamide adenine dinucleotide
LV	left ventricle, left ventricular	NAD <sup>+</sup>	oxidized nicotinamide adenine dinucleotide
M <sub>1</sub> -M <sub>5</sub>	muscarinic (parasympathetic) ACh receptors	NADH	reduced nicotinamide adenine dinucleotide
MAC	membrane attack complex, minimum alveolar concentration	NADP <sup>+</sup>	oxidized nicotinamide adenine dinucleotide phosphate
MALT	mucosa-associated lymphoid tissue	NADPH	reduced nicotinamide adenine dinucleotide phosphate
MAO	monoamine oxidase	NBME	National Board of Medical Examiners
MAOI	monoamine oxidase inhibitor	NBOME	National Board of Osteopathic Medical Examiners
MAP	mean arterial pressure, mitogen-activated protein	NBPME	National Board of Podiatric Medical Examiners
Max*	maxillary sinus		

\*Image abbreviation only

ABBREVIATION	MEANING
NE	norepinephrine
NF	neurofibromatosis
NFAT	nuclear factor of activated T-cell
NH <sub>3</sub>	ammonia
NH <sub>4</sub> <sup>+</sup>	ammonium
NK	natural killer [cells]
N <sub>M</sub>	muscarinic ACh receptor in neuromuscular junction
NMDA	N-methyl-d-aspartate
NMJ	neuromuscular junction
NMS	neuroleptic malignant syndrome
N <sub>N</sub>	nicotinic ACh receptor in autonomic ganglia
NRMP	National Residency Matching Program
NNRTI	non-nucleoside reverse transcriptase inhibitor
NO	nitric oxide
N <sub>2</sub> O	nitrous oxide
NPH	neutral protamine Hagedorn, normal pressure hydrocephalus
NPV	negative predictive value
NRTI	nucleoside reverse transcriptase inhibitor
NSAID	nonsteroidal anti-inflammatory drug
NSE	neuron-specific enolase
NSTEMI	non-ST-segment elevation myocardial infarction
Nu*	nucleolus
OAA	oxaloacetic acid
OCD	obsessive-compulsive disorder
OCP	oral contraceptive pill
ODC	oxygen-hemoglobin dissociation curve
OH	hydroxy
1,25-OH D <sub>3</sub>	calcitriol (active form of vitamin D)
25-OH D <sub>3</sub>	storage form of vitamin D
OPV	oral polio vaccine
OR	odds ratio
OS	opening snap
OSA	obstructive sleep apnea
OVLT	organum vasculosum of the lamina terminalis
P-body	processing body (cytoplasmic)
P-450	cytochrome P-450 family of enzymes
PA	posteroanterior, pulmonary artery
PABA	<i>para</i> -aminobenzoic acid
Paco <sub>2</sub>	arterial PCO <sub>2</sub>
PaCO <sub>2</sub>	alveolar PCO <sub>2</sub>
PAH	<i>para</i> -aminohippuric acid
PAN	polyarteritis nodosa
Pao <sub>2</sub>	partial pressure of oxygen in arterial blood
PAO <sub>2</sub>	partial pressure of oxygen in alveolar blood
PAP	Papanicolaou [smear], prostatic acid phosphatase, posteromedial papillary muscle
PAPPA	pregnancy-associated plasma protein A
PAS	periodic acid-Schiff
Pat*	patella
PBP	penicillin-binding protein
PC	platelet count, pyruvate carboxylase
PCA	posterior cerebral artery
PCC	prothrombin complex concentrate

ABBREVIATION	MEANING
PCL	posterior cruciate ligament
PCO <sub>2</sub>	partial pressure of carbon dioxide
PCom	posterior communicating [artery]
PCOS	polycystic ovarian syndrome
PCP	phenacylidine hydrochloride, <i>Pneumocystis jirovecii</i> pneumonia
PCR	polymerase chain reaction
PCT	proximal convoluted tubule
PCV13	pneumococcal conjugate vaccine
PCWP	pulmonary capillary wedge pressure
PDA	patent ductus arteriosus, posterior descending artery
PDE	phosphodiesterase
PDGF	platelet-derived growth factor
PDH	pyruvate dehydrogenase
PE	pulmonary embolism
PECAM	platelet-endothelial cell adhesion molecule
PECO <sub>2</sub>	expired air PCO <sub>2</sub>
PEP	phosphoenolpyruvate
PF	platelet factor
PK	phosphofructokinase
PK-2	phosphofructokinase-2
PFT	pulmonary function test
PG	phosphoglycerate
P <sub>i</sub>	plasma interstitial osmotic pressure, inorganic phosphate
PICA	posterior inferior cerebellar artery
PID	pelvic inflammatory disease
PiO <sub>2</sub>	Po <sub>2</sub> in inspired air
PIP	proximal interphalangeal [joint]
PIP <sub>2</sub>	phosphatidylinositol 4,5-bisphosphate
PIP <sub>3</sub>	phosphatidylinositol 3,4,5-bisphosphate
PKD	polycystic kidney disease
PKR	interferon- $\alpha$ -induced protein kinase
PKU	phenylketonuria
PLP	pyridoxal phosphate
PML	progressive multifocal leukoencephalopathy
PMN	polymorphonuclear [leukocyte]
P <sub>net</sub>	net filtration pressure
PNET	primitive neuroectodermal tumor
PNS	peripheral nervous system
Po <sub>2</sub>	partial pressure of oxygen
PO <sub>4</sub> <sup>3-</sup>	phosphate
Pop*	popliteal artery
Pop a*	popliteal artery
Post*	posterior
PPAR	peroxisome proliferator-activated receptor
PPD	purified protein derivative
PPI	proton pump inhibitor
PPM	parts per million
PPSV23	pneumococcal polysaccharide vaccine
PPV	positive predictive value
PR3-ANCA/c-ANCA	cytoplasmic antineutrophil cytoplasmic antibody
PrP	prion protein
PRPP	phosphoribosylpyrophosphate

\*Image abbreviation only

ABBREVIATION	MEANING
PSA	prostate-specific antigen
PSS	progressive systemic sclerosis
PT	prothrombin time
PTEN	phosphatase and tensin homolog
PTH	parathyroid hormone
PTHrP	parathyroid hormone-related protein
PTSD	post-traumatic stress disorder
PTT	partial thromboplastin time
PV	plasma volume, venous pressure, portal vein
Pv*	pulmonary vein
PVC	polyvinyl chloride
PVR	pulmonary vascular resistance
R	correlation coefficient, right, R variable [group]
R <sub>3</sub>	Registration, Ranking, & Results [system]
RA	right atrium
RAAS	renin-angiotensin-aldosterone system
RANK-L	receptor activator of nuclear factor- $\kappa$ B ligand
RAS	reticular activating system
RBF	renal blood flow
RCA	right coronary artery
REM	rapid eye movement
RER	rough endoplasmic reticulum
Rh	<i>rhesus</i> antigen
RLL*	right lower lobe (of lungs)
RLQ	right lower quadrant
RML*	right middle lobe (of lung)
RNA	ribonucleic acid
RNP	ribonucleoprotein
ROS	reactive oxygen species
RPF	renal plasma flow
RPGN	rapidly progressive glomerulonephritis
RPR	rapid plasma reagin
RR	relative risk, respiratory rate
rRNA	ribosomal ribonucleic acid
RS	Reed-Sternberg [cells]
RSC*	right subclavian artery
RSV	respiratory syncytial virus
RTA	renal tubular acidosis
RUL*	right upper lobe (of lung)
RUQ	right upper quadrant
RV	residual volume, right ventricle, right ventricular
RVH	right ventricular hypertrophy
[S]	substrate concentration
SA	sinoatrial
SAA	serum amyloid-associated [protein]
SAM	S-adenosylmethionine
SARS	severe acute respiratory syndrome
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2 (virus)
SCC	squamous cell carcinoma
SCD	sudden cardiac death
SCID	severe combined immunodeficiency disease
SCJ	squamocolumnar junction
SCM	sternocleidomastoid muscle
SCN	suprachiasmatic nucleus

ABBREVIATION	MEANING
SD	standard deviation
SE	standard error [of the mean]
SEP	Spoken English Proficiency
SER	smooth endoplasmic reticulum
SERM	selective estrogen receptor modulator
SGLT	sodium-glucose transporter
SHBG	sex hormone-binding globulin
SIADH	syndrome of inappropriate [secretion of] antidiuretic hormone
SIDS	sudden infant death syndrome
SJS	Stevens-Johnson syndrome
SLE	systemic lupus erythematosus
SLL	small lymphocytic lymphoma
SLT	Shiga-like toxin
SMA	superior mesenteric artery
SMX	sulfamethoxazole
SNARE	soluble NSF attachment protein receptor
SNC	substantia nigra pars compacta
SNP	single nucleotide polymorphism
SNr	substantia nigra pars reticulata
SNRI	serotonin and norepinephrine receptor inhibitor
snRNA	small nuclear RNA
snRNP	small nuclear ribonucleoprotein
SO	superior oblique [muscle]
SOAP	Supplemental Offer and Acceptance Program
Sp*	spleen
spp	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
St*	stomach
ST	Shiga toxin
StAR	steroidogenic acute regulatory protein
STEMI	ST-segment elevation myocardial infarction
STI	sexually transmitted infection
STN	subthalamic nucleus
SV	splenic vein, stroke volume
SVC	superior vena cava
SVR	systemic vascular resistance
SVT	supraventricular tachycardia
T*	thalamus, trachea
t <sub>1/2</sub>	half-life
T <sub>3</sub>	triiodothyronine
T <sub>4</sub>	thyroxine
TAPVR	total anomalous pulmonary venous return
TB	tuberculosis
TBG	thyroxine-binding globulin
TBV	total blood volume
3TC	dideoxythiacytidine [lamivudine]
TCA	tricarboxylic acid [cycle], tricyclic antidepressant
Tc cell	cytotoxic T cell
TCR	T-cell receptor

\*Image abbreviation only

ABBREVIATION	MEANING
TDF	tenofovir disoproxil fumarate
TdT	terminal deoxynucleotidyl transferase
TE	tracheoesophageal
TFT	thyroid function test
TG	triglyceride
TGF	transforming growth factor
Th cell	helper T cell
THF	tetrahydrofolic acid
TI	therapeutic index
TIA	transient ischemic attack
Tib*	tibia
TIBC	total iron-binding capacity
TIPS	transjugular intrahepatic portosystemic shunt
TLC	total lung capacity
T <sub>m</sub>	maximum rate of transport
TMP	trimethoprim
TN	true negative
TNF	tumor necrosis factor
TNM	tumor, node, metastases [staging]
TOP	topoisomerase
ToRCHeS	<i>Toxoplasma gondii</i> , rubella, CMV, HIV, HSV-2, syphilis
TP	true positive
tPA	tissue plasminogen activator
TPO	thyroid peroxidase, thrombopoietin
TPP	thiamine pyrophosphate
TPPA	<i>Treponema pallidum</i> particle agglutination assay
TPR	total peripheral resistance
TR	tricuspid regurgitation
TRAP	tartrate-resistant acid phosphatase
TRECs	T-cell receptor excision circles
TRH	thyrotropin-releasing hormone
tRNA	transfer ribonucleic acid
TSH	thyroid-stimulating hormone
TSI	triple sugar iron
TSS	toxic shock syndrome
TSST	toxic shock syndrome toxin
TTP	thrombotic thrombocytopenic purpura
TTR	transthyretin
TV	tidal volume
TXA <sub>2</sub>	thromboxane A <sub>2</sub>
UDP	uridine diphosphate

\*Image abbreviation only

ABBREVIATION	MEANING
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 <sub>1</sub> , V <sub>2</sub>	vasopressin receptors
VC	vital capacity
V <sub>d</sub>	volume of distribution
VD	physiologic dead space
V(D)J	variable, (diversity), joining gene segments rearranged to form Ig genes
VDRL	Venereal Disease Research Laboratory
VEGF	vascular endothelial growth factor
V <sub>H</sub>	variable region, heavy chain [antibody]
VHL	von Hippel-Lindau [disease]
VIP	vasoactive intestinal peptide
VIPoma	vasoactive intestinal polypeptide-secreting tumor
VJ	light-chain hypervariable region [antibody]
V <sub>L</sub>	variable region, light chain [antibody]
VLCFA	very-long-chain fatty acids
VLDL	very low density lipoprotein
VMA	vanillylmandelic acid
VMAT	vesicular monoamine transporter
V <sub>max</sub>	maximum velocity
VPL	ventral posterior nucleus, lateral
VPM	ventral posterior nucleus, medial
VPN	vancomycin, polymyxin, nystatin [media]
̇/̇Q	ventilation/perfusion [ratio]
VRE	vancomycin-resistant enterococcus
VSD	ventricular septal defect
V <sub>T</sub>	tidal volume
VTE	venous thromboembolism
vWF	von Willebrand factor
VZV	varicella-zoster virus
VMAT	vesicular monoamine transporter
XR	X-linked recessive
XX/XY	normal complement of sex chromosomes for female/male
ZDV	zidovudine [formerly AZT]

## SECTION IV

# Image Acknowledgments

In this edition, in collaboration with MediQ Learning, LLC, and a variety of other partners, we are pleased to include the following clinical images and diagrams for the benefit of integrative student learning.

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### Biochemistry

- 34 Chromatin structure.** Electron micrograph showing heterochromatin, euchromatin, and nucleolus. This image is a derivative work, adapted from the following source, available under : Roller RA, Rickett JD, Stickle WB. The hypobranchial gland of the estuarine snail *Stramonita haemastoma canaliculata* (Gray) (Prosobranchia: Muricidae): a light and electron microscopical study. *Am Malac Bull*. 1995;11(2):177-190. Available at <https://archive.org/details/americann101119931994amer>.
- 49 Cilia structure: Image A.** Nine doublet + 2 singlet arrangement of microtubule.  Courtesy of Louisa Howard and Michael Binder. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MediQ Learning, LLC are reserved.
- 49 Cilia structure: Image B.** Cilia structure of basal body. This image is a derivative work, adapted from the following source, available under : Riparbelli MG, Cabrera OA, Callaini G, et al. Unique properties of *Drosophila* spermatocyte primary cilia. *Biol Open*. 2013 Nov 15; 2(11): 1137-1147. DOI: 10.1242/bio.20135355.
- 49 Cilia structure: Image C.** Dextrocardia. This image is a derivative work, adapted from the following source, available under : Oluwadare O, Ayoka AO, Akomolafe RO, et al. The role of electrocardiogram in the diagnosis of dextrocardia with mirror image atrial arrangement and ventricular position in a young adult Nigerian in Ile-Ife: a case report. *J Med Case Rep*. 2015;9:222. DOI: 10.1186/s13256-015-0695-4.
- 51 Osteogenesis imperfecta: Image A.** Skeletal deformities in upper extremity of child. This image is a derivative work, adapted from the following source, available under : Vanakker OM, Hemelsoet D, De Paepe. Hereditary connective tissue diseases in young adult stroke: a comprehensive synthesis. *Stroke Res Treat*. 2011;712903. DOI: 10.4061/2011/712903. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MediQ Learning, LLC are reserved.
- 51 Osteogenesis imperfecta: Image B.** Blue sclera. This image is a derivative work, adapted from the following source, available under : Wheatley K, Heng EL, Sheppard M, et al. A case of spontaneous intestinal perforation in osteogenesis imperfecta. *J Clin Med Res*. 2010;2(4):198-200. DOI: 10.4021/jocmr369w.
- 51 Ehlers-Danlos syndrome: Images A and B.** Hyperextensibility of skin (A) and DIP joint (B). These images are a derivative work, adapted from the following source, available under : Whitaker JK, Alexander P, Chau DYS, et al. Severe conjunctivochalasis in association with classic type Ehlers-Danlos syndrome. *BMC Ophthalmol*. 2012;2:47. DOI: 10.1186/1471-2415-12-47.
- 52 Elastin.** Pes escavatum. This image is a derivative work, adapted from the following source, available under : De Maio F, Fichera A, De Luna V, et al. Orthopaedic aspects of Marfan syndrome: the experience of a referral center for diagnosis of rare diseases. *Adv Orthop*. 2016; 2016: 8275391. DOI 10.1155/2016/8275391.
- 55 Karyotyping.** Paar C, Herber G, Voskova, et al. This image is a derivative work, adapted from the following source, available under : A case of acute myeloid leukemia (AML) with an unreported combination of chromosomal abnormalities: gain of isochromosome 5p, tetrasomy 8 and unbalanced translocation der(19)t(17;19)(q23;p13). *Mol Cytogenet*. 2013;6:40. DOI: 10.1186/1755-8166-6-40.
- 55 Fluorescence in situ hybridization.** This image is a derivative work, adapted from the following source, available under : Paar C, Herber G, Voskova, et al. A case of acute myeloid leukemia (AML) with an unreported combination of chromosomal abnormalities: gain of isochromosome 5p, tetrasomy 8 and unbalanced translocation der(19)t(17;19)(q23;p13). *Mol Cytogenet*. 2013;6:40. DOI: 10.1186/1755-8166-6-40.
- 57 Genetic terms.** Café-au-lait spots. This image is a derivative work, adapted from the following source, available under : Dumitrescu CE and Collins MT. *Orphanet J Rare Dis*. 2008;3:12. DOI: 10.1186/1750-1172-3-12.
- 61 Muscular dystrophies.** Fibrofatty replacement of muscle.  Courtesy of the Department of Health and Human Services and Dr. Edwin P. Ewing, Jr. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MediQ Learning, LLC are reserved.
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- 67 Vitamin B<sub>3</sub>.** 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 Web site. Dec 4, 2008. Available at: <http://cnx.org/contents/3d3db2e-8e98-496f-91c2-fe94e93428a1@3/3/>.
- 70 Vitamin D.** X-ray of lower extremity in child with rickets. This image is a derivative work, adapted from the following source, available

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- 84 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.
- 85 Cystinuria.** Hexagonal cystine stones in urine. This image is a derivative work, adapted from the following source, available under : Courtesy of Cayla Devine.
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- 88 Lysosomal storage diseases: Image B.** Angiokeratomas. This image is a derivative work, adapted from the following source, available under : Burlina AP, Sims KB, Politei JM, et al. Early diagnosis of peripheral nervous system involvement in Fabry disease and treatment of neuropathic pain: the report of an expert panel. *BMC Neurol.* 2011;11:61. DOI: 10.1186/1471-2377-11-61. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MediIQ Learning, LLC are reserved.
- 88 Lysosomal storage diseases: Image C.** Gaucher cells in Gaucher disease. This image is a derivative work, adapted from the following source, available under : Sokolowska B, Skomra D, Czartoryska B, et al. Gaucher disease diagnosed after bone marrow trephine biopsy—a report of two cases. *Folia Histochem Cytopiol.* 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 MediIQ Learning, LLC are reserved.
- 88 Lysosomal storage diseases: Image D.** Foam cells in Niemann-Pick disease. This image is a derivative work, adapted from the following source, available under : Prieto-Potin I, Roman-Blas JA, Martinez-Calatrava MJ, et al. Hypercholesterolemia boosts joint destruction in chronic arthritis. An experimental model aggravated by foam macrophage infiltration. *Arthritis Res Ther.* 2013;15:R81. DOI: 10.1186/ar4261.
- 94 Abetalipoproteinemia.** Small bowel mucosa shows clear enterocytes. Courtesy of Dr. Michael Bonert.
- ### Immunology
- 96 Lymph node: Images A and B.** Lymph node histology. These images are a derivative work, adapted from the following source, available under : Navid Golpur.
- 98 Thymus.** “Sail sign” on x-ray of normal thymus in neonate. This image is a derivative work, adapted from the following source, available under : Di Serafino M, Esposito F, Severino R, et al. Think thymus, think well: the chest x-ray thymic signs. *J Pediatr Radiol Care.* 2016;1(2):108-109. DOI: 10.19104/jpmc.2016.108.
- 107 Complement disorders.** Urine discoloration in paroxysmal nocturnal hemoglobinuria. This image is a derivative work, adapted from the following source, available under : Nakamura N, Sugawara T, Shirato K, et al. *J Med Case Reports.* 2011;5:550. doi: 10.1186/1752-1947-5-550
- 117 Immunodeficiencies: Image A.** Spider angioma (telangiectasia). This image is a derivative work, adapted from the following source, available under : Liapakis IE, Englander M, Sinani R, et al. Management of facial telangiectasias with hand cautery. *World J Plast Surg.* 2015 Jul;4(2):127-133.
- 117 Immunodeficiencies: Image B.** Giant granules in granulocytes in Chédiak-Higashi syndrome. This image is a derivative work, adapted from the following source, available under : Bharti S, Bhatia P, Bansal D, et al. The accelerated phase of Chédiak-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 MediIQ Learning, LLC are reserved.
- ### Microbiology
- 125 Stains: Image A.** *Trypanosoma lewisi* on Giemsa stain. Courtesy of the Department of Health and Human Services and Dr. Mae Melvin.
- 125 Stains: Image B.** Periodic acid-Schiff stain reveals *Tropheryma whipplei* infection. This image is a derivative work, adapted from the following source, available under : Courtesy of Dr. Ed Uthman.
- 125 Stains: Image C.** *Mycobacterium tuberculosis* on Ziehl-Neelsen stain. Courtesy of the Department of Health and Human Services and Dr. George P. Kubica.
- 125 Stains: Image D.** *Cryptococcus neoformans* on India ink stain. Courtesy of the Department of Health and Human Services.
- 125 Stains: Image E.** *Coccidioides immitis* on silver stain. Courtesy of the Department of Health and Human Services and Dr. Edwin P. Ewing, Jr.
- 127 Encapsulated bacteria.** Capsular swelling of *Streptococcus pneumoniae* using the Neufeld-Quellung test. Courtesy of the Department of Health and Human Services.
- 128 Catalase-positive organisms.** Oxygen bubbles released during catalase reaction. This image is a derivative work, adapted from the following source, available under : Stefano Nase. The image may have been modified by cropping, labeling, and/or captions. MediIQ Learning, LLC makes this available under .
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- 135 α-hemolytic bacteria.** α-hemolysis. This image is a derivative work, adapted from the following source, available under : Y. Tambe. The image may have been modified by cropping, labeling, and/or captions. MediIQ Learning, LLC makes this available under .
- 135 β-hemolytic bacteria.** β-hemolysis. This image is a derivative work, adapted from the following source, available under : Wikimedia Commons.
- 135 *Staphylococcus aureus*.** Courtesy of the Department of Health and Human Services and Dr. Richard Facklam.
- 136 *Streptococcus pneumoniae*.** Courtesy of the Department of Health and Human Services and Dr. Mike Miller.
- 136 *Streptococcus pyogenes*: (group A streptococci).** This image is a derivative work, adapted from the following source, available under : Y. Tambe. The image may have been modified by cropping, labeling, and/or captions. MediIQ Learning, LLC makes this available under .
- 137 *Bacillus anthracis*.** Ulcer with black eschar. Courtesy of the Department of Health and Human Services and James H. Steele.
- 138 Clostridia: Image A.** Gas gangrene due to *Clostridium perfringens*. This image is a derivative work, adapted from the following source, available under : Schröpfer E, Rauthe S, Meyer T. Diagnosis and misdiagnosis of necrotizing soft tissue infections: three case reports. *Cases J.* 2008;1:252. DOI: 10.1186/1757-1626-1-252.

- 138 Clostridia: Image B.** Pseudomembranous enterocolitis on colonoscopy. This image is a derivative work, adapted from the following source, available under : 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 available under .
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- 139 Nocardia vs Actinomyces: Image A.** *Nocardia* on acid-fast stain. This image is a derivative work, adapted from the following source, available under : Venkataramana K. Human *Nocardia* infections: a review of pulmonary nocardiosis. *Cereus*. 2015;7(8):e304. DOI: 10.7759/cereus.304.
- 139 Nocardia vs Actinomyces: Image B.** *Actinomyces israelii* on Gram stain. Courtesy of the Department of Health and Human Services.
- 140 Mycobacteria.** Acid-fast stain. Courtesy of the Department of Health and Human Services and Dr. George P. Kubica
- 140 Tuberculosis.** Langhans giant cell in caseating granuloma. Courtesy of J. Hayman.
- 141 Leprosy: Image A.** “Glove and stocking” distribution. This image is a derivative work, adapted from the following source, available under : Courtesy of Bruno Jehel.
- 142 Neisseria: Image A.** Intracellular *N gonorrhoeae*. Courtesy of the Department of Health and Human Services and Bill Schwartz.
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- 143 Pseudomonas aeruginosa: Image A.** Blue-green pigment on centrimide agar. This image is a derivative work, adapted from the following source, available under : Hansen. The image may have been modified by cropping, labeling, and/or captions. MediQ Learning, LLC makes this available under .
- 143 Pseudomonas aeruginosa: Image B.** Ecthyma gangrenosum. This image is a derivative work, adapted from the following source, available under : Uludokumaci S, Balkan II, Mete B, et al. Ecthyma gangrenosum-like lesions in a febrile neutropenic patient with simultaneous *Pseudomonas* sepsis and disseminated fusariosis. *Turk J Haematol*. 2013 Sep;30(3):321-4. DOI: 10.4274/tjh.2012.0030.
- 145 Klebsiella.** Courtesy of the Department of Health and Human Services.
- 145 Campylobacter jejuni.** Courtesy of the Department of Health and Human Services.
- 146 Vibrio cholerae.** This image is a derivative work, adapted from the following source, available under : Phetsouvanh R, Nakatsu M, Arakawa E, et al. Fatal bacteraemia 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.
- 146 Helicobacter pylori.** Courtesy of the Department of Health and Human Services, Dr. Patricia Fields, and Dr. Collette Fitzgerald.
- 146 Spirochetes.** Appearance on darkfield microscopy. Courtesy of the Department of Health and Human Services.
- 146 Lyme disease: Image A.** *Ixodes* tick. Courtesy of the Department of Health and Human Services and Dr. Michael L. Levin.
- 146 Lyme disease: Image B.** Erythema migrans. Courtesy of the Department of Health and Human Services and James Gathany.
- 147 Syphilis: Image A.** Painless chancre in primary syphilis. Courtesy of the Department of Health and Human Services and M. Rein.
- 147 Syphilis: Image B.** Treponeme on darkfield microscopy. Courtesy of the Department of Health and Human Services and Renelle Woodall.
- 147 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.
- 147 Syphilis: Image E.** Condyloma lata. Courtesy of the Department of Health and Human Services and Susan Lindsley.
- 147 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.
- 147 Syphilis: Image G.** Congenital syphilis. Courtesy of the Department of Health and Human Services and Dr. Norman Cole.
- 147 Syphilis: Image H.** Hutchinson teeth. Courtesy of the Department of Health and Human Services and Susan Lindsley.
- 148 Gardnerella vaginalis.** Courtesy of the Department of Health and Human Services and M. Rein.
- 150 Rickettsial diseases and vector-borne illnesses: Image A.** Rash of Rocky Mountain spotted fever. Courtesy of the Department of Health and Human Services.
- 150 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.
- 150 Rickettsial diseases and vector-borne illnesses: Image C.** *Anaplasma phagocytophili* in neutrophil. Courtesy of the Department of Health and Human Services and Dumler JS, Choi K, Garcia-Garcia JC, et al. Human granulocytic anaplasmosis. *Emerg Infect Dis*. 2005. DOI 10.3201/eid1112.050898.
- 150 Mycoplasma pneumoniae.** This image is a derivative work, adapted from the following source, available under : Rottem S, Kosower ND, Kornspan JD. Contamination of tissue cultures by *Mycoplasma*. In: Ceccherini-Nelli L, ed. *Biomedical tissue culture*. 2016. DOI: 10.5772/51518.
- 151 Systemic mycoses: Image A.** *Histoplasma*. Courtesy of the Department of Health and Human Services and Dr. D.T. McClenan.
- 151 Systemic mycoses: Image B.** *Blastomyces dermatitidis* undergoing broad-base budding. Courtesy of the Department of Health and Human Services and Dr. Libero Ajello.

- 151 Systemic mycoses: Image C.** Coccidiomycosis with endospheres.  Courtesy of the Department of Health and Human Services.
- 151 Systemic mycoses: Image D.** "Captain's wheel" shape of *Paracoccidioides*.  Courtesy of the Department of Health and Human Services and Dr. Lucille K. Georg.
- 152 Cutaneous mycoses: Image G.** Tinea versicolor. This image is a derivative work, adapted from the following source, available under : Sarah (Rosenau) Korf. The image may have been modified by cropping, labeling, and/or captions. MediQ Learning, LLC makes this available under .
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- 153 Opportunistic fungal infections: Image B.** Germ tubes of *Candida albicans*. This image is a derivative work, adapted from the following source, available under : Y. Tambe. The image may have been modified by cropping, labeling, and/or captions. MediQ Learning, LLC makes this available under .
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- 153 Opportunistic fungal infections: Image E.** Conidiophores of *Aspergillus fumigatus*.  Courtesy of the Department of Health and Human Services.
- 153 Opportunistic fungal infections: Image F.** Aspergilloma in left lung. This image is a derivative work, adapted from the following source, available under : Souilamas R, Souilamas JI, Alkhamees K, et al. Extra corporeal membrane oxygenation in general thoracic surgery: a new single veno-venous cannulation. *J Cardiothorac Surg*. 2011;6:52. DOI: 10.1186/1749-8090-6-52.
- 153 Opportunistic fungal infections: Image G.** *Cryptococcus neoformans*.  Courtesy of the Department of Health and Human Services and Dr. Leanor Haley.
- 153 Opportunistic fungal infections: Image H.** *Cryptococcus neoformans* on mucicarmine stain.  Courtesy of the Department of Health and Human Services and Dr. Leanor Haley.
- 153 Opportunistic fungal infections: Image I.** Mucor.  Courtesy of the Department of Health and Human Services and Dr. Lucille K. Georg.
- 153 Opportunistic fungal infections: Image J.** Mucormycosis. This image is a derivative work, adapted from the following source, available under : Jiang N, Zhao G, Yang S, et al. A retrospective analysis of eleven cases of invasive rhino-orbito-cerebral mucormycosis presented with orbital apex syndrome initially. *BMC Ophthalmol*. 2016; 16: 10. DOI: 10.1186/s12886-016-0189-1.
- 154 *Pneumocystis jirovecii*: Image A.** Interstitial opacities in lung. This image is a derivative work, adapted from the following source, available under : Chuang C, Zhanhong X, Yinyin G, et al. Unsuspected *Pneumocystis* pneumonia in an HIV-seronegative patient with untreated lung cancer: circa case report. *J Med Case Rep*. 2007;1:15. DOI: 10.1186/1752-1947-1-115.
- 154 *Pneumocystis jirovecii*: Image B.** CT of lung. This image is a derivative work, adapted from the following source, available under : Allen CM, Al-Jahdali HH, Irion KL, et al. Imaging lung manifestations of HIV/AIDS. *Ann Thorac Med*. 2010 Oct-Dec; 5(4): 201-216. DOI: 10.4103/1817-1737.69106.
- 154 *Pneumocystis jirovecii*: Image C.** Disc-shaped yeast. This image is a derivative work, adapted from the following source, available under : Kirby S, Satoskar A, Brodsky S, et al. Histological spectrum of pulmonary manifestations in kidney transplant recipients on sirolimus inclusive immunosuppressive regimens. *Diagn Pathol*. 2012;7:25. DOI: 10.1186/1746-1596-7-25.
- 154 *Sporothrix schenckii*.** Subcutaneous mycosis. This image is a derivative work, adapted from the following source, available under : Govender NP, Maphanga TG, Zulu TG, et al. An outbreak of lymphocutaneous sporotrichosis among mine-workers in South Africa. *PLoS Negl Trop Dis*. 2015 Sep; 9(9): e0004096. DOI: 10.1371/journal.pntd.0004096.
- 155 Protozoa—gastrointestinal infections: Image A.** *Giardia lamblia* trophozoite. This image is a derivative work, adapted from the following source, available under : Lipoldová M. Giardia and Vilém Dušan Lambl. *PLoS Negl Trop Dis*. 2014;8:e2686. DOI: 10.1371/journal.pntd.0002686.
- 155 Protozoa—gastrointestinal infections: Image B.** *Giardia lamblia* cyst.  Courtesy of the Department of Health and Human Services.
- 155 Protozoa—gastrointestinal infections: Image C.** *Entamoeba histolytica* trophozoites.  Courtesy of the Department of Health and Human Services.
- 155 Protozoa—gastrointestinal infections: Image D.** *Entamoeba histolytica* cyst.  Courtesy of the Department of Health and Human Services.
- 155 Protozoa—gastrointestinal infections: Image E.** *Cryptosporidium* oocysts.  Courtesy of the Department of Health and Human Services.
- 156 Protozoa—CNS infections: Image A.** Ring-enhancing lesions in brain due to *Toxoplasma gondii*. This image is a derivative work, adapted from the following source, available under : Agrawal A, Bhake A, Sangole VM, et al. Multiple-ring enhancing lesions in an immunocompetent adult. *J Glob Infect Dis*. 2010 Sep-Dec;2(3):313-4. DOI: 10.4103/0974-777X.68545.
- 156 Protozoa—CNS infections: Image B.** *Toxoplasma gondii* tachyzoite.  Courtesy of the Department of Health and Human Services and Dr. L.L. Moore, Jr.
- 156 Protozoa—CNS infections: Image C.** *Naegleria fowleri* amoebas.  Courtesy of the Department of Health and Human Services.
- 156 Protozoa—CNS infections: Image D.** *Trypanosoma brucei gambiense*.  Courtesy of the Department of Health and Human Services and Dr. Mae Melvin.
- 157 Protozoa—hematologic infections: Image A.** *Plasmodium* trophozoite ring form.  Courtesy of the Department of Health and Human Services.
- 157 Protozoa—hematologic infections: Image B.** *Plasmodium* schizont containing merozoites.  Courtesy of the Department of Health and Human Services and Steven Glenn.
- 157 Protozoa—hematologic infections: Image C.** *Babesia* with ring form and with "Maltese cross" form.  Courtesy of the Department of Health and Human Services.
- 158 Protozoa—others: Image A.** *Trypanosoma cruzi*.  Courtesy of the Department of Health and Human Services and Dr. Mae Melvin.
- 158 Protozoa—others: Image B.** Cutaneous leishmaniasis. This image is a derivative work, adapted from the following source, available under : Sharara SL, Kanj SS. War and infectious diseases: challenges of the Syrian civil war. *PLoS Pathog*. 2014 Nov;10(11):e1004438. DOI: 10.1371/journal.ppat.1004438.
- 158 Protozoa—others: Image C.** *Leishmania* spp.  Courtesy of the Department of Health and Human Services and Dr. Francis W. Chandler. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MediQ Learning, LLC are reserved.
- 158 Protozoa—others: Image D.** *Trichomonas vaginalis*.  Courtesy of the Department of Health and Human Services.
- 159 Nematodes (roundworms): Image A.** *Enterobius vermicularis* eggs.  Courtesy of the Department of Health and Human Services, BG Partin, and Dr. Moore.

- 159 Nematodes (roundworms): Image B.** *Ascaris lumbricoides* egg. Courtesy of the Department of Health and Human Services.
- 159 Nematodes (roundworms): Image C.** *Ancylostoma* spp rash. This image is a derivative work, adapted from the following source, available under : Archer M. Late presentation of cutaneous larva migrans: a case report. *Cases J.* 2009; 2: 7553. doi:10.4076/1757-1626-2-7553.
- 159 Nematodes (roundworms): Image D.** *Trichinella spiralis* cysts in muscle. This image is a derivative work, adapted from the following source, available under : Franssen FFJ, Fonville M, Takumi K, et al. *Vet Res.* 2011; 42(1): 113. DOI: 10.1186/1297-9716-42-113.
- 159 Nematodes (roundworms): Image E.** Elephantiasis. Courtesy of the Department of Health and Human Services.
- 160 Cestodes (tapeworms): Image A.** *Taenia solium*. Courtesy of the Department of Health and Human Services Robert J. Galindo. The image may have been modified by cropping, labeling, and/or captions. MediQ Learning, LLC makes this available under .
- 160 Cestodes (tapeworms): Image B.** Neurocysticercosis. This image is a derivative work, adapted from the following source, available under : Coyle CM, Tanowitz HB. Diagnosis and treatment of neurocysticercosis. *Interdiscip Perspect Infect Dis.* 2009;2009:180742. DOI: 10.1155/2009/180742. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MediQ Learning, LLC are reserved.
- 160 Cestodes (tapeworms): Image C.** *Echinococcus granulosus*. Courtesy of the Department of Health and Human Services.
- 160 Cestodes (tapeworms): Image D.** Hydatid cyst of *Echinococcus granulosus*. Courtesy of the Department of Health and Human Services and Dr. I. Kagan.
- 160 Cestodes (tapeworms): Image E.** *Echinococcus granulosus* cyst in liver. This image is a derivative work, adapted from the following source, available under : Ma Z, Yang W, Yao Y, et al. The adventitia resection in treatment of liver hydatid cyst: a case report of a 15-year-old boy. *Case Rep Surg.* 2014;2014:123149. DOI: 10.1155/2014/123149.
- 160 Trematodes (flukes): Image A.** *Schistosoma mansoni* egg with lateral spine. Courtesy of the Department of Health and Human Services.
- 160 Trematodes (flukes): Image B.** *Schistosoma haematobium* egg with terminal spine. Courtesy of the Department of Health and Human Services.
- 161 Ectoparasites: Image A.** Seabies. This image is a derivative work, adapted from the following source, available under : Siegfried EC, Hebert AA. Diagnosis of atopic dermatitis: mimics, overlaps, and complications. *Clin Med.* 2015 May; 4(5): 884–917. DOI: 10.3390/jcm4050884.
- 161 Ectoparasites: Image B.** Nit of a louse. Courtesy of the Department of Health and Human Services and Joe Miller.
- 164 DNA viruses.** Febrile pharyngitis. This image is a derivative work, adapted from the following source, available under : Balfour HH Jr, Dunmire SK, Hogquist KA. *Clin Transl Immunology.* 2015 Feb 27. DOI: 10.1038/cti.2015.1.
- 165 Herpesviruses: Image A.** Keratoconjunctivitis in HSV-1 infection. This image is a derivative work, adapted from the following source, available under : 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.
- 165 Herpesviruses: Image B.** Herpes labialis. Courtesy of the Department of Health and Human Services and Dr. Herrmann.
- 165 Herpesviruses: Image E.** Shingles (varicella-zoster virus infection). This image is a derivative work, adapted from the following source,
- available under : Fisle. The image may have been modified by cropping, labeling, and/or captions. MediQ Learning, LLC makes this available under .
- 165 Herpesviruses: Image F.** Hepatosplenomegaly due to EBV infection. This image is a derivative work, adapted from the following source, available under : Gow NJ, Davidson RN, Ticehurst R, et al. Case report: no response to liposomal daunorubicin in a patient with drug-resistant HIV-associated visceral leishmaniasis. *PLoS Negl Trop Dis.* 2015 Aug; 9(8):e0003983. DOI: 10.1371/journal.pntd.0003983.
- 165 Herpesviruses: Image G.** Atypical lymphocytes in Epstein-Barr virus infection. This image is a derivative work, adapted from the following source, available under : Courtesy of Dr. Ed Uthman. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MediQ Learning, LLC are reserved.
- 165 Herpesviruses: Image I.** Roseola. Courtesy of Emiliano Burzagli.
- 165 Herpesviruses: Image J.** Kaposi sarcoma. Courtesy of the Department of Health and Human Services.
- 166 HSV identification.** Positive Tzanck smear in HSV-2 infection. This image is a derivative work, adapted from the following source, available under : Dr. Yale Rosen. The image may have been modified by cropping, labeling, and/or captions. MediQ Learning, LLC makes this available under .
- 168 Rotavirus.** Courtesy of the Department of Health and Human Services and Erskine Palmer.
- 169 Rubella virus.** Rubella rash. Courtesy of the Department of Health and Human Services.
- 170 Acute laryngotracheobronchitis.** Steele sign. Reproduced, with permission, from Dr. Frank Gaillard and www.radiopaedia.org.
- 170 Measles (rubeola) virus: Image A.** Koplik spots. Courtesy of the Department of Health and Human Services. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MediQ Learning, LLC are reserved.
- 170 Measles (rubeola) virus: Image B.** Rash of measles. Courtesy of the Department of Health and Human Services.
- 170 Mumps virus.** Swollen neck and parotid glands. Courtesy of the Department of Health and Human Services.
- 171 Rabies virus: Image A.** Transmission electron micrograph. Courtesy of the Department of Health and Human Services Dr. Fred Murphy, and Sylvia Whitfield.
- 171 Rabies virus: Image B.** Negri bodies. Courtesy of the Department of Health and Human Services and Dr. Daniel P. Perl.
- 171 Ebola virus.** Courtesy of the Department of Health and Human Services and Cynthia Goldsmith.
- 172 Zika virus.** This image is a derivative work, adapted from the following source, available under : Rocha YRR, Costa JRC, Costa PA, et al. Radiological characterization of cerebral phenotype in newborn microcephaly cases from 2015 outbreak in Brazil. *PLoS Currents* 2016 Jun 8;8. DOI: 10.1371/currents.outbreaks.e854dbf51b8075431a05b39042c00244.
- 180 Osteomyelitis.** X-ray (left) and MRI (right) views. This image is a derivative work, adapted from the following source, available under : Huang P-Y, Wu P-K, Chen C-F, et al. Osteomyelitis of the femur mimicking bone tumors: a review of 10 cases. *World J Surg Oncol.* 2013;11:283. DOI: 10.1186/1477-7819-11-283.
- 181 Common vaginal infections: Image B.** Motile trichomonads. Courtesy of Joe Miller.
- 181 Common vaginal infections: Image C.** *Candida* vulvovaginitis. Courtesy of Mikael Häggström.
- 182 TORCH infections: Image A.** “Blueberry muffin” rash. This image is a derivative work, adapted from the following source, available under

- 181** **Benmiloud S, Elhaddou G, Belghiti ZA, et al.** Blueberry muffin syndrome. *Pan Afr Med J.* 2012;13:23.
- 182** **TORCH infections: Image B.** Cataract in infant with congenital rubella.  Courtesy of the Department of Health and Human Services .
- 182** **TORCH infections: Image C.** Periventricular calcifications in congenital cytomegalovirus infection. This image is a derivative work, adapted from the following source, available under  Bonthius D, Perlman S. Congenital viral infections of the brain: lessons learned from lymphocytic choriomeningitis virus in the neonatal rat. *PLoS Pathog.* 2007;3:e149. DOI: 10.1371/journal.ppat.0030149. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MediQ Learning, LLC are reserved.
- 183** **Red rashes of childhood: Image C.** Child with scarlet fever. This image is a derivative work, adapted from the following source, available under  www.badbabodop.co.uk.
- 183** **Red rashes of childhood: Image D.** Chicken pox.  Courtesy of the Department of Health and Human Services and Dr. JD Millar.
- 184** **Sexually transmitted infections: Image A.** Chancroid.  Courtesy of the Department of Health and Human Services and Dr. Greg Hammond.
- 184** **Sexually transmitted infections: Image B.** Donovanosis.  Courtesy of the Department of Health and Human Services and Dr. Pinozzi.
- 185** **Pelvic inflammatory disease: Image A.** Purulent cervical discharge. This image is a derivative work, adapted from the following source, available under  SOS-AIDS Amsterdam The image may have been modified by cropping, labeling, and/or captions. MediQ Learning, LLC makes this available under .
- 185** **Pelvic inflammatory disease: Image B.** Adhesions in Fitz-Hugh–Curtis syndrome.  Courtesy of Hic et nunc.
- 190** **Vancomycin.** Red man syndrome. This image is a derivative work, adapted from the following source, available under  O'Meara P, Borici-Mazi R, Morton R, et al. DRESS with delayed onset acute interstitial nephritis and profound refractory eosinophilia secondary to vancomycin. *Allergy Asthma Clin Immunol.* 2011;7:16. DOI: 10.1186/1710-1492-7-16.
- Pathology**
- 209** **Necrosis: Image A.** Coagulative necrosis.  Courtesy of the Department of Health and Human Services and Dr. Steven Rosenberg.
- 209** **Necrosis: Image B.** Liquefactive necrosis.  Courtesy of Daftblogger.
- 209** **Necrosis: Image C.** Caseous necrosis. This image is a derivative work, adapted from the following source, available under  Dr. Yale Rosen. The image may have been modified by cropping, labeling, and/or captions. MediQ Learning, LLC makes this available under .
- 209** **Necrosis: Image D.** Fat necrosis. This image is a derivative work, adapted from the following source, available under  Patho. The image may have been modified by cropping, labeling, and/or captions. MediQ Learning, LLC makes this available under .
- 209** **Necrosis: Image E.** Fibrinoid necrosis. This image is a derivative work, adapted from the following source, available under  Dr. Yale Rosen. The image may have been modified by cropping, labeling, and/or captions. MediQ Learning, LLC makes this available under .
- 209** **Necrosis: Image F.** Acral gangrene.  Courtesy of the Department of Health and Human Services and William Archibald.
- 210** **Ischemia.** This image is a derivative work, adapted from the following source, available under  Van Assche LM, Kim HW, Jensen CJ, et al. A new CMR protocol for non-destructive, high resolution, ex-vivo assessment of the area at risk simultaneous with infarction: validation with histopathology. *J Cardiovasc Magn Reson.* 2012; 14(Suppl 1): O7. DOI: 10.1186/1532-429X-14-S1-O7.
- 210** **Types of infarcts: Image B.** Pale infarct.  Courtesy of the Department of Health and Human Services and the Armed Forces Institute of Pathology.
- 212** **Types of calcification.** Dystrophic calcification. This image is a derivative work, adapted from the following source, available under  Chun J-S, Hong R, Kim J-A. Osseous metaplasia with mature bone formation of the thyroid gland: three case reports. *Oncol Lett.* 2013;6:977-979. DOI: 10.3892/ol.2013.1475. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MediQ Learning, LLC are reserved.
- 212** **Lipofuscin.** This image is a derivative work, adapted from the following source, available under  Dr. Michael Bonert. The image may have been modified by cropping, labeling, and/or captions. MediQ Learning, LLC makes this available under .
- 213** **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.
- 213** **Amyloidosis: Image B.** Apple green birefringence under polarized light. This image is a derivative work, adapted from the following source, available under  Dr. Ed Uthman.
- 215** **Acute inflammation.** Pericardium with severe inflammation, neutrophilic infiltration and fibrin with entrapped clusters of bacteria. This image is a derivative work, adapted from the following source, available under  Faida Ajili, et al. Coexistence of pyoderma gangrenosum and sweet's syndrome in a patient with ulcerative colitis. *Pan Afr Med J.* 2015 Jun 24. DOI: 10.11604/pamj.2015.21.151.6364.
- 218** **Granulomatous diseases.** Granuloma.  Courtesy of Sanjay Mukhopadhyay.
- 219** **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.
- 219** **Scar formation: Image B.** Keloid scar. This image is a derivative work, adapted from the following source, available under  Dr. Andreas Settje. The image may have been modified by cropping, labeling, and/or captions. MediQ Learning, LLC makes this available under .
- 220** **Neoplasia and neoplastic progression.** Cervical tissue. This image is a derivative work, adapted from the following source, available under  Courtesy of Dr. Ed Uthman. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MediQ Learning, LLC are reserved.
- 224** **Common metastases: Image A.** Brain metastases from breast cancer. This image is a derivative work, adapted from the following source, available under  Jmarchn. The image may have been modified by cropping, labeling, and/or captions. MediQ Learning, LLC makes this available under .
- 224** **Common metastases: Image B.** Brain metastasis.  Courtesy of the Department of Health and Human Services and the Armed Forces Institute of Pathology.
- 224** **Common metastases: Image C.** Liver metastasis. This image is a derivative work, adapted from the following source, available under  Dr. James Heilmann The image may have been modified by cropping, labeling, and/or captions. MediQ Learning, LLC makes this available under .
- 224** **Common metastases: Image D.** Liver metastasis.  Courtesy of J. Hayman.
- 224** **Common metastases: Image E.** Bone metastasis. This image is a derivative work, adapted from the following source, available under  Dr. Paul Hellerhoff.

- 224 Common metastases: Image F.** Bone metastasis. This image is a derivative work, adapted from the following source, available under : Courtesy of M Emmanuel.
- 228 Psammoma bodies.** Courtesy of the Department of Health and Human Services and the Armed Forces Institute of Pathology.

### Cardiovascular

- 292 Anatomy of the heart: Image A.** MRI showing normal cardiac anatomy. This image is a derivative work, adapted from the following source, available under : Zhang J, Chen L, Wang X, et al. Compounding local invariant features and global deformable geometry for medical image registration. *PLoS One*. 2014;9(8):e105815. DOI: 10.1371/journal.pone.0105815.
- 292 Anatomy of the heart: Image B.** X-ray showing normal cardiac anatomy. This image is a derivative work, adapted from the following source, available under : Karippacheril JG, Joseph TT. Negative pressure pulmonary oedema and haemorrhage, after a single breath-hold: Diaphragm the culprit? *Indian J Anaesth*. 2010 Jul-Aug;54(4):361–363. DOI: 10.4103/0019-5049.68391.
- 306 Congenital heart diseases: Image A.** “Egg on string” appearance on x-ray of the chest in D-transposition of the great vessels. This image is a derivative work, adapted from the following source, available under : Aloriany IA, Barlas NB, Al-Boukai AA. Pictorial essay: Infants of diabetic mothers. *Indian J Radiol Imaging*. 2010 Aug;20(3):174–181. DOI: 10.4103/0971-3026.69349.
- 306 Congenital heart diseases: Image B.** Tetralogy of Fallot. This image is a derivative work, adapted from the following source, available under : Rashid AKM. Heart diseases in Down syndrome. In: Dey S, ed. Down syndrome. DOI: 10.5772/46009. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MediQ Learning, LLC are reserved.
- 307 Congenital heart diseases: Image C.** Ventricular septal defect. This image is a derivative work, adapted from the following source, available under : Bardo DME, Brown P. Cardiac multidetector computed tomography: basic physics of image acquisition and clinical applications. *Curr Cardiol Rev*. 2008 Aug;4(3):231–243. DOI: 10.2174/157340308785160615.
- 307 Congenital heart diseases: Image D.** Atrial septal defect. This image is a derivative work, adapted from the following source, available under : Teo KSL, Dundon BK, Molaei P, et al. Percutaneous closure of atrial septal defects leads to normalisation of atrial and ventricular volumes. *J Cardiovasc Magn Reson*. 2008;10(1):55. DOI: 10.1186/1532-429X-10-55.
- 307 Congenital heart diseases: Image E.** Patent ductus arteriosus. This image is a derivative work, adapted from the following source, available under : Henjes CR, Nolte I, Wesfaedt P. Multidetector-row computed tomography of thoracic aortic anomalies in dogs and cats: patent ductus arteriosus and vascular rings. *BMC Vet Res*. 2011;7:57. DOI: 10.1186/1746-6148-7-57.
- 307 Congenital heart diseases: Image F.** MRI showing coarctation of the aorta. This image is a derivative work, adapted from the following source, available under : Vergales JE, Gangemi JJ, Rhueban KS, Lim DS. Coarctation of the aorta — the current state of surgical and transcatheter therapies. *Curr Cardiol Rev*. 2013 Aug; 9(3): 211–219. DOI: 10.2174/1573403X11309990032.
- 308 Hypertension.** “String of beads” appearance in fibromuscular dysplasia. This image is a derivative work, adapted from the following source, available under : Plouin PF, Perdu J, LaBatide-Alanore A, et al. Fibromuscular dysplasia. *Orphanet J Rare Dis*. 2007;7:28. DOI: 10.1186/1750-1172-2-28. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MediQ Learning, LLC are reserved.
- 309 Hyperlipidemia signs: Image C.** Tendinous xanthoma. This image is a derivative work, adapted from the following source, available under : Raffa W, Hassam B. Xanthomas tendineux et tubéreux révélant une hypercholestérolémie familiale. *Pan Afr Med J*. 2013; 15: 49. DOI: 10.11604/pamj.2013.15.49.2636.
- 309 Arteriosclerosis: Image A.** Hyaline type. This image is a derivative work, adapted from the following source, available under : Dr. Michael Bonert. The image may have been modified by cropping, labeling, and/or captions. MediQ Learning, LLC makes this available under .
- 309 Arteriosclerosis: Image B.** Hyperplastic type. This image is a derivative work, adapted from the following source, available under : Paco Larosa. The image may have been modified by cropping, labeling, and/or captions. MediQ Learning, LLC makes this available under .
- 309 Arteriosclerosis: Image C.** Monckeberg sclerosis (medial calcific sclerosis). This image is a derivative work, adapted from the following source, available under : Couri CE, da Silva GA, Martinez JA, et al. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MediQ Learning, LLC are reserved.
- 311 Aortic dissection.** This image is a derivative work, adapted from the following source, available under : Qi Y, Ma X, Li G, et al. Three-dimensional visualization and imaging of the entry tear and intimal flap of aortic dissection using CT virtual intravascular endoscopy. *PLoS One*. 2016; 11(10): e0164750. DOI: 10.1371/journal.pone.0164750.
- 313 Evolution of myocardial infarction: Images A and B.** Heart tissue at 0–24 hours (image A) and 1–3 days (image B) after myocardial infarction. These images are a derivative work, adapted from the following source, available under : Chang J, Nair V, Luk A, et al. Pathology of myocardial infarction. *Diagn Histopath*. 2013;19:7–12. DOI: <https://doi.org/10.1016/j.mpdhp.2012.11.001>.
- 313 Evolution of myocardial infarction: Image C.** Heart tissue 3–14 days after myocardial infarction. This image is a derivative work, adapted from the following source, available under : Diarmid AK, Pellicori P, Cleland JG, et al. Taxonomy of segmental myocardial systolic dysfunction. *Eur Heart J*. 2017 Apr 1;38(13):942–954. DOI: 10.1093/euroheartj/ehw140.
- 313 Evolution of myocardial infarction: Image D.** Heart tissue after myocardial infarction showing dense fibrous scar replacing myocyte loss. This image is a derivative work, adapted from the following source, available under : Michaud K, Basso C, d'Amati G, et al on behalf of the Association for European Cardiovascular Pathology. Diagnosis of myocardial infarction at autopsy: AECVP reappraisal in the light of the current clinical classification. *Virchows Arch*. 2020;476:179–194.
- 317 Myocardial infarction complications: Image A.** Papillary muscle rupture. This image is a derivative work, adapted from the following source, available under : Routy B, Huynh T, Fraser R, et al. Vascular endothelial cell function in catastrophic antiphospholipid syndrome: a case report and review of the literature. *Case Rep Hematol*. 2013;2013:710365. DOI: 10.1155/2013/710365.
- 317 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.
- 317 Myocardial infarction complications: Image C.** Free wall rupture of left ventricle. This image is a derivative work, adapted from the following source, available under : Zacarias ML, da Trindade H, Tsutsui J, et al. Left ventricular free wall impeding rupture in post-myocardial infarction period diagnosed by myocardial contrast echocardiography: case report. *Cardiovasc Ultrasound*. 2006;4:7. DOI: 10.1186/1476-7120-4-7.
- 318 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.
- 318 Cardiomyopathies: Image B.** Hypertrophic obstructive cardiomyopathy. This image is a derivative work, adapted from the following source, available under : Benetti MA, Belo Nunes RA, Benvenuti LA. Case 2/2016 - 76-year-old male with hypertensive heart disease, renal tumor and shock. *Arq Bras Cardiol.* 2016 May; 106(5): 439–446. DOI: 10.5935/abc.20160067.
- 319 Heart failure.** Pedal edema. This image is a derivative work, adapted from the following source, available under : Dr. James Heilman. The image may have been modified by cropping, labeling, and/or captions. MediQ Learning, LLC makes this available under .
- 320 Cardiac tamponade: Image A.** CT showing cardiac tamponade. This image is a derivative work, adapted from the following source, available under : Yousaf T, Kramer J, Kopiec A, et al. A rare case of cardiac tamponade induced by chronic rheumatoid arthritis. *J Clin Med Res.* 2015 Sep;7(9):720–723. DOI: 10.14740/jocmr2226w.
- 320 Cardiac tamponade: Image B.** ECG showing cardiac tamponade. This image is a derivative work, adapted from the following source, available under : Maharaj SS, Chang SM. Cardiac tamponade as the initial presentation of systemic lupus erythematosus: a case report and review of the literature. *Pediatr Rheumatol Online J.* 2015; 13: 9. DOI: 10.1186/s12969-015-0005-0.
- 321 Bacterial endocarditis: Image A.** Vegetations on heart valves. Courtesy of the Department of Health and Human Services and Dr. Edwin P. Ewing, Jr.
- 321 Bacterial endocarditis: Image C.** Osler nodes. This image is a derivative work, adapted from the following source, available under : Yang ML, Chen YH, Lin WR, et al. Case report: infective endocarditis caused by *Brevundimonas vesicularis*. *BMC Infect Dis.* 2006;6:179. DOI: 10.1186/1471-2334-6-179.
- 321 Bacterial endocarditis: Image D.** Janeway lesions on sole. This image is a derivative work, adapted from the following source, available under : Courtesy of DeNanneke.
- 322 Rheumatic fever.** Aschoff body and Anitschkow cells. This image is a derivative work, adapted from the following source, available under : Dr. Ed Uthman. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MediQ Learning, LLC are reserved.
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- Endocrine**
- 334 Thyroid development.** Thyroglossal duct cyst. This image is a derivative work, adapted from the following source, available under : Adelchi C, Mara P, Melissa L, et al. Ectopic thyroid tissue in the head and neck: a case series. *BMC Res Notes.* 2014;7:790. DOI: 10.1186/1756-0500-7-790.
- 348 Hypothyroidism vs hyperthyroidism: Image A.** Pretibial myxedema. This image is a derivative work, adapted from the following source, available under : Fred H, van Dijk HA. Images of memorable cases: case 144. Connexions Web site. Dec 8, 2008. Available at: <https://cnx.org/contents/SCJeD6JM@3/Images-of-Memorable-Cases-Case-144>.
- 348 Hypothyroidism vs hyperthyroidism: Image B.** Onycholysis. This image is a derivative work, adapted from the following source, available under : Alborz Fallah. This image may have been modified by cropping, labeling, and/or captions. MediQ Learning, LLC makes this available under .
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- 349 Hypothyroidism: Image C.** Subacute granulomatous thyroiditis histology. This image is a derivative work, adapted from the following source, available under : Dr. Michael Bonert. This image may have been modified by cropping, labeling, and/or captions. MediQ Learning, LLC makes this available under .
- 349 Hypothyroidism: Image E.** Before and after treatment of congenital hypothyroidism. Courtesy of the Department of Health and Human Services.
- 349 Hypothyroidism: Image F.** Congenital hypothyroidism. This image is a derivative work, adapted from the following source, available under : Sadasiv Swain. 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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- 352 Hypoparathyroidism.** Shortened 4th and 5th digits. This image is a derivative work, adapted from the following source, available under : Ferrario C, Gastaldi G, Portmann L, et al. Bariatric surgery in an obese patient with Albright hereditary osteodystrophy: a case report. *J Med Case Rep.* 2013; 7: 111. DOI: 10.1186/1752-1947-7-111.
- 353 Hyperparathyroidism.** Multiple lytic lesions. This image is a derivative work, adapted from the following source, available under : Khaoula BA, Kaouther BA, Ines C, et al. An unusual presentation of primary hyperparathyroidism: pathological fracture. *Case Rep Orthop.* 2011;2011:521578. DOI: 10.1155/2011/521578. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MediQ Learning, LLC are reserved.
- 357 Adrenal insufficiency.** Mucosal hyperpigmentation in primary adrenal insufficiency. Courtesy of FlatOut. 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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- 361 Carcinoid syndrome.** Courtesy of the Department of Health and Human Services and the Armed Forces Institute of Pathology.
- Gastrointestinal**
- 368 Ventral wall defects: Image A.** Gastroschisis. This image is a derivative work, adapted from the following source, available under : Zvizdic Z. Gastroschisis with concomitant jejunoo-ileal atresia complicated by jejunal perforation. *J Neonatal Surg.* 2016 Apr-Jun; 5(2): 25.
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- 368 Ventral wall defects.** Drawings of gastroschisis (left) and omphalocele (right). Courtesy of the Department of Health and Human Services.
- 368 Ventral wall defects: Image C.** Congenital diaphragmatic hernia. This image is a derivative work, adapted from the following source, available under Rastogi MV, LaFranchi SH. Congenital hypothyroidism. *Orphanet J Rare Dis.* 2010;5:17. DOI: 10.1186/1750-1172-5-17.
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- 372 Digestive tract anatomy.** Histology of stomach wall. This image is a derivative work, adapted from the following source, available under Alexander Klepnev.
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- 372 Digestive tract histology: Image B.** Parietal cells and chief cells. This image is a derivative work, adapted from the following source, available under Ziolkowska N, Lewczuk B, Petrynski P, et al. Light and electron microscopy of the European Beaver (*Castor fiber*) stomach reveal unique morphological features with possible general biological significance. *PLoS One.* 2014;9(4):e94590. DOI: 10.1371/journal.pone.0094590. This image may have been modified by cropping, labeling, and/or captions. MediQ Learning, LLC makes this available under .
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- 372 Digestive tract histology: Image D.** Ileum histology and Peyer patches. This image is a derivative work, adapted from the following source, available under CoRus13. This image may have been modified by cropping, labeling, and/or captions. MediQ Learning, LLC makes this available under .
- 372 Digestive tract histology: Image E.** Colon histology. This image is a derivative work, adapted from the following source, available under Athikhun.suw. This image may have been modified by cropping, labeling, and/or captions. MediQ Learning, LLC makes this available under .
- 377 Liver tissue architecture: Image A.** Portal triad. This image is a derivative work, adapted from the following source, available under
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- 377 Liver tissue architecture: Image B.** Kupffer cells. This image is a derivative work, adapted from the following source, available under Dr. Michael Bonert. The image may have been modified by cropping, labeling, and/or captions. MediQ Learning, LLC makes this available under .
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- 382 Gastrointestinal secretory products.** Histology of gastric pit. This image is a derivative work, adapted from the following source, available under Dr. Michael Bonert. The image may have been modified by cropping, labeling, and/or captions. MediQ Learning, LLC makes this available under .
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- 387 Esophageal pathologies: Image A.** White pseudomembrane of *Candida* infection in esophagitis. This image is a derivative work, adapted from the following source, available under Takahashi Y, Nagata N, Shimbo T. Long-term trends in esophageal candidiasis prevalence and associated risk factors with or without HIV infection: lessons from an endoscopic study of 80,219 patients. *PLoS One.* 2015; 10(7): e0133589. DOI: 10.1371/journal.pone.0133589.
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- 387 Esophageal pathologies: Image C.** Esophageal varices on CT. This image is a derivative work, adapted from the following source, available under Dr. Paul Hellerhoff. The image may have been modified by cropping, labeling, and/or captions. MediQ Learning, LLC makes this available under .
- 387 Esophageal pathologies: Image D.** Pneumomediastinum. This image is a derivative work, adapted from the following source, available under Wikimedia Commons. The image may have been modified by cropping, labeling, and/or captions. MediQ Learning, LLC makes this available under .
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- 390 **Ulcer complications.** Free air under diaphragm in perforated ulcer. Reproduced, with permission, from Dr. Frank Gaillard and www.radiopaedia.org.
- 391 **Malabsorption syndromes: Image A.** Celiac disease. This image is a derivative work, adapted from the following source, available under  Celiac disease. Sedda S, Caruso R, Marafini I, et al. Pyoderma gangrenosum in refractory celiac disease: a case report. *BMC Gastroenterol*. 2013; 13: 162. DOI: 10.1186/1471-230X-13-162.
- 391 **Malabsorption syndromes: Image B.** *Tropheryma whipplei* on PAS stain. This image is a derivative work, adapted from the following source, available under  Tran HA. Reversible hypothyroidism and Whipple's disease. *BMC Endocr Disord*. 2006;6:3. DOI: 10.1186/1472-6823-6-3.
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- 392 **Inflammatory bowel diseases: Images B and C.** Normal mucosa (B) and punched-out ulcers (C) in ulcerative colitis. These images are a derivative work, adapted from the following source, available under  Ishikawa D, Ando T, Watanabe O, et al. Images of colonic real-time tissue sonoelastography correlate with those of colonoscopy and may predict response to therapy in patients with ulcerative colitis. *BMC Gastroenterol*. 2011;11:29. DOI: 10.1186/1471-230X-11-29.
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- 394 **Zenker diverticulum.** This image is a derivative work, adapted from the following source, available under  Courtesy of Bernd Brägelmann.
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- 397 **Colonic polyps: Image B.** Adenomatous polyps in tubular adenoma. This image is a derivative work, adapted from the following source, available under  Shussman N, Wexner SD. Colorectal polyps and polyposis syndromes. *Gastroenterol Rep (Oxf)*. 2014 Feb;2(1):1-15. DOI: 10.1093/gastro/got041.
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- 401 Alcoholic liver disease: Image C.** Sclerosis in alcoholic cirrhosis. This image is a derivative work, adapted from the following source, available under Dr. Michael Bonert. The image may have been modified by cropping, labeling, and/or captions. MediQ Learning, LLC makes this available under .
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- 402 Liver tumors: Image B.** Hepatocellular carcinoma/hepatoma. Reproduced, with permission, from Jean-Christophe Fournet and Humpath.
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- 406 Cholelithiasis and related pathologies: Image A.** Gross specimen of gallstones. This image is a derivative work, adapted from the following source, available under Courtesy of M. Emmanuel.
- 406 Cholelithiasis and related pathologies: Image B.** Large gallstone. This image is a derivative work, adapted from the following source, available under Spangler R, Van Pham T, Khoujah D, et al. Abdominal emergencies in the geriatric patient. *Int J Emerg Med.* 2014; 7: 43. DOI: 10.1186/s12245-014-0043-2.
- 407 Cholelithiasis and related pathologies: Image C.** Porcelain gallbladder. This image is a derivative work, adapted from the following source, available under Fred H, van Dijk H. Images of memorable cases: case 19. Connexions Web site. December 4, 2008. Available at: <http://cnx.org/content/m14939/1.3/>. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MediQ Learning, LLC are reserved.
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- 407 Acute pancreatitis: Image B.** Pancreatic pseudocyst. This image is a derivative work, adapted from the following source, available under Thomas Zimmerman. The image may have been modified by cropping, labeling, and/or captions. MediQ Learning, LLC makes this available under .
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- 408 Pancreatic adenocarcinoma: Image B.** CT scan. Courtesy of MBq. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MediQ Learning, LLC are reserved.
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- 416 Neutrophils: Image B.** Dohle bodies. This image is a derivative work, adapted from the following source, available under isis325.
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- 425 RBC morphology.** Sickle cell. Courtesy of the Department of Health and Human Services and the Sickle Cell Foundation of Georgia, Jackie George, and Beverly Sinclair.
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- 429 Microcytic, hypochromic anemia: Image D.** Lead lines in lead poisoning. Reproduced, with permission, from Dr. Frank Gaillard and www.radiopaedia.org.
- 429 Microcytic, hypochromic anemia: Image E.** Sideroblastic anemia. This image is a derivative work, adapted from the following source, available under : Paulo Henrique Orlandi Mourao. The image may have been modified by cropping, labeling, and/or captions. MediQ Learning, LLC makes this available under .
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- 439 Non-Hodgkin lymphoma: Image B.** Jaw lesion in Burkitt lymphoma. This image is a derivative work, adapted from the following source, available under : Bi CF, Tang Y, Zhang WY, et al. Sporadic Burkitt lymphomas of children and adolescents in Chinese: a clinicopathological study of 43 cases. *Diagn Pathol*. 2012;7:72. DOI:10.1186/1746-1596-7-72.
- 439 Non-Hodgkin lymphoma: Image C.** Primary CNS lymphoma. This image is a derivative work, adapted from the following source, available under : Mansour A, Qandeel M, Abdel-Razeq H, et al. MR imaging features of intracranial primary CNS lymphoma in immune competent patients. *Cancer Imaging*. 2014;14(1):22. DOI: 10.1186/1470-7330-14-22.
- 439 Non-Hodgkin lymphoma: Image D.** Mycosis fungoides/Sézary syndrome. This image is a derivative work, adapted from the following source, available under : Chaudhary S, Bansal C, Ranga U, et al. Erythrodermic mycosis fungoides with hypereosinophilic syndrome: a rare presentation. *Ecancermedicalscience*. 2013;7:337. DOI:10.3332/ecancer.2013.337
- 440 Plasma cell dyscrasias: Image C.** This image is a derivative work, adapted from the following source, available under : Mehrotra R, Singh M, Singh PA, et al. Should fine needle aspiration biopsy be the first pathological investigation in the diagnosis of a bone lesion? An algorithmic approach with review of literature. *Cytojournal*. 2007; 4: 9. DOI: 10.1186/1742-6413-4-9.
- 441 Myelodysplastic syndromes.** Neutrophil with bilobed nuclei. This image is a derivative work, adapted from the following source, available under : Lukaszewska J, Allison RW, Stepkowska J. Congenital Pelger-Huët anomaly in a Danish/Swedish farmdog: case report. *Acta Vet Scand*. 2011; 53(1): 14. DOI: 10.1186/1751-0147-53-14.
- 442 Leukemias: Image A.** This image is a derivative work, adapted from the following source, available under : Chiaretti S, Zini G, Bassan R. Diagnosis and subclassification of acute lymphoblastic leukemia. *Mediterr J Hematol Infect Dis*. 2014; 6(1): e2014073. DOI: 10.4084/MJHID.2014.073.
- 442 Leukemias: Image C.** Hairy cell leukemia. This image is a derivative work, adapted from the following source, available under : Chan SM, George T, Cherry AM, et al. Complete remission of primary plasma cell leukemia with bortezomib, doxorubicin, and dexamethasone: a case report. *Cases J*. 2009;2:121. DOI: 10.1186/1757-1626-2-121.
- 443 Myeloproliferative neoplasms: Image A.** Erythromelalgia in polycythemia vera. This image is a derivative work, adapted from the following source, available under : Fred H, van Dijk H. Images of memorable cases: case 151. Connexions Web site. December 4, 2008. Available at <http://cnx.org/content/m14932/1.3/>.
- 443 Myeloproliferative neoplasms: Image C.** Myelofibrosis. This image is a derivative work, adapted from the following source, available under : Courtesy of Dr. Ed Uthman.
- 444 Langerhans cell histiocytosis: Image A.** Lytic bone lesion. This image is a derivative work, adapted from the following source, available under : Dehkordi NR, Rajabi P, Naimi A, et al. Langerhans cell histiocytosis following Hodgkin lymphoma: a case report from Iran. *J Res Med Sci*. 2010;15:58-61. PMCID PMC3082786.
- 444 Langerhans cell histiocytosis: Image B.** Birbeck granules. This image is a derivative work, adapted from the following source, available under : Dr. Yale Rosen. The image may have been modified by cropping, labeling, and/or captions. MediQ Learning, LLC makes this available under .
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- 446 Warfarin.** This image is a derivative work, adapted from the following source, available under : Bakoyannis C, Karaolanis G, Patelis N. Dabigatran in the treatment of warfarin-induced skin necrosis: A new hope. *Case Rep Dermatol Med*. 2016; 2016: 3121469. DOI: 10.1155/2016/3121469.

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- 456 Rotator cuff muscles.** Glenohumeral instability. This image is a derivative work, adapted from the following source, available under : Koike Y, Sano H, Immura I, et al. Changes with time in skin temperature of the shoulders in healthy controls and a patient with shoulder-hand syndrome. *Ups J Med Sci* 2010;115:260-265. DOI: 10.3109/03009734.2010.503354. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MediQ Learning, LLC are reserved.
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- 458 Brachial plexus lesions: Image B.** Winged scapula. This image is a derivative work, adapted from the following source, available under : Boukhris J, Boussouga M, Jaafar A, et al. Stabilisation dynamique d'un winging scapula (à propos d'un cas avec revue de la littérature). *Pan Afr Med J.* 2014; 19: 331. DOI: 10.11604/pamj.2014.19.331.3429.
- 459 Wrist region: Image B.** Anatomic snuff box. This image is a derivative work, adapted from the following source, available under : Rhemrev SJ, Ootes D, Beeres FJP, et al. Current methods of diagnosis and treatment of scaphoid fractures. *Int J Emerg Med.* 2011;4:4. DOI: 10.1186/1865-1380-4-4.
- 466 Motoneuron action potential to muscle contraction.** Two muscle sarcomeres in parallel. This image is a derivative work, adapted from the following source, available under : Ottenheijm CAC, Heunks LMA, Dekhuijzen RPN. Diaphragm adaptations in patients with COPD. *Respir Res.* 2008; 9(1): 12. DOI: 10.1186/1465-9921-9-12.
- 470 Clavicle fractures.** X-ray of clavicle fracture. This image is a derivative work, adapted from the following source, available under : Paladini P, Pellegrini A, Merolla G, et al. Treatment of clavicle fractures. *Transl Med UniSa.* 2012 Jan-Apr;2:47-58.
- 470 Wrist and hand injuries: Image A.** Thenar eminence atrophy in carpal tunnel syndrome. Courtesy of Dr. Harry Gouvas.
- 470 Wrist and hand injuries: Image B.** Metacarpal neck fracture. This image is a derivative work, adapted from the following source, available under : Bohr S, Pallua N. Early functional treatment and modern cast making for indications in hand surgery. *Adv Orthop.* 2016; 2016: 5726979. DOI: 10.1155/2016/5726979.
- 471 Common knee conditions: Image A.** ACL tear. This image is a derivative work, adapted from the following source, available under : Chang MJ, Chang CB, Choi J-Y, et al. Can magnetic resonance imaging findings predict the degree of knee joint laxity in patients undergoing anterior cruciate ligament reconstruction? *BMC Musculoskelet Disord.* 2014;15:214. DOI: 10.1186/1471-2474-15-214. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MediQ Learning, LLC are reserved.
- 471 Common knee conditions: Images B and C.** Prepatellar bursitis (B) and Baker cyst (C). These images are a derivative work, adapted from the following source, available under : Hirji Z, Hunhun JS, Choudur HN. Imaging of the bursae. *J Clin Imaging Sci.* 2011;1:22. DOI: 10.4103/2156-7514.80374. The images may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MediQ Learning, LLC are reserved.
- 474 Common pediatric fractures: Image A.** Greenstick fracture. This image is a derivative work, adapted from the following source, available under : Randsborg PH, Sivertsen EA. Classification of distal radius fractures in children: good inter- and intraobserver reliability, which improves with clinical experience. *BMC Musculoskelet Disord.* 2013;13:6. DOI: 10.1186/1471-2474-13-6.
- 474 Common pediatric fractures: Image B.** Torus (buckle) fracture. This image is a derivative work, adapted from the following source, available under : Aksel Seyahi, et al. Tibial torus and toddler's fractures misdiagnosed as transient synovitis: a case series. *J Med Case Reports.* 2011; 5: 305. DOI: 10.1186/1752-1947-5-305.
- 474 Osteoporosis.** Vertebral compression fractures of spine. This image is a derivative work, adapted from the following source, available under : Imani F, Gharaei H, Rahimzadeh P, et al. Management of painful vertebral compression fracture with kyphoplasty in a severe cardio-respiratory compromised patient. *Anesth Pain Med.* 2012 summer;2(1):42-45. DOI: 10.5812/aapm.5030.
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- 475 Osteomalacia/rickets: Image A.** Clinical photo and x-ray of leg deformity in rickets. This image is a derivative work, adapted from the following source, available under : Linglart A, Biosse-Duplan M, Briot K, et al. Therapeutic management of hypophosphatemic rickets from infancy to adulthood. *Endocr Connect.* 2014;3:R13-R30. DOI: 10.1530/EC-13-0103.
- 475 Osteomalacia/rickets: Image B.** Rachitic rosary on chest x-ray. This image is a derivative work, adapted from the following source, available under : Ayadi ID, Hamida EB, Rebbeh RB, et al. Perinatal lethal type II osteogenesis imperfecta: a case report. *Pan Afr Med J.* 2015;21:11. DOI: 10.11604/pamj.2015.21.11.6834.
- 475 Osteitis deformans.** Thickened calvarium. This image is a derivative work, adapted from the following source, available under : Dawes L. Paget's disease. [Radiology Picture of the Day Website]. Published June 21, 2007. Available at <http://www.radpod.org/2007/06/21/pagets-disease/>.
- 475 Avascular necrosis of bone.** Bilateral necrosis of femoral head. This image is a derivative work, adapted from the following source, available under : Ding H, Chen S-B, Lin S, et al. The effect of postoperative corticosteroid administration on free vascularized fibular grafting for treating osteonecrosis of the femoral head. *Sci World J.* 2013;708014. DOI: 10.1155/2013/708014. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MediQ Learning, LLC are reserved.
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- 477 Primary bone tumors: Image C.** Giant cell tumor. Reproduced, with permission, from Dr. Frank Gaillard and [www.radiopaedia.org](http://www.radiopaedia.org).
- 477 Primary bone tumors: Image D.** Codman triangle in osteosarcoma. This image is a derivative work, adapted from the following source, available under : Xu SF, Yu XC, Zu M, et al. Limb function and quality of life after various reconstruction methods according to tumor location following resection of osteosarcoma in distal femur. *BMC Musculoskelet Disord.* 2014; 15: 453. DOI: 10.1186/1471-2474-15-453.
- 477 Primary bone tumors: Image E.** Starburst pattern in osteosarcoma. This image is a derivative work, adapted from the following source, available under : Ding H, Yu G, Tu Q, et al. Computer-aided resection and endoprosthesis design for the management of malignant bone tumors around the knee: outcomes of 12 cases. *BMC Musculoskelet Disord.* 2013; 14: 331. DOI: 10.1186/1471-2474-14-331.

- 478 Osteoarthritis vs rheumatoid arthritis: Image A.** Osteoarthritis. This image is a derivative work, adapted from the following source, available under Visser J, Busch VJJF, de Kievit-van der Heijden IM, et al. Non-Hodgkin's lymphoma of the synovium discovered in total knee arthroplasty: a case report. *BMC Res Notes*. 2012;5:449. DOI: 10.1186/1756-0500-5-449.
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- 478 Osteoarthritis vs rheumatoid arthritis: Image C.** Histology of rheumatoid nodule. This image is a derivative work, adapted from the following source, available under Gomez-Rivera F, El-Naggar AK, Guha-Thakurta N, et al. Rheumatoid arthritis mimicking metastatic squamous cell carcinoma. *Head Neck Oncol*. 2011;3:26. DOI: 10.1186/1758-3284-3-26.
- 479 Gout: Image B.** Uric acid crystals under polarized light. This image is a derivative work, adapted from the following source, available under Robert J. Galindo. The image may have been modified by cropping, labeling, and/or captions. MediQ Learning, LLC makes this available under .
- 479 Gout: Image C.** Podagra. This image is a derivative work, adapted from the following source, available under Roddy E. Revisiting the pathogenesis of podagra: why does gout target the foot? *J Foot Ankle Res*. 2011;4:13. DOI: 10.1186/1757-1146-4-13.
- 479 Calcium pyrophosphate deposition disease.** Calcium phosphate crystals. This image is a derivative work, adapted from the following source, available under Dieppe P, Swan A. Identification of crystals in synovial fluid. *Ann Rheum Dis*. 1999 May;58(5):261–263.
- 480 Sjögren syndrome: Image A.** Lymphocytic infiltration. Courtesy of the Department of Health and Human Services.
- 480 Sjögren syndrome: Image B.** Dry tongue. This image is a derivative work, adapted from the following source, available under Negrato CA, Tarzia O. Buccal alterations in diabetes mellitus. *Diabetol Metab Syndr*. 2010;2:3. DOI: 10.1186/1758-5996-2-3.
- 480 Septic arthritis.** Joint effusion. This image is a derivative work, adapted from the following source, available under Dr. James Heilman. The image may have been modified by cropping, labeling, and/or captions. MediQ Learning, LLC makes this available under .
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- 481 Seronegative spondyloarthropathies: Image C, right.** Bamboo spine. Courtesy of Heather Hawker.
- 483 Polymyositis/dermatomyositis: Image A.** Gottron papules of dermatomyositis. This image is a derivative work, adapted from the following source, available under Pan Afr Med J. 2015; 21: 89. DOI: 10.11604/pamj.2015.21.89.6971.
- 485 Vasculitides: Image A.** Temporal arteritis histology. This image is a derivative work, adapted from the following source, available under Marvin. The image may have been modified by cropping, labeling, and/or captions. MediQ Learning, LLC makes this available under .
- 485 Vasculitides: Image B.** Angiogram in patient with Takayasu arteritis. Courtesy of the Department of Health and Human Services and Justin Ly.
- 485 Vasculitides: Image C.** Gangrene as a consequence of Buerger disease. This image is a derivative work, adapted from the following source, available under Afsjard A, Mozaffar M, Malekpour F, et al. The wound healing effects of iloprost in patients with Buerger's disease: claudication and prevention of major amputations. *Iran Red Crescent Med J*. 2011;13:420-423.
- 485 Vasculitides: Image D.** Strawberry tongue in patient with Kawasaki disease. This image is a derivative work, adapted from the following source, available under Courtesy of Natr.
- 485 Vasculitides: Image E.** Coronary artery aneurysm in Kawasaki disease. This image is a derivative work, adapted from the following source, available under Wikimedia Commons. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MediQ Learning, LLC are reserved.
- 485 Vasculitides: Image F.** Polyarteritis nodosa. Reproduced, with permission, from Dr. Frank Gaillard and www.radiopaedia.org.
- 485 Vasculitides: Image G.** Churg-Strauss syndrome histology. This image is a derivative work, adapted from the following source, available under Dr. Michael Bonert. The image may have been modified by cropping, labeling, and/or captions. MediQ Learning, LLC makes this available under .
- 485 Vasculitides: Image H.** Granulomatosis with polyangiitis (formerly Wegener) and PR3-ANCA/c-ANCA. Courtesy of M.A. Little.
- 485 Vasculitides: Image I.** Henoch-Schönlein purpura. Courtesy of Okwikikim.
- 485 Vasculitides: Image J.** MPO-ANCA/p-ANCA in microscopic polyangiitis. Courtesy of and M.A. Little.
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- 488 Epithelial cell junctions: Image B.** Large, electron-dense actin structures within adherens junction. This image is a derivative work, adapted from the following source, available under Taylor RR, Jagger DJ, Saeed SR, et al. Characterizing human vestibular sensory epithelia for experimental studies: new hair bundles on old tissue and implications for therapeutic interventions in ageing. *Neurobiol Aging*. 2015 Jun;36(6):2068–2084. DOI: 10.1016/j.neurobiolaging.2015.02.013.
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- 490 Seborrheic dermatitis.** This image is a derivative work, adapted from the following source, available under Roymishali.
- 491 Common skin disorders: Image O.** Urticaria. This image is a derivative work, adapted from the following source, available under

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- 492 Vascular tumors of skin: Image C.** Glomus tumor under fingernail. This image is a derivative work, adapted from the following source, available under Hazani R, Houle JM, Kasdan ML, et al. Glomus tumors of the hand. *Eplasty*. 2008;8:e48. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MediQ Learning, LLC are reserved.
- 493 Skin infections: Image C.** Erysipelas. This image is a derivative work, adapted from the following source, available under Courtesy of Klaus D. Peter.
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- 498 Skin cancer: Image D.** Basal cell palisading nuclei. This image is a derivative work, adapted from the following source, available under Yuri T. Jadotte, MD, et al. Superficial spreading basal cell carcinoma of the face: a surgical challenge. *Eplasty*. 2010; 10: e46. Published online 2010 Jun 21.

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- 506 Posterior fossa malformations: Image B.** Dandy-Walker malformation. This image is a derivative work, adapted from the following source, available under Krupa K, Bekiesinska-Figatowska M. Congenital and acquired abnormalities of the corpus callosum: a pictorial essay. *Biomed Res Int*. 2013;2013:265619. DOI: 10.1155/2013/265619.
- 506 Syringomyelia.** Reproduced, with permission, from Dr. Frank Gaillard and www.radiopaedia.org.

- 508 Myelin.** Myelinated neuron. Courtesy of the Electron Microscopy Facility at Trinity College.
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- 518 Cerebral arteries—cortical distribution.** Cortical watershed areas. This image is a derivative work, adapted from the following source, available under Isabel C, Lecler A, Turc G, et al. Relationship between watershed infarcts and recent intra plaque haemorrhage in carotid atherosclerotic plaque. *PLoS One*. 2014;9(10):e108712. DOI: 10.1371/journal.pone.0108712.
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- 531 Intracranial hemorrhage: Images A and B.** Axial CT of brain showing epidural blood. These images are a derivative work, adapted from the following source, available under Dr. Paul Hellerhoff. The image may have been modified by cropping, labeling, and/or captions. MediQ Learning, LLC makes this available under .
- 531 Intracranial hemorrhage: Image C.** Subdural hematoma. This image is a derivative work, adapted from the following source, available under Dr. James Heilman. The image may have been modified by cropping, labeling, and/or captions. MediQ Learning, LLC makes this available under .
- 531 Intracranial hemorrhage: Image E.** Subarachnoid hemorrhage. This image is a derivative work, adapted from the following source, available under Hakan T, Turk CC, Celik H. Intra-operative real time intracranial subarachnoid haemorrhage during glial tumour resection: a case report. *Cases J*. 2008;1:306. DOI: 10.1186/1757-1626-1-306. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MediQ Learning, LLC are reserved.
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- J, et al. Rapid identification of a major diffusion/perfusion mismatch in distal internal carotid artery or middle cerebral artery ischemic stroke. *BMC Neurol.* 2012 Nov 5;12:132. DOI: 10.1186/1471-2377-12-132. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MediQ Learning, LLC are reserved.
- 533 Effects of strokes: Image B.** Lacunar infarct of lenticulostriate artery. This image is a derivative work, adapted from the following source, available under : Zhou L, Ni J, Yao M, et al. High-resolution MRI findings in patients with capsular warning syndrome. *BMC Neurol.* 2014;14:16. DOI: 10.1186/1471-2377-14-16.
- 533 Effects of strokes: Image C.** Infarction of posterior cerebellar artery. This image is a derivative work, adapted from the following source, available under : Nouh A, Remke J, Ruland S. Ischemic posterior circulation stroke: a review of anatomy, clinical presentations, diagnosis, and current management. *Front Neurol.* 2014 Apr 7;5:30. DOI: 10.3389/fneur.2014.00030.
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- 534 Aneurysms.** Saccular aneurysm. This image is a derivative work, adapted from the following source, available under : Kayhan A, Koc O, Keskin S. The role of bone subtraction computed tomographic angiography in determining intracranial aneurysms in non-traumatic subarachnoid hemorrhage. *Iran J Radiol.* 2014 May; 11(2): e12670. DOI: 10.5812/iranjradiol.12670.
- 539 Neurodegenerative disorders: Image A.** Lewy body in substantia nigra. This image is a derivative work, adapted from the following source, available under : Werner CJ, Heyne-von Haussen R, Mall G, et al. Parkinson's disease. *Proteome Sci.* 2008;6:8. DOI: 10.1186/1477-5956-6-8. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MediQ Learning, LLC are reserved.
- 539 Neurodegenerative disorders: Image B.** Gross specimen of normal brain. This image is a derivative work, adapted from the following source, available under : Niedowicz DM, Nelson PT, Murphy MP. Alzheimer's disease: pathological mechanisms and recent insights. *Curr Neuropharmacol.* 2011 Dec;9(4):674-84. DOI: 10.2174/157015911798376181.
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- 539 Neurodegenerative disorders: Image G.** Frontotemporal dementia: Pick bodies in frontotemporal dementia (Pick disease). This image is a derivative work, adapted from the following source, available under : Neumann M. Molecular neuropathology of TDP-43 proteinopathies. *Int J Mol Sci.* 2009 Jan; 10(1): 232–246. DOI: 10.3390/ijms10010232.
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- 542 Other demyelinated and dysmyelinating disorders: Image A.** Central pontine myelinolysis. This image is a derivative work, adapted from the following source, available under : Wikimedia Commons. The image may have been modified by cropping, labeling, and/or captions. MediQ Learning, LLC makes this available under .
- 542 Other demyelinating and dysmyelinating disorders: Image B.** Progressive multifocal leukoencephalopathy. This image is a derivative work, adapted from the following source, available under : Garrote H, de la Fuente A, Ona R, et al. Long-term survival in a patient with progressive multifocal leukoencephalopathy after therapy with rituximab, fludarabine and cyclophosphamide for chronic lymphocytic leukemia. *Exp Hematol Oncol.* 2015;4:8. DOI: 10.1186/s40164-015-0003-4.
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- 543 Neurocutaneous disorders: Image B.** Leptomeningeal angioma in Sturge-Weber syndrome. Reproduced, with permission, from Dr. Frank Gaillard and www.radiopaedia.org.
- 543 Neurocutaneous disorders: Image C.** Tuberous sclerosis. This image is a derivative work, adapted from the following source, available under : Fred H, van Dijk H. Images of memorable cases: case 143. Connexions Web site. December 4, 2008. Available at: <http://cnx.org/content/m14923/1.3/>.
- 543 Neurocutaneous disorders: Image D.** Ash leaf spots in tuberous sclerosis. This image is a derivative work, adapted from the following source, available under : Tonekaboni SH, Tousi P, Ebrahimi A, et al. Clinical and para clinical manifestations of tuberous sclerosis: a cross sectional study on 81 pediatric patients. *Iran J Child Neurol.* 2012;6:25-31. PMCID PMC3943027.
- 543 Neurocutaneous disorders: Image E.** Angiomyolipoma in tuberous sclerosis. This image is a derivative work, adapted from the following source, available under : KGH. The image may have been modified by cropping, labeling, and/or captions. MediQ Learning, LLC makes this available under .
- 543 Neurocutaneous disorders: Image F.** Café-au-lait spots in neurofibromatosis. This image is a derivative work, adapted from the following source, available under : Wikimedia Commons. The image may have been modified by cropping, labeling, and/or captions. MediQ Learning, LLC makes this available under .
- 543 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

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- 543 Neurocutaneous disorders: Image J.** Brainstem and spinal cord hemangioblastomas in von Hippel-Lindau disease. This image is a derivative work, adapted from the following source, available under Park DM, Zhuang Z, Chen L, et al. von Hippel-Lindau disease-associated hemangioblastomas are derived from embryologic multipotent cells. *PLoS Med.* 2007 Feb;4(2):e60. DOI: 10.1371/journal.pmed.0040060.
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- 544 Adult primary brain tumors: Image E.** Meningioma with dural tail. This image is a derivative work, adapted from the following source, available under Smits A, Zetterling M, Lundin M, et al. Neurological impairment linked with cortico-subcortical infiltration of diffuse low-grade gliomas at initial diagnosis supports early brain plasticity. *Front Neurol.* 2015;6:137. DOI: 10.3389/fneur.2015.00137.
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- 545 Adult primary brain tumors: Image I.** Field of vision in bitemporal hemianopia. This image is a derivative work, adapted from the following source, available under Wikimedia Commons. The image may have been modified by cropping, labeling, and/or captions. MediQ Learning, LLC makes this available under .
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- 545 Adult primary brain tumors: Image L.** Schwannoma. This image is a derivative work, adapted from the following source, available under Shah AA, Latoo S, Ahmad I, et al. Schwannoma causing resorption of zygomatic arch. *J Oral Maxillofac Pathol.* 2011;15(1):80-84. DOI: 10.4103/0973-029X.80020.
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- 546 Childhood primary brain tumors: Image D.** Medulloblastoma histology. This image is a derivative work, adapted from the following source, available under KGH. The image may have been modified by cropping, labeling, and/or captions. MediQ Learning, LLC makes this available under .
- 546 Childhood primary brain tumors: Image E.** MRI of ependymoma. This image is a derivative work, adapted from the following source, available under Dr. Paul Hellerhoff. The image may have been modified by cropping, labeling, and/or captions. MediQ Learning, LLC makes this available under .
- 546 Childhood primary brain tumors: Image F.** Ependymoma histology. This image is a derivative work, adapted from the following source, available under Dr. Michael Bonert. The image may have been modified by cropping, labeling, and/or captions. MediQ Learning, LLC makes this available under .
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- 553 Conjunctivitis.** This image is a derivative work, adapted from the following source, available under Baiyeroju A, Bowman R,

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- 555 Glaucoma: Image D.** Acute angle closure glaucoma. This image is a derivative work, adapted from the following source, available under : Courtesy of Dr. Jonathan Trobe.
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- 557 Retinitis pigmentosa.** Courtesy of EyeRounds.
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- 586 Trichotillomania.** Courtesy of Robodoc.
- Renal**
- 602 Potter sequence.** Courtesy of the Department of Health and Human Services and the Armed Forces Institute of Pathology.
- 603 Horseshoe kidney.** This image is a derivative work, adapted from the following source, available under : Rispoli P, Destefanis P, Garneri P, et al. Inferior vena cava prosthetic replacement in a patient with horseshoe kidney and metastatic testicular tumor: technical considerations and review of the literature. *BMC Urol*. 2014;14:40. DOI: 10.1186/1471-2490-14-40.
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- 620 Nephritic syndrome: Image A.** Histology of acute poststreptococcal glomerulonephritis. This image is a derivative work, adapted from the following source, available under : Dr. Michael Bonert. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this available under .
- 620 Nephritic syndrome: Image B.** Immunofluorescence of acute poststreptococcal glomerulonephritis. This image is a derivative work, adapted from the following source, available under : Immunofluorescence of acute poststreptococcal glomerulonephritis. Oda T, Yoshizawa N, Yamakami K, et al. The role of nephritis-associated plasmin receptor (napr) in glomerulonephritis associated with streptococcal infection. *Biomed Biotechnol*. 2012;2012:417675. DOI 10.1155/2012/417675.
- 620 Nephritic syndrome: Image C.** Histology of rapidly progressive glomerulonephritis. Courtesy of the Department of Health and Human Services and Uninformed Services University of the Health Sciences.

- 620 Nephritic syndrome: Image D.** “Tram tracks” in membranoproliferative glomerulonephritis. This image is a derivative work, adapted from the following source, available under Kiremitci S, Ensari A. Classifying lupus nephritis: an ongoing story. *Scientific World Journal*. 2014; 2014: 580620. DOI: 10.1155/2014/580620.
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- 621 Nephrotic syndrome: Image B.** Histology of focal segmental glomerulosclerosis. This image is a derivative work, adapted from the following source, available under Dr. Michael Bonert. The image may have been modified by cropping, labeling, and/or captions. MediQ Learning, LLC makes this available under .
- 621 Nephrotic syndrome: Image D.** Diabetic glomerulosclerosis with Kimmelstiel-Wilson lesions. This image is a derivative work, adapted from the following source, available under Doc Mari. The image may have been modified by cropping, labeling, and/or captions. MediQ Learning, LLC makes this available under .
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- 624 Pyelonephritis: Image A.** This image is a derivative work, adapted from the following source, available under Dr. Michael Bonert. The image may have been modified by cropping, labeling, and/or captions. MediQ Learning, LLC makes this available under .
- 624 Pyelonephritis: Image B.** CT scan. Courtesy of the Department of Health and Human Services and the Armed Forces Institute of Pathology.
- 626 Acute tubular necrosis: Image A.** Muddy brown casts. This image is a derivative work, adapted from the following source, available under Dr. Serban Niculescu.
- 626 Renal papillary necrosis.** Courtesy of the Department of Health and Human Services and William D. Craig, Dr. Brent J. Wagner, and Mark D. Travis.
- 627 Renal cyst disorders: Image C.** Ultrasound of simple cyst. This image is a derivative work, adapted from the following source, available under Nevit Dilmen. The image may have been modified by cropping, labeling, and/or captions. MediQ Learning, LLC makes this available under .
- 628 Renal cell carcinoma: Image A.** Histology. This image is a derivative work, adapted from the following source, available under Dr. Yale Rosen. The image may have been modified by cropping, labeling, and/or captions. MediQ Learning, LLC makes this available under .
- 628 Renal cell carcinoma: Image B.** Gross specimen. This image is a derivative work, adapted from the following source, available under Dr. Ed Uthman. This image may have been modified by cropping, labeling, and/or captions. MediQ Learning, LLC makes this available under .
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- 642 Umbilical cord: Image A.** Cross-section of umbilical cord. This image is a derivative work, adapted from the following source, available under Dr. Ed Uthman. The image may have been modified by cropping, labeling, and/or captions. MediQ Learning, LLC makes this available under .
- 642 Umbilical cord: Image B.** Meckel diverticulum. This image is a derivative work, adapted from the following source, available under Mathur P, Gupta R, Simlot A, et al. Congenital pouch colon with double Meckel's diverticulae. *J Neonatal Surg*. 2013 Oct-Dec; 2(4): 48.
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- 650 Female reproductive epithelial histology.** Transformation zone. This image is a derivative work, adapted from the following source, available under Courtesy of Dr. Ed Uthman. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MediQ Learning, LLC are reserved.
- 652 Seminiferous tubules.** This image is a derivative work, adapted from the following source, available under Dr. Anil Rao. The image may have been modified by cropping, labeling, and/or captions. MediQ Learning, LLC makes this available under .
- 665 Pregnancy complications.** Ectopic pregnancy. This image is a derivative work, adapted from the following source, available under Li W, Wang G, Lin T, et al. Misdiagnosis of bilateral tubal pregnancy: a case report. *J Med Case Rep*. 2014;8:342. DOI: 10.1186/1752-1947-8-342.
- 666 Hydatidiform mole: Image A.** Cluster of cluster of grapes appearance in complete hydatidiform mole. This image is a derivative work, adapted from the following source, available under Dr. Ed Uthman

- 666 Choriocarcinoma: Image B.** “Cannonball” metastases. This image is a derivative work, adapted from the following source, available under Lekanidi K, Vlachou PA, Morgan B, et al. Spontaneous regression of metastatic renal cell carcinoma: case report. *J Med Case Rep.* 2007;1:89. DOI: 10.1186/1752-1947-1-89.
- 668 Vulvar pathology: Image A.** Bartholin cyst. Courtesy of the Department of Health and Human Services and Susan Lindsley.
- 668 Vulvar pathology: Image B.** Lichen sclerosis. This image is a derivative work, adapted from the following source, available under Lambert J. Pruritus in female patients. *Biomed Res Int.* 2014;2014:541867. DOI: 10.1155/2014/541867.
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- 668 Vulvar pathology: Image D.** Extramallary Paget disease. This image is a derivative work, adapted from the following source, available under Wang X, Yang W, Yang J. Extramammary Paget’s disease with the appearance of a nodule: a case report. *BMC Cancer.* 2010;10:405. DOI: 10.1186/1471-2407-10-405.
- 669 Polycystic ovarian syndrome.** This image is a derivative work, adapted from the following source, available under Kopera D, Wehr E, Obermayer-Pietsch B. Endocrinology of hirsutism. *Int J Trichology.* 2010;2(1):30–35. doi:10.4103/0974-7753.66910
- 671 Ovarian tumors: Image C.** Dysgerminoma. This image is a derivative work, adapted from the following source, available under Montesinos L, Acién P, Martínez-Beltrán M, et al. Ovarian dysgerminoma and synchronous contralateral tubal pregnancy followed by normal intra-uterine gestation: a case report. *J Med Rep.* 2012;6:399. DOI: 10.1186/1752-1947-6-399.
- 671 Ovarian tumors: Image D.** Mature cystic teratoma. This image is a derivative work, adapted from the following source, available under Dr. Michael Bonert. The image may have been modified by cropping, labeling, and/or captions. MediQ Learning, LLC makes this available under .
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- 671 Ovarian tumors: Image F.** 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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- 672 Uterine conditions: Image B.** Endometritis with inflammation of the endometrium. This image is a derivative work, adapted from the following source, available under Montesinos L, Acién P, Martínez-Beltrán M, et al. Ovarian dysgerminoma and synchronous contralateral tubal pregnancy followed by normal intra-uterine gestation: a case report. *J Med Rep.* 2012;6:399. DOI: 10.1186/1752-1947-6-399.
- 672 Uterine conditions: Image C.** Endometrial carcinoma. This image is a derivative work, adapted from the following source, available under Izadi-Mood N, Yarmohammadi M, Ahmadi SA, et al. Reproducibility determination of WHO classification of endometrial hyperplasia/well differentiated adenocarcinoma and comparison with computerized morphometric data in curettage specimens in Iran. *Diagn Pathol.* 2009;4:10. DOI:10.1186/1746-1596-4-10.
- 672 Uterine conditions: Image D.** Leiomyoma (fibroid), gross specimen. This image is a derivative work, adapted from the following source, available under Courtesy of Hic et nunc.
- 672 Uterine conditions: Image E.** Leiomyoma (fibroid) histology. This image is a derivative work, adapted from the following source, available under Londero AP, Perego P, Mangioni C, et al. Locally relapsed and metastatic uterine leiomyoma: a case report. *J Med Case Rep.* 2008;2:308. DOI: 10.1186/1752-1947-2-308. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MediQ Learning, LLC are reserved.
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- 673 Benign breast disease: Images B and C.** Phyllodes tumor (B) and phyllodes cyst (C) on ultrasound. These images are a derivative work, adapted from the following source, available under Muttarak MD, Lerntumongtum P, Somwangjaroen A, et al. Phyllodes tumour of the breast. *Biomed Imaging Interv J.* 2006 Apr-Jun;2(2):e33. DOI: 10.2349/bij.2.2.e33.
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- 709 Lung cancer: Image B.** Adenocarcinoma histology. Courtesy of the Department of Health and Human Services and the Armed Forces Institute of Pathology.
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# Index

## A

A-a gradient  
by age, 692  
in oxygen deprivation, 693  
restrictive lung disease, 699  
with oxygen deprivation, 693

Abacavir  
HIV therapy, 203  
HLA subtype hypersensitivity, 100

Abciximab  
antiplatelets, **447**  
mechanism and clinical use, 447  
thrombogenesis and, 421

Abdominal aorta  
and branches, **373**  
atherosclerosis in, 310  
bifurcation of, 687

Abdominal aortic aneurysm, 310

Abdominal pain  
acute mesenteric ischemia, 396  
bacterial peritonitis, 400  
hypercalcemia, 615  
hyperparathyroidism, 353  
intussusception, **395**  
irritable bowel syndrome, **393**  
pancreas divisum, 370  
pancreatic cancer, 408  
polyarteritis nodosa, 484  
postprandial, 373  
RLQ pain, 393  
RUQ pain, 406

Abdominal wall  
caput medusae, 375  
hernias, 379  
ventral wall defects, 368

Abducent nerve (CN VI)  
damage to, 561  
function, **523**  
ocular motility, 560  
palsy, 563

Abduction  
arm, 456, 458  
hip, **461**, 463  
passive abnormal, 463  
passive (knee), 464

Abductor digiti minimi muscle, 460

Abductor pollicis brevis muscle, 460

Abetalipoproteinemia, **94**, 424

Abiraterone, 682

Abnormal passive abduction (knee), 464

Abnormal passive adduction (knee), 464

Abnormal uterine bleeding (AUB), **657**  
heavy or intermenstrual bleeding, 657  
non-structural causes (COEIN), 657  
structural causes (PALM), 657

ABO hemolytic disease of newborn, 415

Abortion  
antiphospholipid syndrome, 482  
ethical situations, 276  
methotrexate for, 450

Abruptio placenta, 664  
cocaine use, 638  
preeclampsia, 667

Abscesses, 493  
acute inflammation and, 215  
brain, 156, 180  
calcification with, 212  
cold staphylococcal, 116  
frontal lobe, 153  
*Klebsiella* spp, 145  
*Staphylococcus aureus*, 135  
liver, 155, 179  
lung, 709  
treatment of lung, 192

Absence seizures, 535

Absolute risk reduction (ARR), 262

AB toxin, 132

Abuse  
child, **579**  
intimate partner violence, 277

Acalculia, 528

Acalculous cholecystitis, 406

Acanthocytes, 424

Acanthocytosis, 94

Acantholysis, 489

Acanthosis, 489

Acanthosis nigricans  
characteristics, 496  
paraneoplastic syndrome, 229  
stomach cancer, 389

Acarbose, 363

Accessory nerve (CN XI)  
arm abduction, 456  
functions, 523  
lesions of, 550

Accessory pancreatic duct, 370, 378

Accommodation eye, 523

Accommodation, eye, 554

Accountable care, 278

Accuracy (validity), 269

Accuracy vs precision, **265**

Acetbutolol, 248, 327

Acetaminophen  
for osteoarthritis, 478  
free radical injury and, 210  
hepatic necrosis from, 252  
mechanism, use and adverse effects, **499**  
toxicity treatment for, 251  
vs aspirin for pediatric patients, 499

Acetazolamide  
glaucoma therapy, 573

idiopathic intracranial hypertension, 540  
mechanism, use and adverse effects, **631**  
sulfa drug, 255

Acetoacetate metabolism, 90

Acetylation  
chromatin, 34  
drug metabolism, 234  
histones, 34  
posttranslation, 45

Acetylcholine (ACh)  
anticholinesterase effect on, 244  
change with disease, 510  
*Clostridium botulinum* inhibition of release, 138  
pacemaker action potential and, 301

Acetylcholine (ACh) receptor agonists, 571

Acetylcholine (ACh) receptors  
autoantibodies to, 486  
types of, **239**

Acetylcholinesterase (AChE)  
in amniotic fluid, 505  
neural tube defects and, 505

Acetylcholinesterase (AChE)  
inhibitors  
naming convention for, 257  
toxicity treatment for, 251

Acetyl-CoA carboxylase  
fatty acid synthesis, 73  
vitamin B<sub>7</sub> and, 68

Achalasia  
esophageal cancer, 388  
etiology, **386**  
nitric oxide secretion and, 381

Achilles reflex, 527

Achlorhydria  
stomach cancer, 389  
VIPomas, 381

Achondroplasia, **474**  
chromosome disorder, 64  
inheritance, 60  
ossification in, 468

Acid-base physiology, **616**

Acid-fast oocysts, 177

Acid-fast organisms, 125

Acidic amino acids, 81

Acid maltase, 86

Acidosis  
cardiac contractility in, 293  
hyperkalemia with, 614  
metabolic, 85

Acidosis and alkalosis, **616**

Acid phosphatase in neutrophils, 416

Acid reflux  
proton pump inhibitors for, **409**

*Acinetobacter baumannii*  
highly resistant bacteria, 198

Acne, 489, 491  
danazol, 682  
tetracyclines for, 192

Acquired hydrocele (scrotal), 676

Acrodermatitis enteropathica, 71

Acromegaly  
carpal tunnel syndrome, 470  
findings, diagnosis and treatment, **347**

GH, 337  
GH analogs, 336  
octreotide for, 410  
somatostatin analogs for, 336

Actin  
cytoskeleton, 48, 61  
muscular dystrophies, 61

Acting out, 576

Actinic keratosis, 496  
immunotherapy and, 121  
squamous cell carcinoma, 498

*Actinomyces* spp  
comparison with *Nocardia* spp, 139

*Actinomyces israelii*  
culture requirements of, 126  
effects and treatment of, 139  
penicillin G/V for, 187  
pigment production, 128

Activated carriers, **75**  
molecules and form, 75

Active errors, 281

Active immunity, 110  
acquisition of, 110

Acute adrenal insufficiency, 357

Acute bacterial endocarditis, 321

Acute chest syndrome, 432

Acute cholangitis, 406, 407

Acute cholestatic hepatitis  
drug reactions and, 252  
macrolides, 193

Acute coronary syndrome  
ADP receptor inhibitors for, 447  
nitrates for, 326  
treatments for, **317**

Acute cystitis, 618, **624**

Acute disseminated (postinfectious) encephalomyelitis, 542

Acute dystonia  
causes and treatment, 593  
treatment of, 244

Acute gastritis, 389

Acute hemolytic transfusion reactions, 114

Acute hemorrhagic cystitis, 164

Acute inflammation, 215

Acute intermittent porphyria, 434

Acute interstitial nephritis, 625

- Acute kidney injury, **625**  
 Acute laryngotracheobronchitis, **170**  
 Acute local radiation toxicity, 211  
 Acute lymphoblastic leukemia (ALL), 442  
   oncogenes and, 225  
 Acute mesenteric ischemia, 396  
 Acute myelogenous leukemia (AML), 442  
   cytarabine for, 450  
   myelodysplastic syndromes, 442  
 Acute pancreatitis, 405, **407**  
   necrosis and, 209  
 Acute pericarditis, **323**  
 Acute phase proteins, 108  
 Acute phase reactants, **214**  
   IL-6, 108  
 Acute poststreptococcal glomerulonephritis, 620  
 Acute promyelocytic leukemia  
   vitamin A for, 66  
 Acute pulmonary edema  
   opioid analgesics, 572  
 Acute pyelonephritis, 624  
   WBC casts in, 624  
 Acute radiation syndrome, 211  
 Acute respiratory distress syndrome  
   eclampsia and, 667  
   pathophysiology, diagnosis and management, **702**  
   restrictive lung disease, 699  
 Acute transplant rejection, 119  
 Acute tubular necrosis  
   casts in urine, 618  
   etiology, 626  
 Acyclovir  
   mechanism and clinical use, **202**  
 Adalimumab  
   for Crohn disease, 392  
   target and clinical use, 122, 502  
 Adaptive immunity  
   components and mechanism, **99**  
   lymphocytes in, 419  
 Addison disease, 357  
   HLA subtype, 100  
 Additive effect  
   of drugs, 238  
 Adduction  
   arm, 456  
   fingers, 457  
   hip, 461, 462  
   passive (knee), 464  
   thigh, 462  
 Adductor brevis, 461  
 Adductor longus, 461, 462  
 Adductor magnus, 461  
 Adenine  
   Shiga toxins and, 132  
 Adenocarcinomas  
   carcinogens causing, 226  
   esophagus, 388  
   gastric, 217, 227  
   lung, 709  
   nomenclature for, 221  
   nonbacterial thrombotic endocarditis and, 229  
   pancreatic, **408**  
   paraneoplastic syndromes, 229  
   pectinate line and, 376  
   prostatic, 678  
   stomach, 389  
 Adenohypophysis  
   embryologic derivatives, 637  
   hypothalamus and, 513  
 Adenomas  
   bone (parathyroid), 476  
   nomenclature for, 221  
   salivary glands, 386  
   thyroid, 350  
 Adenomatous polyps, 397  
 Adenomyosis (endometrial), 672  
   uterine bleeding from, 657  
 Adenopathy  
   Kawasaki disease, 484  
 Adenosine  
   as antiarrhythmic drug, 332  
   pacemaker action potential and, 301  
 Adenosine deaminase deficiency, 37  
 Adenosine triphosphate (ATP)  
   electron transport chain, 78  
   in TCA cycle, 76  
   production of, **75**, 78  
 Adenosine triphosphate (ATP)  
   synthase inhibitors, 78  
 Adenovirus  
   characteristics of, 163  
   conjunctivitis with, 553  
   envelope and medical importance, 164  
   pneumonia, 707  
 Adherens junction, 488  
 Adhesions, 396  
 Adipose tissue  
   estrogen production, 654  
   in starvation, 91  
   lipolysis, 328  
 Adjustment disorder, 587  
 Adnexal torsion, **649**  
 Adoption study, 260  
 ADP ribosyltransferases, 132  
 Adrenal adenomas  
   Cushing syndrome, 356  
   hyperaldosteronism, 358  
 Adrenal carcinomas  
   Li-Fraumeni syndrome, 225  
   P-glycoprotein in, 228  
 Adrenal cortex  
   progesterone production, 654  
 Adrenal cortex and medulla, **335**  
 Adrenal hyperplasia  
   Cushing syndrome, 356  
 Adrenal insufficiency  
   adrenoleukodystrophy, 48  
   anovulation with, 669  
   fludrocortisone for, 364  
   mechanism and types of, 357  
   vitamin B<sub>2</sub> deficiency, 67  
 Adrenal medulla  
   neuroblastomas of, 358  
   pheochromocytomas in, 358  
 Adrenal steroids, **343**  
 Adrenal zona fasciculata, 344  
 Adrenergic receptor tissue distribution, **240**  
 Adrenocortical atrophy  
   exogenous corticosteroids, 356  
 Adrenocortical insufficiency  
   drug reaction and, 252  
 Adrenocorticotropic hormone (ACTH)  
   in Cushing syndrome, 229, 356  
   secretion of, 336  
   signaling pathways of, 345  
 Adrenoleukodystrophy, 48  
 Adults  
   causes of seizures in, 535  
   common causes of death, 279  
   primary brain tumors, **544**  
 Adult T-cell leukemia, 227  
 Adult T-cell lymphoma, occurrence and causes, 439  
 Advance directives, **272**  
 Aedes mosquitoes  
   Chikungunya virus transmission, 170  
   yellow fever transmission, 171  
   Zika virus transmission, 172  
 Aerobic metabolism  
   ATP production, 70  
   fed state, 91  
   vitamin B<sub>1</sub> (thiamine), 67  
 Aerobic organisms  
   characteristics, 126  
   culture requirements, 126  
 Afatinib, 453  
 Afferent arteriole  
   ANP/BNP effect on, 612  
 Afferent nerves, 303  
 Aflatoxins carcinogenicity, 226  
 African sleeping sickness, 156  
 Afterload  
   approximation of, 293  
   hydralazine, 326  
   in shock, 320  
 Agammaglobulinemia  
   chromosome affected, 64  
 Agar (bacterial culture), 127  
 Agenesis  
   in morphogenesis, 637  
   Müllerian, 645  
   uterovaginal, 662  
 Age-related changes in pharmacokinetics, **250**  
 Age-related macular degeneration, **556**  
 Agnosia, 528  
 Agonists  
   indirect cholinomimetic, 243  
   indirect general, 245  
   indirect sympathomimetics, 245  
   partial, 237  
 Agoraphobia, 586  
 Agranulocytosis  
   drug reaction and, 253  
   sulfa drug allergies, 253  
   thionamides, 364  
 Agraphia, 528  
 AIDS (acquired immunodeficiency syndrome)  
   brain abscess, 180  
   cryptococcal meningitis, 199  
   *Candida albicans*, 153  
   *Cryptosporidium*, 155  
   *Pneumocystis jirovecii*, 154  
   mycobacteria, **140**  
   primary central nervous system lymphoma, 439  
   retinitis, 165  
   retroviruses, 167  
   sexual transmission of, 184  
   time course (untreated), 176  
 Air emboli, 696  
 Akathisia, 514, 537  
 ALA dehydratase, 429, 434  
 Alanine  
   ammonia transport, **82**  
   gluconeogenesis in starvation, 91  
   pyruvate dehydrogenase complex deficiency, 77  
 Alanine aminotransferase (ALT), 77  
   hepatitis viruses, 173  
   in liver damage, 400  
   toxic shock syndrome, 135  
 Alar plate, 504  
 Albendazole  
   cestodes, 160  
 Albinism, 490  
   locus heterogeneity, 57  
   ocular, 61  
 Albumin, 214  
   as liver marker, 400  
   calcium homeostasis, **341**  
   functional liver marker, 400  
 Albuminocytologic dissociation (CSF), 542  
 Albuterol  
   asthma, 712  
   cystic fibrosis, 60  
   uses of, 245  
 Alcohol dehydrogenase, 72  
 Alcohol for sterilization/disinfection, 204  
 Alcoholic cirrhosis, 401  
   cholelithiasis and, 406  
 Alcoholic hepatitis, 401  
 Alcoholic liver disease, **401**  
   aspartate aminotransferase and alanine aminotransferase, 400  
 Alcohol overuse  
   avascular necrosis of bone, 475  
   cataracts, 554  
   cerebella vermis, 528  
   common causes of pneumonia, 179  
   cytochrome P-450 interactions (selected), 255  
   folate deficiency, 430  
   iron granules associated pathology, 426  
   ketone bodies, 90  
   *Klebsiella*, 145  
   Korsakoff syndrome, 66, 581  
   lung abscess, 708  
   nonmegaloblastic anemia, 430  
   psychoactive drug intoxication and withdrawal, 594  
   subdural hematoma, 531  
   Vitamin B<sub>1</sub> deficiency, 66  
   Vitamin B<sub>9</sub> deficiency, 68  
   Vitamin B<sub>12</sub> deficiency, 69  
 Alcohol use disorder, **595**  
   acute gastritis, 389  
   chronic pancreatitis, 407  
   Mallory-Weiss syndrome, 387  
   parathyroid hormone regulation, 340  
 Alcohol withdrawal  
   delirium tremens, 593  
   drug therapy, 566, 596  
   hallucinations in, 581, 582, 593  
   preferred medications for, 596  
 Aldesleukin  
   clinical use, 121  
 Aldolase B, 80  
 Aldose reductase, 81  
 Aldosterone  
   in renal disorders, 615  
   in SIADH, 346  
   renin-angiotensin-aldosterone system, 612  
   secretion of, 358  
   signaling pathways for, 345  
 Aldosterone antagonists, 324  
 Aldosterone resistance, 617  
 Alectinib, 453  
 Alemtuzumab, 452  
 Alendronate, 500  
 Alexia, 532  
 Alirocumab, 328

- Alikiren, **633**  
**ALK** gene  
 lung adenocarcinoma, 225  
 lung cancer, 708  
**Alkaline phosphatase (ALP)**  
 as tumor marker, 227  
 bone disorder lab values, 476  
 hyperparathyroidism and, 353  
 liver damage, 400  
 osteitis deformans, 475  
**Alkalosis**  
 contraction, 60  
 hypokalemia with, 610  
 potassium shifts, 614  
**Alkaptonuria, **84****  
**Alkytating agents**  
 carcinogenicity, 226  
 mechanism, use and adverse effects, 451  
 teratogenicity of, 638  
**Allantois, 642**  
**Allelic heterogeneity, 57**  
**Allergic/anaphylactic reaction**  
 Type I hypersensitivity, 114  
**Allergic bronchopulmonary aspergillosis (ABPA), 153**  
**Allergic contact dermatitis, 491**  
**Allergic reactions**  
 blood transfusion, 114  
 mast cells in, 418  
 Type I hypersensitivity, 112  
**All-trans retinoic acid**  
 for promyelocytic leukemia, 66  
**Allopurinol**  
 for gout, 501  
 kidney stones, 622  
 rash with, 253  
**Alopecia, 449**  
 minoxidil for, 682  
 tinea capitis, 152  
 vitamin A toxicity, 66  
 vitamin B<sub>5</sub> deficiency, 67  
 **$\alpha_1$ -antitrypsin deficiency, 48, **403****  
 COPD and, 52  
 emphysema, 698  
 in germ cell tumors, 677  
 **$\alpha_1$ -blockers**  
 tamsulosin example of, 240  
 **$\alpha_1$ -4-glucosidase;alpha-1 glycoprotein metabolism, 86, 87  
 **$\alpha_1$ -antagonists**  
 BPH treatment, 678  
 **$\alpha_1$ -antitrypsin**  
 elastase inhibition by, 52  
 **$\alpha_1$  selective blockers, 247  
 $\alpha_1$  selective blockers, 247  
 $\alpha_2$  selective blockers, 247  
 **$\alpha_2$ -agonists**  
 muscle spasm treatment, 572  
 sympatholytics, 246  
 Tourette syndrome and, 580  
 **$\alpha$ -agonists**  
 glaucoma therapy, 573  
 **$\alpha$ -amanitin, 42**  
 **$\alpha$ -amylase, 383  
 **$\alpha$ -antagonists**  
 pheochromocytomas, 359  
 **$\alpha$ - $\beta$ -blocker**  
 cocaine overdose, 595  
 **$\alpha$ -blockers**  
 applications and adverse effects, **247**  
 Beers criteria, 250  
 nonselective, 247  
 phenoxybenzamine, 247  
 **$\alpha$  cells**  
 glucagon production by, 341  
 **$\alpha$  cells**  
 pancreatic tumors, 361  
 **$\alpha$ -dystroglycan**  
 muscular dystrophy, 61  
 **$\alpha$ -fetoprotein (AFP)**  
 in germ cell tumors, 677  
 serum tumor marker, 227  
 **$\alpha$ -fetoprotein (AFP)**  
 neural tube defects, 505  
 **$\alpha$ 4-integrin**  
 immunotherapy target, 122  
 **$\alpha$ -galactosidase A**  
 Fabry disease, 88  
 **$\alpha$ -glucosidase inhibitors, 363**  
 **$\alpha$ -hemolytic bacteria**  
 antibiotic tests, 135  
*Streptococcus pneumoniae*, 136  
*Staphylococcus saprophyticus*, 136  
 Viridans group streptococci, 136  
 **$\alpha$ -hemolytic cocci**  
 viridans group streptococci, 136  
 **$\alpha$ -intercalated cells**  
 renal tubular acidosis, 617  
 **$\alpha$ -ketoglutarate**  
 hyperammonemia and, 82  
 hyperammonemia and, 82  
 **$\alpha$ -ketoglutarate dehydrogenase**  
 TCA cycle, 76  
 vitamin B<sub>1</sub> and, 66  
 **$\alpha$ -methyldopa, 246**  
 autoimmune hemolytic anemia, 433  
 hydralazine, 324  
 hypertension in pregnancy, 246  
 procainamide, 330  
**Alpha rhythm (EEG), 512**  
 **$\alpha$ -synuclein, 538**  
 Lewy bodies, 538  
 **$\alpha$ -thalassemia, 428**  
 **$\alpha$ -toxin**  
*Clostridium botulinum*, 138  
**Alpha toxin, 133**  
**Alport syndrome**  
 cataracts and, 554  
 collagen deficiency in, 50  
 nephritic syndrome, 620  
**Alprazolam, 566**  
**Alteplase (tPA), 447, 529**  
**Alternative hypothesis, 268**  
**Alternative splicing, 43**  
**Altitude sickness, 631, 694**  
**Altruism, 577**  
**Aluminum hydroxide, 409**  
**Alveolar cell types**  
 macrophages, 685  
 pneumocytes, 685  
**Alveolar dead space, 688**  
**Alveolar gas equation, **692****  
**Alveolar macrophage, 685**  
**Alveolar PO<sub>2</sub>, 692**  
**Alveolar ventilation, 688**  
**Alveoli**  
 development, 684  
**Alzheimer disease**  
 amyloidosis in, 213  
 drug therapy for, 243, 569  
 neurotransmitter changes with, 510  
 symptoms and histologic findings, 538  
***Amanita phalloides***  
 necrosis caused by, 42  
 RNA polymerase inhibition, 42  
**Amantadine, 568**  
**Amebiasis, 155**  
**Amenorrhea**  
 antiandrogens, 682  
 cystic fibrosis, 60  
 functional hypothalamic, 669  
 menopause diagnosis, 659  
 Müllerian agenesis, 645  
 pituitary prolactinomas, 336  
**Amides (local anesthetics), 571**  
**Amifostine, 453**  
**Amiloride, 632**  
**Amines**  
 MAO inhibitors, **599**  
**Amine whiff test, 148**  
**Amino acids, **81****  
 blood-brain barrier and, 511  
 branched, 84  
 codons for, 37  
 derivatives of, **83**  
 genetic code for, 37  
 in histones, 34  
 metabolism of, 90  
 purine synthesis, 35  
 tRNA, 44  
 urea cycle, 81  
**Aminoacyl-tRNA, 45**  
**Aminoglycosides**  
 magnesium levels and, 340  
 mechanism and clinical use, **191**  
 pregnancy use, 204  
 teratogenicity, 638  
 toxicity of, 254  
**Aminopenicillins**  
 mechanism and use, 188  
**Amiodarone**  
 Class III antiarrhythmic, 331  
 hypothyroidism, 252  
 hypothyroidism with, 349  
 pulmonary fibrosis, 254  
**Amitriptyline**  
 antidepressant, 599  
 migraine headaches, 536  
**Amlodipine, 326**  
**Ammonia**  
 Ornithine transcarbamylase deficiency, 83  
 ornithine transcarbamylase deficiency and, 83  
 transport, **82**  
**Ammonium chloride**  
 overdose treatment, 235  
**Ammonium magnesium phosphate (struvite), 622**  
**Amnesia**  
 brain lesions, 528  
 classification of, **581**  
**Amnionitis**  
*Listeria monocytogenes*, 139  
**Amniotic fluid, **640****  
 disorders, 640  
 emboli of, 696  
 $\alpha$ -fetoprotein in, 505  
**Amoxapine, 599**  
**Amoxicillin**  
 clinical use, 188  
*Haemophilus influenzae*, 142  
*Helicobacter pylori*, 146  
 Lyme disease, 146  
 prophylaxis, 198  
**Amphetamines**  
 intoxication and withdrawal, 594  
 mechanism and use, 245  
 narcolepsy treatment, 591  
 norepinephrine and, 245  
**Amphotericin B**  
*Cryptococcus neoformans*, 153  
*Naegleria fowleri*, 156  
 mechanism and clinical use, 199  
 opportunistic fungal infections, 151  
 systemic mycoses, 151  
**Ampicillin**  
*Clostridium difficile*, 138  
*Listeria monocytogenes*, 139  
 mechanism and use, 188  
 meningitis, 180  
 prophylaxis, 198  
**Ampulla of Vater, 378**  
**Amygdala**  
 lesion effects, 528  
 limbic system, 514  
**Amylase in pancreatitis, 407**  
**Amylin analogs, 363**  
**Amyloid angiopathy**  
 intraparenchymal hemorrhage, 531  
**Amyloidosis**  
 age-related, 213  
 carpal tunnel syndrome, 470  
 common types, **213**  
 hereditary, 213  
 kidney deposition in, 621  
 localized, 213  
 multiple myeloma and, 440  
 restrictive/infiltrative cardiomyopathy, 318  
 systemic, 213  
 with rheumatoid arthritis, 478  
**Amyloid precursor protein (APP), 538**  
**Amyotrophic lateral sclerosis (ALS)**  
 drug therapy for, 569  
 spinal cord lesions, 548  
**Anaerobic metabolism**  
 glycolysis, 74, 75  
 pyruvate metabolism, 77  
**Anaerobic organisms, **127****  
 aspiration and, 179  
*Clostridia* (with exotoxins), 138  
 culture requirements, 126  
 glycyclines, 192  
*Nocardia* vs *Actinomyces*, 139  
 metronidazole, 195  
 necrotizing fasciitis, 493  
 overgrowth in vagina, 148  
 pneumonia caused by, 180  
**Anal atresia, 637**  
**Anal cancer, oncogenic microbes and, 227**  
**Anal fissure, 376**  
**Anal fissures, 376**  
**Anal wink reflex, 527**  
**Anaphase, 46**  
**Anaphylaxis**  
 blood transfusion, 114  
 complement and, 106  
 epinephrine for, 245  
 shock with, 320  
 Type I hypersensitivity, 112  
***Anaplasma* spp**  
 Gram stain, 125  
 transmission, 146, 149  
**Anaplasmosis**  
*Anaplasma* spp, 149  
 vector, 150  
**Anastrozole, 680**  
**Anatomic dead space, 688**  
**Anatomic snuff box, 459**  
**Anatomy**  
 endocrinol, 335  
 gastrointestinal, 370******

- Anatomy (*continued*)
   
heart, 292
   
musculoskeletal, skin and connective tissue, 456
   
nervous system, 507
   
neurological, 507
   
of heart, 287
   
renal, 604
   
reproductive, 648
   
respiratory, 686
   
“Anchovy paste” exudate, 155
   
*Ancylostoma*
  - diseases associated with, 159
  - infection routes, 158
  - intestinal infections, 159
  - microcytic anemia, 159
 Andersen disease, 87
   
Androblastoma, 677
   
Androgen-binding protein
  - Sertoli cell secretion, 652
 Androgenetic alopecia, 682
   
Androgenic steroid abuse, 659
   
Androgen insensitivity syndrome, 662
   
Androgen receptor defect, 663
   
Androgens
  - source and functions, **659**
 Androstenedione, 343, 659
   
Anemias, **427**, 433
  - bacterial endocarditis, 321
  - blood oxygen content, 690
  - blood oxygen in, 690
  - blood transfusion therapy, 438
  - blood viscosity in, 295
  - colorectal cancer, 398
  - in hypertensive emergency, 308
  - intrinsic factor and, 382
  - intrinsic hemolytic, 432
  - kwashiorkor, 71
  - orotic aciduria, 430
  - oxygen deprivation and, 693
  - paroxysmal nocturnal
    - hemoglobinuria, 432
  - pernicious anemia, 389
  - pyruvate kinase deficiency, 432
  - recombinant cytokines for, 121
  - renal failure, 626
  - Reticulocyte index (RI), 427
  - sickle cell anemia, 432
  - sideroblastic, 67, 429
  - vitamin B<sub>9</sub> deficiency, 68
  - vitamin B<sub>12</sub> deficiency, 68, 430
  - Weil disease, 147
  - Wilson disease, 405
 Anemia, classification/taxonomy
  - aplastic, 431
  - extrinsic hemolytic, **433**
  - intrinsic hemolytic, **432**
  - macrocytic, **429**
  - megaloblastic, 430
  - microcytic, hypochromic, **428**
  - nonhemolytic normocytic, **431**
  - normocytic, normochromic, **431**
  - pernicious anemia, 382
  - pure red cell aplasia, 229
  - sideroblastic, 429
 Anemia, drugs causing, 253
  - $\alpha$ -methylldopa, 433
  - amphotericin B, 199
  - aplastic anemia, 431
  - $\beta$ -lactams, 433
  - cephalosporins, 189
 chloramphenicol, 191
  - in sulfa drug allergies, 253
  - isoniazid, 197
 NRTIs, 203
  - penicillin G V, 187
  - thioamides causing, 364
  - trimethoprim, 194
 Anemia of chronic disease, 431
  - rheumatoid arthritis, 478
 Anemia, organisms causing
  - hookworms, 159
  - Ancylostoma*, 159
  - Babesia* spp., 157, 433
  - Diphyllobothrium latum*, 160
  - Escherichia coli*, 145
 Anencephaly, 505
   
Anergy, **110**
  
Anesthetics
  - general principles, **570**
  - inhaled, **570**
  - intravenous, **570**
  - local, **571**
 Aneurysms
  - atherosclerosis, 310
  - Charcot-Bouchard microaneurysm, 534
  - Ehlers-Danlos syndrome, 51
  - saccular, 534
  - superior vena cava syndrome, 710
  - types and risks for, **534**
  - ventricular, 313, 317
 Angelman syndrome
  - chromosome association, 64
  - imprinting disorder in, 58
 Angina
  - aortic stenosis, 300
  - atherosclerosis, 310
  - cocaine causing, 595
  - drug therapy for, 332
  - glycoprotein IIb/IIIa inhibitors for, 447
  - hydralazine contraindication, 326
  - ischemic disease and, 312
  - presentation and types, 312
  - refractory, 327
  - unstable/NSTEMI treatment, 317
  - $\beta$ -blockers for, 248
 Angina, intestinal, 396
   
Angiodysplasia, 396
  - GI bleeding association, 390
 Angioedema, 107
  - scombrotoxin poisoning, 250
  - with ACE inhibitors, 633
 Angiogenesis
  - in cancer, 222
  - wound healing and, 217
 Angiokeratomas, 88
   
Angiomas
  - spider, 117
 Angiosarcomas
  - characteristics of, 492
  - nomenclature for, 221
 Angiotensin converting enzyme (ACE)
  - renin-angiotensin-aldosterone system, 612
 Angiotensin-converting enzyme inhibitors
  - acute coronary syndromes, 317
  - C1 esterase inhibitor deficiency, 107
  - dilated cardiomyopathy, 318
  - dry cough, 254
  - heart failure, 319
  - hypertension, 324
  - mechanism, use and adverse effects, **633**
  - preload/afterload effects, 293
 renal artery stenosis and, 633
  - teratogenicity, 638
 Angiotensin II
  - filtration effects of, 607
  - renin-angiotensin-aldosterone system, 612
  - signaling pathways for, 345
 Angiotensin II receptor blockers
  - heart failure, 319
  - hypertension, 324
  - mechanism, use and adverse effects, **633**
  - naming convention for, 254
 Anhidrosis
  - Hornet syndrome, 559
 Anidulafungin, 200
   
Anisocytosis, 417
   
Anitschkow cells, 322
   
Ankle sprains, **465**
  
Ankylosing spondylitis
  - HLA-subtype, 100
  - reactive arthritis, 481
  - therapeutic antibodies for, 122
 Annular pancreas, 370
   
Anogenital warts, immunotherapy for, 121
   
*Anopheles* mosquito, 157
   
Anopia, visual field defects, 562
   
Anorectal varices
  - portal circulation, 375
 Anorexia
  - hypothalamus and, 513
  - pancreatic adenocarcinoma, 408
  - renal failure, 626
 Anorexia nervosa
  - characteristics of, 590
 Anosmia, zinc deficiency, 71
   
ANOVA tests, 269
   
Anovulation
  - common causes, 669
  - eating disorders, 669
 Antacids, **409**
  
Antagonists
  - ADH, 257
  - endothelin receptor, 257
  - H<sub>2</sub>, 257
  - nonselective, 248
 Anterior cerebral artery
  - cingulate herniation, 547
  - stroke effects, 532
 Anterior circulation strokes, 532
   
Anterior communicating artery
  - saccular aneurysm, 534
 Anterior cruciate ligament (ACL) injury
  - anterior drawer sign in, 462
  - “unhappy triad”, 473
 Anterior drawer sign, 462, 464
   
Anterior hypothalamus, 513
   
Anterior inferior cerebellar artery stroke effects, 532
   
Anterior inferior tibiofibular ligament, 465
   
Anterior nucleus (hypothalamus), 513
   
Anterior pituitary (adenohypophysis), 335
  - sensitivity to TRH, 339
 Anterior spinal artery
  - complete occlusion, 548
  - stroke, 533
 Anterior spinothalamic tract, 526
   
Anterior talofibular ligament, 465
   
Anterograde amnesia
  - benzodiazepines, 570
  - brain lesions, 528
  - CNS insult and, 581
 Anthracosis, 701
   
Anthracyclines
  - cardiomyopathy from, 251
  - mechanism and clinical use, 447
 Anthrax, 132
   
Anthrax toxin
  - Bacillus anthracis* and, 137
 Antiangular therapy
  - ivabradine, 332
  - MVO<sub>2</sub> reduction for, **327**
 Antiapoptotic molecule
  - oncogene product, 225
 Antiarhythmic drugs
  - adenosine, 332
  - calcium channel blockers (class IV), 332
  - magnesium, 332
  - potassium channel blockers (class III), 331
  - sodium channel blockers, 330
  - torsades de pointes, 251
  - $\beta$ -blockers (class IC), 331
 Antibiotics
  - acne treatment, 491
  - Clostridium difficile* with, 138
  - Jarisch-Herxheimer reaction with, 148
  - long QT interval, 315
  - selective growth media, 126
  - torsades de pointes, 251
 Antibodies
  - antibody specificity generation, 101
  - hepatitis viruses, **173**
  - hypersensitivity mediation, 112
  - in adaptive immunity, 99
  - structure and function, 99
  - therapeutic, **122**
 Antibody-dependent cell-mediated cytotoxicity, 101
   
Antibody-drug conjugates, **449**
  
Antibody structure and function, **104**
  
Anticancer monoclonal antibodies
  - agents, uses and adverse effects, **452**
 Anticancer small molecule inhibitors
  - agents, uses and adverse effects, **453**
 Anticardiolipin
  - antiphospholipid syndrome, 482
 Anticardiolipin antibody, 115
   
Anti-CCP antibody, 115
   
Anti-centromere antibodies
  - scleroderma, 487
 Anticentromere autoantibody, 115
   
Anti-CGRP monoclonal antibodies, 536
   
Anticholinergic drugs
  - delirium with, 581
  - toxicity treatment for, 251
 Anticholinesterase drugs, 244
   
Anticholinesterase poisoning, 243
   
Anticipation (genetics), 56
   
Anticoagulant drugs
  - acute coronary syndromes, 317
  - anticoagulant and reversal agent, 447
  - antiphospholipid syndrome, 482
  - coagulation cascade and, 422
 Anticoagulation reversal, **447**
  - targets for, 423
 Anticonvulsant drugs
  - osteoporosis, 474
 Antidepressant drugs
  - atypical, 600
  - fibromyalgia treatment, 483

- for fibromyalgia, 483  
long QT interval with, 315  
monoamine oxidase inhibitors, 599  
selective serotonin reuptake inhibitors, 599  
serotonin-norepinephrine reuptake inhibitors, 599  
torsades de pointes, 251  
tricyclic antidepressants, 599
- Anti-desmoglein (anti-desmosome)** autoantibody, 115
- Anti-digoxin Fab fragments** for cardiac glycoside toxicity, 329 specific toxicity treatments, 251
- Antidiuretic hormone (ADH)** antagonists, 364 function of, 335, 336 hypothalamus synthesis, 513 naming conventions for antagonist, 257  
renin-angiotensin-aldosterone system, 612 signaling pathways of, 345 source, function, and regulation, 337
- Anti-DNA topoisomerase I** autoantibody, 115
- Anti-dsDNA antibody**, 115
- Antiemetic drugs** aprepitant, 410 long QT interval with, 315 metoclopramide, 410 ondansetron, 410 torsades de pointes, 251
- Antiepileptic drugs** rash from, 253 teratogenicity, 638
- antierectile**, 651
- Antifungal drugs** griseofulvin, 48 seborrheic dermatitis, 490 tinea versicolor, 152
- Antifungals** Long QT with, 315
- Antifungal therapy**, 198
- Antigenic shift/drift**, 169
- Antigen-presenting cells (APCs)** B cells as, 418 CD28, 110
- Antigens** active immunity, 110 chronic mucocutaneous candidiasis, 116 HLA I and II, 100 type and memory, 105
- Anti-glomerular basement membrane** autoantibody, 115
- Anti-glutamic acid decarboxylase** autoantibody, 115
- Antigout drugs** colchicine, 48
- Anti-growth signal**, 222
- Anti-HBe**, 174
- Anti-helicase autoantibody**, 115
- Antihelminthic therapy**, 200 mebendazole, 48 naming conventions for, 256
- Anti-hemidesmosome autoantibody**, 115
- Antihistamines** for scombrotoxicity, 250
- Antihistone** autoantibody, 115
- Anti-histone antibody**, 115
- Antihypertensive drugs** hypertension in pregnancy, 667
- Antihypertensives**, 667
- Anti-IgE monoclonal therapy**, 712
- Anti-IL-5 monoclonal therapy**, 712
- Anti-inflammatory drugs**, 499
- Anti-intrinsic factor autoantibody**, 115
- Anti-La/SSB autoantibody**, 115, 480
- Antileukotrienes for asthma**, 712
- Antimetabolites**, 450
- Antimicrobial drugs** naming conventions for, 256 pregnancy contraindications, 204 prophylaxis, 198
- Antimicrobials** embryotoxic, 204
- Antimicrosomal autoantibody**, 115
- Anti-mite/louse therapy**, 200
- Antimitochondrial autoantibody**, 115
- Antimuscarinic drugs** Parkinson disease, 568 reactions to, 254
- Antimycin A** electron transport chain, 78
- Antimycobacterial therapy** prophylaxis and treatment, 196
- Antineoplastics** naming conventions for, 256
- Anti-NMDA receptor paraneoplastic syndrome** encephalitis, 229
- Antinuclear (ANA) antibody**, 115 Sjögren syndrome, 478
- Antioxidants** free radical elimination by, 210
- Antiparasitic drugs** naming convention for, 256
- Antiparietal cell autoantibody**, 115
- Anti-phospholipase A2 receptor** autoantibody, 115
- Antiphospholipid syndrome**, 482 autoantibody, 115 autoantibody in, 115
- Antiplatelet drugs** for acute coronary syndromes, 317 mechanism and clinical use, 447
- Anti-postsynaptic ACh receptor**, autoantibody, 115
- Anti-presynaptic voltage-gated calcium channel**, autoantibody, 115
- Antiprogestins**, 681
- Antiprotozoal therapy** drugs for, 200
- Antiprotozoan drugs**, 200
- Antipseudomonad drugs** fluoroquinolones, 195 penicillins, 188
- Antipsychotic drugs** antimuscarnic reaction, 254 disruptive mood dysregulation disorder, 580 dopaminergic pathways, 514 dystonia with, 593 long QT interval with, 315 mechanism, use and adverse effects, 597
- Parkinson-like syndrome, 254 tardive dyskinesia, 254 torsades de pointes, 251 Tourette syndrome, 596
- Antiretroviral therapy (ART)** HIV therapy, 203
- Antiribonucleoprotein antibodies** Sjögren syndrome, 480
- Anti-Ro/SSA autoantibody**, 480
- anti-Saccharomyces cerevisiae antibodies (ASCA)**, 392
- Anti-Scl-70 autoantibody**, 115
- Anti-Smith autoantibody**, 115
- Anti-smooth muscle antibody**, 115
- Anti-smooth muscle autoantibody**, 115
- Antisocial personality disorder**, 588 early-onset disorder, 580
- Antispasmodics**, 572
- Anti-SRP autoantibody**, 115
- Anti-streptolysin O (ASO) titers**, 322
- Antithrombin** coagulation cascade and, 423 deficiency of, 437
- Antitoxins** as passive immunity, 110
- Anti-TSH receptor autoantibody**, 115
- Antitumor antibiotics**, 449
- Anti-U1 RNP antibodies**, 115, 482
- Anti-U1 RNP (ribonucleoprotein)** autoantibody, 115
- Antiviral therapy** hepatitis C, 204 mechanism and use, 201
- Anti-β2 glycoprotein autoantibody**, 115
- Anti-β<sub>2</sub> glycoprotein antiphospholipid syndrome**, 482
- Anxiety** drug therapy, 566 neurotransmitter changes with, 510
- Anxiety disorders**, 585
- Aorta** branches, 373 coarctation of, 307 diaphragm, 687 syphilitic heart disease, 322 traumatic rupture, 311 traumatic rupture of, 311 "tree bark" appearance, 322
- Aortic aneurysm**, 310 hypertension, 308 Marfan syndrome, 308 syphilitic heart disease, 322
- Aortic arch** derivatives, 289 receptors, 303
- Aortic dissection**, 308, 311 hypertension, 308 Marfan syndrome, 310
- Aortic insufficiency** syphilis, 322
- Aorticopulmonary septum**, 289 embryologic derivatives, 637
- Aortic regurgitation**, 297 aortic dissection, 311 heart murmurs with, 300 Marfan syndrome, 308
- Aortic root dilation** heart murmur with, 300
- Aortic stenosis**, 297, 300 heart murmurs, 300 macroangiopathic anemia, 433 Williams syndrome, 308
- Aortic valve** cardiac cycle, 296 embryological development of, 289
- Aortitis** syphilis, 147, 184
- Aortocaval compression syndrome**, 667
- APC gene** adenomatous colonic polyps and, 397 colorectal cancer and, 399
- Familial adenomatous polyposis**, 397 tumor suppression, 225
- "Ape hand", 457
- Apgar score**, 658
- α (type I) error, 268
- Aphasia** MCA stroke, 532 types of, 534
- Apixaban**, 446 factor Xa inhibitors, 446
- Aplasia**, 637
- Aplasia cutis** methimazole, 364
- Aplastic anemia**, 431 chloramphenicol, 192 drug reaction and, 253 HBV, 174 neutropenia with, 431 thionamides, 364
- Aplastic crisis** hereditary spherocytosis, 432 sickle cell anemia, 432
- Apolipoproteins** functions, 93 functions of, 93
- Apoptosis** BCL-2 gene, 225 corticosteroids, 433 evasion of, 222 malignant tumors, 221 of keratocytes, 496 pathways for, 208 vs necrosis, 209
- Appendicitis** causes, signs and treatment, 393 mittelschmerz vs, 655
- Appetite regulation** endocannabinoids, 344 ghrelin, 344, 381 leptin, 344
- "Apple core" lesion (X-ray), 398
- Apraclonidine**, 573
- Aprepitant** mechanism and clinical use, 410 with chemotherapy, 453
- Aquagenic pruritus**, 443
- Aqueous humor pathway**, 554
- Arabinosyltransferase**, 197
- Arachidonic acid pathways**, 499
- Arachnodactyly**, 52
- Arachnoid granulations**, 519, 540
- Arachnoid mater** derivation, 511 meningioma, 543
- Area postrema**, 513
- Area under the curve**, 233
- Arenaviruses** characteristics and medical importance, 167
- Argatroban**, 446
- Arginine** classification, 81 cystinuria, 85 kidney stones and, 622
- Argyll Robertson pupil** syphilis, 147
- Argyll Robertson pupils** in syphilis, 184 tabes dorsalis, 548
- Aripiprazole**, 597
- Arm abduction** muscles and nerves, 456
- Arm adduction**, 457
- Armadillos (disease vectors)**, 149

- Aromatase, 659  
 Aromatase inhibitors, **680**  
 Aromatic amines, carcinogenicity, 226  
 Arrhythmias  
   amphotericin B, 199  
   diphtheria, 139  
   drug reactions and, 249  
   hypokalemia and, 615  
   local anesthetics and, 571  
   macrolides, 193  
   McArdle disease, 87  
   MI complication, 317  
   muscular dystrophy, 61  
   shock caused by, 320  
   sleep apnea and, 703  
   stimulants and, 594  
   TCA toxicity, 593  
   thyroid hormones and, 364  
   with sudden cardiac death, 312
- Arsenic  
   angiosarcomas, 492  
   carcinogenicity of, 226  
   glycolysis and, 73  
   squamous cell carcinoma, 498  
   toxicity symptoms, 76  
   toxicity treatment, 250
- Artemether, 200  
 Arterial oxygen saturation, 690  
 Arterial ulcer, 495  
 Arteriolosclerosis, **309**  
 Arteriosclerosis, 309  
 Arteriovenous malformations (AVMs)  
   hereditary hemorrhagic telangiectasia, **324**  
 Arteriovenous shunts  
   osteitis deformans, 475
- Arteritis  
   giant cell (temporal), 484
- Artesunate  
   malaria, 157, 200
- Arthralgias  
   alkaptonuria, 84  
   coccidiomycosis, 151  
   hepatitis viruses, 173  
   rubella, 169  
   serum sickness, 113  
   vitamin A toxicity, 66
- Arthritis  
   carpal tunnel syndrome and, 470  
   celecoxib for, 500  
   chlamydiae, 148, 184  
   gonorrhea, 142, 180, 184  
   *Campylobacter jejuni*, 145  
   immunosuppressants, 120  
   *Staphylococcus aureus*, 135  
   lupus, 481  
   Lyme disease, 146  
   osteoarthritis vs rheumatoid arthritis, 478  
   psoriatic, 481  
   reactive arthritis, 481  
   systemic juvenile idiopathic arthritis, 480  
   ulcerative colitis, 392
- Yersinia enterocolitica, 144
- Arthropathy, hemochromatosis, 405
- Arthus reaction  
   Type III hypersensitivity, 113
- Arylsulfatase A  
   metachromatic leukodystrophy, 88
- Asbestos, carcinogenicity, 226  
 Asbestos-related disease, 701
- Ascaris* spp., 158  
*Ascaris lumbricoides*  
   intestinal infection, 159
- Ascending colon, 370  
 Aschoff bodies, 322  
 Ascites  
   diuretic for, 632  
   spontaneous bacterial peritonitis, 400
- Ascorbic acid, 67
- Asenapine, 597
- Aseptic meningitis  
   mumps, 170  
   picornaviruses, 167
- Asherman syndrome, 672
- Ashkenazi Jews  
   disease incidence, 84
- Aspartame, 84
- Aspartate aminotransferase (AST)  
   hepatitis, 173  
   liver damage, 400  
   toxic shock syndrome, 135
- Aspartic acid, 81
- Aspergillosis  
   bronchiectasis, 699  
   echinocandins, 200  
   *Aspergillus fumigatus*, 153
- Aspergillus fumigatus*, 153  
   HIV-positive adults, 177
- Aspergillus* spp.  
   aflatoxins carcinogenicity, 226  
   in immunodeficiency, 118
- Aspiration  
   ARDS and, 702  
   in utero "breathing", 684  
   lung abscess, 708  
   reflux-related, 369, 387  
   Zenker diverticulum, 394
- Aspiration pneumonia  
   alcoholics, 179  
   clindamycin, 192  
   lung anatomy and, 687  
   nosocomial infections, 185
- Aspirin  
   acute coronary syndromes, 317  
   as weak acid, 235  
   cyclooxygenase, 421  
   hemolysis in G6PD deficiency, 253  
   Kawasaki disease, 484  
   mechanism and clinical use, 447  
   mechanism, use and adverse effects, 500  
   Reye syndrome, **400**  
   Reye syndrome and, 499  
   thrombogenesis and, 421  
   transient ischemic attack, 529  
   uncoupling agent, 78  
   zero-order elimination of, 233
- Asplenia  
   RBC inclusions with, 426  
   RBC morphology with, 425
- Asterixis, 537  
   hepatic encephalopathy, 400
- Asteroid bodies, 700
- Asthma  
   albuterol for, 245  
   drug therapy, 712  
   eosinophilic granulomatosis, 485  
   obstructive lung disease, 698
- Astigmatism, 553
- Astrocytes, 507, 511
- Ataxia  
   abetalipoproteinemia, 94  
   lithium toxicity, 593  
   metachromatic leukodystrophy, 88  
   opsoclonus-myoclonus syndrome, 229  
   prions, **178**
- psychoactive drug intoxication, 594  
 streptomycin, 197  
 syphilis, 147  
 tabes dorsalis, 548  
 truncal, 528  
 vitamin B<sub>12</sub> deficiency, 548  
 vitamin E deficiency, 70  
 Wernicke-Korsakoff syndrome, 528, 595
- Atelectasis  
   etiology, **704**  
   physical findings, 704  
   pleural effusions and, 704
- Atenolol, 248
- Atezolizumab, 452
- Atherosclerosis, **310**  
   aneurysm and, 310  
   diabetes mellitus and, 354  
   familial dyslipidemias, 94  
   homocystinuria, 85  
   location and risk factors, 310  
   renovascular disease, 628  
   stable angina with, 312  
   transplant rejection, 119
- Athetosis, 528, 537
- Atomoxetine, 580
- Atonic seizures, 535
- Atopic dermatitis (eczema), 489, 491
- Atopic reactions  
   Type I hypersensitivity, 112
- Atovaquone  
   babesiosis, 157  
   *P. falciparum*, 200  
   malaria, 157
- Atria  
   depolarization/repolarization of, 301  
   embryologic development of, 288
- Atrial fibrillation  
   ECG tracing of, 316
- Atrial flutter  
   ECG tracings, 316
- "Atrial kick", 296
- Atrial natriuretic peptide (ANP), 213, **303**  
   in SIADH, 346  
   renin-angiotensin-aldosterone system, 612  
   signaling pathways for, 345
- Atrial septal defect (ASD)  
   congenital disease, 307
- Down syndrome, 308  
   fetal alcohol syndrome, 308
- Atrioventricular (AV) block  
   Lyme disease, 146  
   types of, **316**
- Atrioventricular (AV) node  
   Class IC antiarrhythmics, 329  
   conduction pathway, 302  
   ECG and, 301  
   myocardial action potential, 301
- Atrioventricular canals, 289
- Atrioventricular valves  
   embryologic development of, 288
- Atrophic gastritis  
   gastrin in, 381
- Atrophy  
   amyotrophic lateral sclerosis, 548  
   characteristics of, 206  
   motor neuron signs, 547  
   neurodegenerative disorders, 538  
   optic disc/nerve, 555  
   skeletal muscle, 467
- Atropine  
   β-blocker overdose, 331  
   effects of, 243
- for anticholinergic toxicity, 243  
 toxicity treatment, 251  
 organ system and application, **244**
- Attack rate (risk quantification), 263
- Attention-deficit hyperactivity disorder  
   early onset disorder, 580  
   preferred drugs for, 596
- Attributable risk, 262
- Atypical (2nd-generation) antipsychotics  
   mechanism and use, 597
- Atypical antidepressants, 599
- Atypical antipsychotic drugs  
   bipolar disorder and, 584  
   MDD with psychotic features, 584  
   postpartum psychosis treatment, 585  
   preferred medications for selected conditions, 596  
   schizophrenia treatment, 583, 596, 597  
   serotonin 5-HT2 receptor and, 597
- Atypical pneumonias  
   chlamydiae, 148  
   macrolides, 192  
   organisms causing, 179  
   typical organisms, 707
- Auerbach plexus, 386
- Auer rods  
   in AML, 442
- Auramine-rhodamine stain, 125
- Auscultation of heart, maneuvers for, **299**
- Auspitz sign, 491
- Autism spectrum disorder  
   double Y males and, 661  
   early onset disorder, 580  
   fragile X syndrome, 62
- Autoantibodies, 115
- Autoclaves  
   disinfection/sterilization, **204**  
   for spore-forming bacteria, 129
- Autodigestion, 407
- Autoimmune diseases  
   acute pericarditis, 323  
   blistering skin, 494  
   diabetes mellitus Type 1, 355  
   Dressler syndrome, 317  
   interferon-induced, 109  
   myocarditis with, 323  
   rheumatoid arthritis, 478  
   self-antigen in, 99  
   Sjögren syndrome, 480  
   SLE, 482  
   therapeutic agents for, 122
- Autoimmune disease therapy agents for, 122
- Autoimmune gastritis, 389
- Autoimmune hemolytic anemia  
   causes and findings, 433  
   cephalosporins, 189
- Autoimmune hepatitis, **401**  
   drug reactions, 252
- Autoimmune hypothyroidism, 174
- Autoimmune lymphoproliferative syndrome, 208
- Autoimmune thrombocytopenia, 121
- Autonomic drugs  
   actions of, 242  
   bladder dysfunction action on, 240  
   naming conventions for, 257
- Autonomic insufficiency, 245

- Autonomic nervous system (ANS)  
  delirium tremens, 593  
  dysregulation in inflammatory demyelinating polyradiculopathy, 542  
  in serotonin syndrome, 593  
limbic system in, 513  
  male sexual response, **651**
- Autonomic receptors, **239**
- Autonomy (ethics), 270
- Autoregulation of blood flow, 304
- Autosomal dominant diseases  
  achondroplasia, 474  
  acute intermittent porphyria, 434  
  ADPKD, 534  
  Brugada syndrome, 315  
  Charcot-Marie-Tooth disease, 542  
  elastin syndrome, 51, 52  
  familial adenomatous polyposis, 397  
  hereditary spherocytosis, 432  
  hyper-IgE syndrome, 116  
  hypertrophic cardiomyopathy, 318  
  inheritance modes, **59**  
  juvenile polyposis syndrome, 397  
  malignant hyperthermia susceptibility, 570  
  multiple endocrine neoplasias, 360  
  neurofibromatosis, 543  
  Peutz-Jeghers syndrome, 397  
  polycystic kidney disease, 627  
  pseudohypoparathyroidism, 352  
  pseudopseudohypoparathyroidism, 352  
  Romano-Ward syndrome, 315  
  tuberous sclerosis, 543  
  tubulointerstitial kidney disease, 627  
  von Hippel-Lindau disease, 543
- Autosomal dominant polycystic kidney disease  
  associated disorders, 627  
  chromosome association, 64  
  renal cyst disorders, **627**  
  saccular aneurysms and, 534
- Autosomal dominant tubulointerstitial kidney disease, 627
- Autosomal recessive diseases, 59  
   $5\alpha$ -reductase deficiency, 663  
  abetalipoproteinemia, 94  
  adenosine deaminase deficiency, 117  
  alkaptonuria, 84  
  Bernard-Soulier syndrome, 436  
  Chédiak-Higashi syndrome, 117  
  cystic fibrosis, **60**  
  Friedreich ataxia, 549  
  Glanzmann thrombasthenia, 436  
  hemochromatosis, 405  
  hereditary hyperbilirubinemias, 404  
  Jervell and Lange-Nielsen syndrome, 315  
  Kartagener syndrome, 49  
  leukocyte adhesion deficiency, 117  
  maple syrup urine disease, 80, 84  
  pyruvate kinase deficiency, 432  
  SCID, 37  
  Wilson disease, 405
- Autosomal recessive polycystic kidney disease, 627  
  associated disorders, 627  
  Potter sequence, 602
- Autosomal trisomies  
  Down syndrome (trisomy 21), 63  
  Edwards syndrome (trisomy 18), 63
- findings with, **63**  
  karyotyping for, 55  
  Patau syndrome (trisomy 13), 63
- Avanafil, 249
- Avascular necrosis  
  femoral head, 473  
  scaphoid bone, 459  
  Sickle cell anemia, 432
- Avascular necrosis of bone, **475**
- Avelumab, 452
- Aversive stimulus (positive punishment), 576
- Avoidant personality disorder, 588
- Axilla/lateral thorax, 465
- Axillary nerve  
  injury and presentation, 456  
  injury presentation, 456  
  neurovascular pairing, 465
- Axonal injury  
  causes of, 533  
  characteristics of, 510
- Axonal trafficking, 48
- Axonemal dynein, 49
- Azathioprine, 450  
  immunosuppressant, 120  
  immunosuppression, 120  
  pancreatitis caused by, 252
- Azithromycin  
  babesiosis, 157  
  chlamydiae, 148  
  *Mycobacterium avium-intracellulare*, 139  
  in cystic fibrosis, 60  
  macrolides, 193  
  prophylaxis in HIV, 198
- Azoles  
  mechanism, use and adverse effects, **199**  
  vaginal infections, 181
- Aztacronam, 190
- B**
- B19 virus, 164
- Babesia* spp  
  hematologic infections, 157  
  Lyme disease, 146
- Babesioses, 157
- Babinski reflex/sign  
  infant development, 578  
  motor neuron lesions, 547  
  primitive reflexes, 527
- Bacillary angiomatosis, 492  
  animal transmission, 149  
  HIV-positive adults, 177
- Bacillus anthracis*, 137  
  toxin in, 132
- Bacillus cereus*, **138**  
  food poisoning, 178
- Bacitracin  
  gram-positive antibiotic test, 134  
  sensitivity to, 135, 136
- Baclofen  
  mechanism and use, 572  
  multiple sclerosis, 541
- Bacteremia  
  brain abscesses, 180  
  cutaneous anthrax, 137  
  daptomycin, 195  
  *Streptococcus bovis*, 137
- Bacteria  
  biofilm-producing, 128  
  exotoxins in, **132**  
  genetics, 130  
  hemolytic, 136  
  infections in immunodeficiency, 118
- normal flora, 178  
  phage infection of, 130  
  pigment-producing, 128  
  spore-forming, 129  
  treatment of highly resistant, 198  
  virulence factors, 127, 135, 143, 144, 145  
  zoonotic, **149**
- Bacterial endocarditis, **321**  
  daptomycin, 195
- Bacterial exotoxin mechanisms  
  increase fluid secretion, 132  
  inhibit phagocytic ability, 132  
  inhibit protein synthesis, 132  
  lyse cell membranes, 133  
  superantigens causing shock, 133
- Bacterial genetics  
  conjugation, 130  
  transduction, 130  
  transformation, 130  
  transposition, 131
- Bacterial infections  
  myocarditis with, 323  
  skin, 493  
  with immunodeficiency, 118
- Bacterial peritonitis (spontaneous), 400
- Bacterial structures, **124**
- Bacterial toxin mechanisms  
  inhibit release of neurotransmitter, 132
- Bacterial vaginosis  
  characteristics of, 158  
  *Gardnerella vaginalis*, 148  
  signs and symptoms, 181
- Bacterial virulence factors, **129**
- Bacteroides fragilis*, 179
- Bacteroides* spp  
  alcoholism, 179  
  clindamycin, 192  
  culture requirements of, 126  
  metronidazole, 195  
  nosocomial infections, 182  
  “Bag of worms”, 675
- Baker cyst, 463, 471
- BAK protein, 208
- Balancing (quality measurement), 280
- Bamboo spine, 481
- Band cells, 416
- Barbiturates  
  intoxication and withdrawal, 594  
  mechanism, use and adverse effects, **566**  
  naming convention for, 256
- Barlow maneuver, 473
- Baroreceptors, 303
- Barr bodies, 34
- Barrett esophagus, 388
- Bartholin cyst/abscess, 668
- Bartonella* spp  
  animal transmission, 149  
  bacillary angiomatosis, 492  
  Gram Stain, 125  
  in HIV positive adults, 177  
  transmission, 149
- Bartonella quintana*, 161
- Bartter syndrome  
  renal disorder features, 615  
  renal tubular defects, 610
- Basal cell carcinoma  
  5-fluorouracil for, 450  
  characteristics of, 498
- Basal ganglia  
  function and pathways, 516  
  intrapancrechymal hemorrhage, 531
- intrapancrechymal hemorrhages, 531
- lesion effects, 528
- movement disorders, 537
- thalamic connections, 513
- Basal lamina, 50
- Basal nucleus of Meynert, 510
- Basal plate, 504
- Base excision repair, 39
- Basement membrane  
  blood-brain barrier, 511  
  collagen in, 50
- Basic amino acids, 81
- Basilar artery  
  herniation syndromes, 547  
  stroke effects, 532
- Basilar membrane (cochlea), 551
- Basiliximab  
  immunosuppressant, 120  
  immunosuppression, 120
- Basophilia, 418
- Basophilic stippling  
  associated pathology, 426  
  sideroblastic anemia, 426
- Basophils, **418**  
  IgE antibody, 104  
  BAX protein, 208
- B-cell lymphomas  
  HIV-positive adults, 177
- B cells  
  activation, 103, 105  
  adaptive immunity, 99  
  anergy, 110  
  cell surface proteins, 110  
  disorders of, 116, 117  
  functions of, 99, 101  
  immunodeficiency infections, 118  
  neoplasms, 442  
  non-Hodgkin lymphoma, 438  
  spleen, 98
- BCG vaccine  
  IL-12 receptor deficiency and, 116
- BCL gene  
  mutation in lymphoma, 439  
  oncogenes, 225
- Bcl-2 protein, 208
- BCR-ABL, 225
- Bead-like costochondral junctions, 475
- Becker muscular dystrophy, 61
- Beckwith-Wiedemann syndrome, 368, 629
- Beers criteria, 250
- Behavioral therapy, 596
- Behavior modulation  
  limbic system and, 513
- Behçet syndrome, 484
- Bell palsy  
  facial nerve lesions, 550
- Bell-shaped distribution, 267
- Bence Jones proteinuria, 440
- Bendazoles, 159
- Bends, 475
- Beneficence (ethics), 270
- Benign paroxysmal positional vertigo, 552
- Benign prostatic hyperplasia, **678**  
  inhibitors for, 240
- Benign tumors, 221  
  bones, 476  
  breast, 673
- Benralizumab, 712
- Benzathine penicillin G, 198
- Benzene  
  aplastic anemia, 253
- Benzidine, 226

- Benzocaine, 571  
 Benzodiazepines  
   addictive risk, 566  
   alcohol withdrawal, 596  
 Beers criteria, 250  
   clinical use and adverse effects, 566  
   cocaine overdose, 595  
   epilepsy therapy, 564  
   epilepsy treatment, 564  
   intoxication and withdrawal, 594  
   mechanism, use and adverse effects, 566  
   naming convention for, 256  
   phobias, 586  
   sleep effects, 512  
   toxicity treatment for, 251  
 Benzoyl peroxide for acne, 491  
 Benztropine, 244, 568  
 Berkson bias, 265  
 Bernard-Soulier syndrome, 421, 436  
 Berry aneurysm, 534  
 Berylliosis, 701  
 Beryllium carcinogenicity, 226  
 $\beta_1$ -blockade, 293  
 $\beta_2$ -microglobulin  
   MHC I and II and, 100  
 $\beta_2$ -agonists  
   asthma, 712  
 $\beta$ -adrenergic agonist  
   potassium shifts, 614  
 $\beta$ -adrenergic agonists  
   potassium shifts, 614  
 $\beta$ -adrenergic effects  
   of T3, 339  
 $\beta$ -blockers  
   for pheochromocytomas, 359  
   for thyroid storm, 350  
   pheochromacytoma treatment, 359  
   thyrotoxicosis, 339  
 $\beta$ -blockers  
   acute coronary syndromes, 317  
   adverse effects of, 248  
   and epinephrine, 245  
   angina, 327, 331  
   antianginal therapy, 327  
   anticholinergic toxicity, 243  
   aortic dissection, 311  
   aortic dissections, 308  
   applications, actions and adverse effects, 248  
 Cardiomyopathy (hypertrophic), 248  
   chronic stable angina, 332  
   cocaine intoxication/withdrawal, 595  
   cocaine overdose, 595  
   dilated cardiomyopathy, 318  
   essential tremor, 537  
   for cocaine intoxication, 245  
   generalized anxiety disorder, 585  
   glaucoma, 248  
   glaucoma therapy, 573  
   heart failure, 247, 319  
   heart failure therapy, 319  
   hyperkalemia, 614  
   hypertrophic cardiomyopathy, 318  
   juxtaglomerular apparatus effects, 613  
   migraine headaches, 536  
   naming convention for, 257  
   overdose treatment, 331  
   phobias, 586  
   selectivity, 248  
   Starling curves, 294  
   toxicity treatment, 251
- $\beta$  cells  
   insulin secretion by, 342  
   pancreatic tumors, 361  
   Type 1 and Type 2 diabetes, 355  
 $\beta$ -dystroglycan  
   muscular dystrophy, 61  
 $\beta$  (Type II) error (statistical testing), 268  
 $\beta$ -galactosidase  
   E coli production, 144  
 $\beta$ -glucan, 200  
 $\beta$ -glucuronidase, 416  
 $\beta$ -hemolysis, 133  
 $\beta$ -hemolytic bacteria, 135  
   common colonization sites, 135  
*Streptococcus agalactiae* (Group A strep), 137  
*Streptococcus pyogenes* (Group A strep), 136  
 $\beta$ -hydroxybutyrate, 90  
 $\beta$ -interferon  
   multiple sclerosis, 541  
 $\beta$ -lactam antibiotics, 433  
 $\beta$ -lactam antibiotics, 187  
 $\beta$ -lactamase inhibitors, 188, 189  
 $\beta$ -oxidation, 48  
   very-long-chain fatty acids (VLCFA), 48  
 $\beta$ -prophage  
   Corynebacterium exotoxin encoding, 139  
 Beta rhythm (EEG), 512  
 $\beta$ -thalassemia  
   allelic heterogeneity, 57  
   anemia with, 428  
   chromosome abnormality, 64  
 $\beta$ -thalassemia major, 428  
 $\beta$ -thalassemia minor, 428  
 Betaxolol, 248, 573  
 Bethanechol, 243  
 Bevacizumab, 452  
 Bezafibrate, 328  
 Bias and study errors  
   types and reduction strategies, 266  
 Bicalutamide, 682  
 Bicarbonate  
   carbon dioxide transport, 694  
   overdose treatment, 235  
   pancreatic insufficiency, 391  
   salicylate toxicity, 251  
   secretion and action, 382  
   TCA toxicity, 235  
 Biceps brachii muscle  
   Erb palsy, 458  
 Biceps femoris, 462, 463  
 Biceps reflex, 527  
 Bicornuate uterus, 646  
 Bicuspid aortic valve  
   aortic dissection and, 311  
   coarctation of aorta and, 307  
   heart murmur with, 300  
   thoracic aortic aneurysms and, 310  
   Turner syndrome, 307  
 Bifid ureter, 603  
 Biguanide drugs, 363  
 Bilaminar disc, 636  
 Bilateral adenopathy, 700  
 Bilateral renal agenesis  
   Potter sequence, 602  
 Bile  
   composition and functions of, 384  
   secretin effect on, 381  
 Bile acid resins, 328  
   reabsorption of, 328  
   synthesis of, 48
- Bile canaliculus, 377  
 Bile ducts, 378  
 Biliary atresia, 403  
 Biliary cholangitis, primary autoantibody, 115  
 Biliary cirrhosis, 405  
   cystic fibrosis, 60  
 Biliary colic, 406  
 Biliary structures, 378  
 Biliary tract disease  
   gallstones, 378  
   hyperbilirubinemia with, 404  
*Clonorchis sinensis*, 160  
   pathology, epidemiology and features of, 405  
 Biliary tract infections  
   Enterococci, 137  
 Bilirubin, 385  
   hereditary hyperbilirubinemias, 404  
   liver marker, 400  
   toxic shock syndrome, 135  
 Bimatoprost, 573  
 Bimodal distribution, 267  
 Binge-eating disorder, 590, 599  
 Bioavailability, 233  
   area under the curve from, 233  
   calculation of, 233  
 Biochemistry  
   cellular, 46  
   genetics, 55  
   laboratory techniques, 52  
   metabolism, 73  
   molecular, 34  
   nutrition, 65  
 Biochemistry laboratory techniques  
   blotting procedures, 53  
   CRISPR/Cas9, 53  
   enzyme-linked immunosorbent assay, 54  
   fluorescence in situ hybridization, 55  
   gene expression modifications, 53, 56  
   karyotyping, 55  
   microarrays, 54  
   molecular cloning, 55  
   polymerase chain reaction, 52  
   RNA interference, 56  
 Biofilm-producing bacteria  
   in vivo, 128  
*Staphylococcus epidermidis*, 135  
*Pseudomonas aeruginosa*, 143  
 Biologic agents  
   naming conventions for, 258  
 Bipolar disorder  
   lithium for, 598  
   preferred drugs for, 596  
   types of, 584  
 Bipolar I, 584  
 Bipolar II, 584  
 Birbeck granules  
   Langerhans cell histiocytosis, 444  
 Birth, death with preterm, 279  
 Bismuth  
   mechanism and clinical use, 409  
 Bisoprolol, 248  
 Bisphosphonates  
   esophagitis with, 252  
   mechanism, use and adverse effects, 500  
   naming convention for, 256  
   osteogenesis imperfecta treatment, 51  
   osteoporosis treatment, 474
- "Bite cells", 424  
 Bitemporal hemianopia  
   craniopharyngioma, 546  
   optic chiasm compression, 534  
   pituitary lesions, 562  
   pituitary apoplexy, 347  
 Bitot spots, 66  
 Bivalirudin, 446  
 Black lung disease, 701  
 Bladder  
   bethanechol effect on, 243  
   BPH and, 678  
   development of, 642  
   extrophy, 647  
   genitourinary trauma, 651  
   placenta percreta invasion, 664  
   spasm treatment, 244  
   squamous cell carcinoma, 629  
   urachus, 642  
   urgency in cystitis, 244  
   urothelial carcinoma, 629  
 Bladder cancer  
   cisplatin/carboplatin for, 451  
   hematuria with, 618  
   hypercalcemia and, 229  
*Schistosoma haematobium*, 227  
 "Blast crisis", 442  
 Blastocyst implantation, 636  
*Blastomyces* spp  
   amphotericin B, 199  
   itraconazole, 199  
 Blastomycosis, 151  
 Bleeding  
   adenomatous polyps, 397  
   direct factor Xa inhibitors, 446  
   glycoprotein IIb/IIIa inhibitors, 447  
   thrombolytics, 447  
   variceal, 381  
 Bleeding time, 436, 500  
 Bleomycin  
   mechanism and clinical use, 449  
   pulmonary fibrosis, 254  
 Blepharospasm, 537  
 Blindness  
   giant cell arteritis, 484  
*Chlamydia trachomatis*, 148  
*Onchocerca volvulus*, 158  
*Toxocara canis*, 158, 159  
 neonatal, 142  
 Blistering skin disorders, 494  
 Blood  
   coagulation and kinin pathways, 422  
   in placenta, 640  
   oxygen content, 690  
   viscosity of, 692  
 Blood-brain barrier  
   anesthetics, 570  
   at hypothalamus, 513  
   function and mechanism, 511  
 L-DOPA, 569  
 Blood flow  
   autoregulation, 304  
   exercise response, 694  
 Blood groups, 415  
 Blood-nerve permeability barrier, 510  
 Blood pH  
   diuretic effects on, 632  
 Blood pressure  
   angiotensin II effects, 612  
   antianginal therapy, 327  
   cortisol effect on, 344  
   fenoldopam and, 327  
   renal disorders and, 615  
   sympathomimetic effect on, 245

- Blood-testis barrier, 652  
 Blood transfusions  
     components for, 438  
     reactions, 114  
     risks of, 438  
 Blood vessels  
     collagen in, 50  
     hereditary hemorrhagic telangiectasia, 324  
 Blood volume  
     regulation, 612  
 Bloody diarrhea  
     *Campylobacter jejuni*, 145  
     *Shigella*, 144  
     organisms causing, 179  
     ulcerative colitis vs Crohn disease, 392  
 Blotting procedures, 53  
 Blown pupil  
     CN III damage, 561  
     saccular aneurysms, 534  
 "Blue babies", 306  
 "Blueberry muffin" rash  
     cytomegalovirus, 182  
     *Toxoplasma gondii*, 182  
     rubella, 169, 182  
 Blue sclerae, 51  
 Blumer shelf, 389  
 BMPR2 gene, 703  
 Body compartments, 233  
 Body dysmorphic disorder, 586  
 Boerhaave syndrome, 387  
 Bombesin, 358  
 Bone cell biology, 469  
 Bone crises, 88  
 Bone disorders  
     adult T-cell lymphoma and, 439  
     lab values in, 476  
     Langerhans cell histiocytosis, 444  
     lytic ("punched out"), 440  
     osteogenesis imperfecta, 51  
 Bone formation, 468  
 Bone lesions  
     Burkitt lymphoma, 439  
 Bone marrow  
     cytokine stimulation of, 121  
     immune system organs, 96  
     myelofibrosis, 443  
     RBC inclusions in, 426  
     suppression, 199  
 Bone mineral density scan, 474  
 Bones  
     collagen in, 50  
     lytic/blastic metastases, 224  
     primary bone tumors, 476  
     renal osteodystrophy, 626  
 Bone tumors  
     benign, 476  
     malignant, 477  
 Bordet-Gengou agar, 126  
*Bordetella pertussis*, 143  
     culture requirements, 126  
     macrolides, 193  
     toxin production, 132  
     vaccines, 143  
*Borrelia burgdorferi*  
     animal transmission, 149  
     coinfection with, 157  
     Lyme disease, 146  
     tetracyclines, 192  
*Borrelia* spp  
     stains for, 125  
*Borrelia recurrentis*  
     animal transmission, 149  
     vectors, 161  
 Bortezomib, 453  
 Bosentan, 711  
 Botulinum toxin  
     lysogenic transduction, 130  
     passive antibodies for, 110  
     symptoms of, 138  
     toxin effects, 132  
 Bovine spongiform encephalopathy (BSE), 178  
 Bowen disease, 675  
 Bowenoid papulosis, 675  
 Bow legs (genu varum), 475  
 Bowman space, 606  
 Boxer's fracture, 468  
 Brachial artery, 465  
 Brachial plexus lesions  
     injury deficits and presentation, 458  
     Pancoast tumor, 710  
 Brachiocephalic syndrome, 710  
 Brachiocephalic vein, 710  
 Brachioradialis reflex, 527  
 Bradford Hill criteria, 261  
 Bradycardia  
     amiodarone and, 331  
     atropine for, 244  
     β-blockers and, 248  
 Bradykinin  
     angiotensin-converting enzyme inhibitor effects, 633  
     C1 esterase inhibitor deficiency, 107  
 BRAF gene  
     melanomas and, 498  
     oncogenes, 225  
     papillary thyroid carcinoma and, 351  
     serrated polyps and, 397  
 Brain  
     blood flow autoregulation, 304  
     embryologic derivation, 637  
     infarcts, 209  
     ischemia in, 210  
     metastasis to, 224  
 Brain abscesses  
     *Staphylococcus aureus*, 180  
     *Toxoplasma gondii*, 177  
     otitis media, 180  
     Viridans streptococci, 180  
 Brain cysts, 161  
 Brain death, 276, 517  
 Brain development  
     regional specification, 504  
 Brain injury  
     gastritis with, 389  
     hypopituitarism from, 347  
 Brain lesions (common), 528  
 Brain natriuretic peptide (BNP) in SIADH, 346  
     renin-angiotensin-aldosterone system, 612  
     signaling pathways for, 345  
 Brain stem  
     dorsal view, 520, 521  
     ventral view, 520  
 Brain/stem/cerebellar syndromes  
     multiple sclerosis, 541  
 Brain tumors  
     adult primary, 544  
     childhood primary, 546  
     hallucinations with, 582  
     metastatic source, 224  
 Branched-chain ketoacid dehydrogenase  
     vitamin B1 and, 66  
 BRCA1/BRCA2 genes, 225  
     DNA repair in, 39  
     tumor suppressor genes, 225  
 Breast cancer  
     aromatase inhibitors for, 680  
     hormonal contraception  
         contraindication, 681  
     hypercalcemia and, 229  
     incidence/mortality of, 223  
     invasive carcinomas, 674  
     noninvasive carcinomas, 674  
     oncogenes and, 225  
     paclitaxel for, 451  
     paraneoplastic cerebellar degeneration and, 229  
     presentation and characteristics, 674  
     trastuzumab for, 452  
     tumor suppressor genes and, 225  
 Breast diseases  
     benign, 673  
 Breast milk  
     prolactin and, 336  
 Breast/ovarian cancer  
     BRCA2 mutation, 64  
     incomplete penetrance, 56  
 Breast pathology, 673  
 Breathing  
     respiratory muscle weakness, 699  
 Breath sounds  
     bronchial, 704  
     diminished, 706  
     physical findings, 704  
 Brenner tumor, 670  
 Breslow thickness, 498  
 Brief psychotic disorder, 583  
 Brimonidine, 573  
 Brittle bone disease  
     gene defects in, 51  
 Broad ligament, 649  
 Broca area, 534  
     MCA stroke, 532  
 Broca (expressive) aphasia, 534  
 Bromocriptine, 568  
 Bronchi, 686  
 Bronchial carcinoid tumor, 709  
 Bronchiectasis  
     cystic fibrosis, 60  
     *Aspergillus fumigatus*, 153  
     Kartagener syndrome, 49  
 Bronchioles  
     histamine receptors and, 241  
 Bronchiolitis obliterans, 119, 707  
 Bronchitis  
     cystic fibrosis, 60  
     *Haemophilus influenzae*, 142  
 Bronchoconstriction, 712  
 Bronchodilation, 712  
     sympathetic receptors and, 241  
 Bronchogenic carcinomas  
     asbestosis and, 701  
     carcinogens causing, 226  
 Bronchogenic cysts, 684  
 Bronchopneumonia, 707  
 Bronchopulmonary dysplasia  
     free radical injury, 210  
     "Bronze diabetes", 405  
 Brown-Séquard syndrome, 549  
     Horner syndrome, 549  
 "Brown tumors", 476  
*Brucella* spp  
     culture requirements, 126  
     facultative intracellular, 127  
     disease, transmission and source, 149  
     zoonotic infections, 149  
 Brucellosis, 149  
 Brugada syndrome, 312, 315  
 Bruising  
     scurvy, 69  
 Brunner glands  
     bicarbonate production, 382  
     duodenum, 372  
 Bruxism, 512, 595, 596  
 B<sub>5</sub> (pantothenic acid)  
     solubility of, 65  
 BTK gene, 116  
 B-type natriuretic peptide, 303  
 Budd-Chiari syndrome, 402  
     portal hypertension in, 399  
 Budesonide, 712  
 Buerger disease, 484  
 Buffalo hump, 356  
 Bugs  
     causing food-borne illness, 178  
 Bulbus cordis, 290  
 Bulimia nervosa, 590  
     Mallory-Weiss syndrome, 387  
     preferred drugs for, 596  
     SSRIs for, 599  
 Bulk-forming laxatives, 411  
 Bullae, 493  
     characteristics, 489  
     dermatitis herpetiformis, 495  
     impetigo, 493  
     skin lesions, 489  
 Bull neck lymphadenopathy, 132  
 Bullous impetigo, 493  
 Bullous pemphigoid, 489  
     autoantibody, 115  
     pathophysiology and morphology, 494  
 Bulls-eye erythema, 146  
 Bumetanide, 631  
 BUN (blood urea nitrogen)  
     ornithine transcarbamylase deficiency, 83  
 Bundled payment, 278  
 Bundle of His, 302  
 Bunyaviruses  
     characteristics and medical importance, 167  
 Bupivacaine, 571  
 Bupivacaine, 571  
 Buprenorphine, 572  
     morphine and, 237  
     opioid detoxification, 600  
 Bupropion, 600  
     seizures with, 254  
*Burkholderia cepacia*  
     complex, 142  
 Burkitt lymphoma  
     chromosomal translocations and, 444  
     EBV, 165  
     occurrence and genetics, 439  
     oncogenes and, 225, 227  
     oncogenic microbes and, 227  
 Burnout vs fatigue, 281  
 Burns  
     classification, 497  
     shock with, 320  
     sunburn, 496  
     testosterone/methyltestosterone for, 682  
 "Burr cells", 424  
 Bursitis  
     prepatellar, 471  
 Burton line  
     lead poisoning, 429  
 Buspirone  
     mechanism and clinical use, 598  
 Busulfan  
     mechanism and clinical use, 451  
     toxicity, 451

Butorphanol, 572, 573  
 "Butterfly glioma", 544

**C**

C1 esterase inhibitor deficiency, 107  
 C5-C9 deficiencies, 107  
 CA 15-3/CA27-29 (tumor markers), 227  
 CA 19-9 (tumor marker), 227, 408  
 CA 125 (tumor marker), 227  
 CAAT box, 41  
 Cachexia, 228  
 TNF- $\alpha$ , 108  
 Café-au-lait spots  
 McCune-Albright syndrome, 57  
 Caffeine intoxication and withdrawal, 594  
 Calcification  
 dystrophic, 228  
 types of, 212  
 Calcineurin, 120  
 Calcinosis cutis, 487  
 Calcitonin  
 source, function, and regulation, 341  
 tumor marker, 227  
 Calcitonin gene-related peptide, 536  
 Calcitriol, 613  
 Calcium  
 in bone disorders, 476  
 in cardiac muscle, 301  
 in osteomalacia/rickets, 475  
 kidney stones, 69, 622  
 Calcium carbonate, 409  
 Calcium channel blockers, 326  
 angina, 326  
 contractility in, 293  
 coronary vasospasm, 251  
 cutaneous flushing, 251  
 gingival hyperplasia, 253  
 hypertension, 326  
 hypertension treatment, 324  
 hypertrophic cardiomyopathy, 318  
 mechanism, use and adverse effects, 326  
 Raynaud phenomenon, 486  
 Calcium channel blockers (class IV) antiarrhythmic drugs, 332  
 Calcium channels  
 ethosuximide effect on, 564  
 Lambert-Eaton myasthenic syndrome, 229  
 myocardial action potential, 301  
 opioid effect on, 572  
 pacemaker action potential, 301  
 Calcium homeostasis, 341  
 Calcium pyrophosphate deposition disease, 479  
 Calcium pyrophosphate deposition disease, 479  
 Calcium-sensing receptor (CaSR), 365  
 Calculous cholecystitis, 406  
 Calicivirus  
 characteristics of, 167  
 California encephalitis, 167  
 Calluses (dermatology), 489  
 Calretinin, 702  
 cAMP (cyclic adenosine monophosphate)  
 endocrine hormone messenger, 345  
 fructose bisphosphatase-2 and, 76  
 heat-labile/heat-stable toxin effects, 132  
 hyperparathyroidism, 353  
*Vibrio cholerae*, 146  
 CAMP factor, 137

*Campylobacter* spp  
 animal transmission, 149  
 bloody diarrhea, 179  
 reactive arthritis and, 481  
 transmission, 149  
*Campylobacter jejuni*, 145  
 Canagliflozin, 363  
 Cancer  
 common metastases, 224  
 deaths from, 279  
 epidemiology, 223  
 ESR in, 215  
 GI bleeding, 390  
 hallmarks of, 222  
 immune evasion in, 222  
 mortality of, 223  
 oncogenic microbes, 227  
 pneumoconioses, 701  
 Cancer therapy targets, 448  
 alkylating agents, 451  
 antibody-drug conjugates, 449  
 anticancer monoclonal antibodies, 452  
 anticancer small molecule inhibitors, 453  
 antimetabolites, 450  
 antitumor antibiotics, 449  
 cell cycle, 448, 449  
 microtubule inhibitors, 451  
 platinum compounds, 451  
 topoisomerase inhibitors, 452  
 Candesartan, 633  
*Candida albicans*, 153  
 HIV-positive adults, 177  
 in HIV patients, 177  
 in HIV positive adults, 177  
 skin infections, 116  
*Candida* spp, 321  
 amphotericin B, 199  
 echinocandins, 200  
 immunodeficiency infections, 118  
 infections in immunodeficiency, 118  
 in immunodeficiencies, 116  
 osteomyelitis, 180  
 vulvovaginitis, 181  
 Candidate identification number (CIN), 5  
 Candidiasis  
 cortisol and, 344  
*Candida albicans*, 153  
 nystatin, 199  
 Cannibalism, 178  
 "Cannibal" metastases, 666  
 Capacity-limited elimination, 234  
 Capecitabine  
 5-F-dUMP, 36  
 "Cape-like" sensory loss, 506  
 Capillary fluid exchange, 305  
 Capitate bone, 459  
 Capitation, 278  
 Caplan syndrome, 701  
 Capsule (bacterial), 124  
 Captain's wheel formation  
 Paracoccidioidomycosis, 151  
 Captopril, 633  
 Caput medusae, 375  
 Carbachol, 243, 573  
 Carbamazepine  
 agranulocytosis, 253  
 aplastic anemia, 253  
 epilepsy, 564  
 epilepsy therapy, 564  
 Carbamoyl phosphate, 83  
 Carbamoyl phosphate synthetase, 73  
 Carbamoyl phosphate synthetase I  
 urea cycle, 73  
 Carbapenems  
 mechanism and use, 190  
 Carbipoda/levodopa  
 mechanism, use and adverse effects, 569  
 Carbohydrate absorption, 383  
 Carbohydrate metabolism  
 inborn errors of, 80  
 Carbol fuchs, 125  
 Carbon dioxide ( $\text{CO}_2$ )  
 retention, 703  
 transport, 694  
 Carbon monoxide (CO)  
 blood oxygen in poisoning, 690  
 electron transport inhibition, 78  
 oxygen deprivation, 693  
 poisoning, 691  
 toxicity treatment, 251  
 Carbon tetrachloride  
 free radical injury and, 210  
 Carboplatin  
 mechanism and clinical use, 451  
 Carboplatin toxicity, 451  
 Carboxylases, 73  
 Carboxypeptidase, 383  
 Carcinoembryonic antigen (CEA)  
 (tumor marker), 227  
 Carcinogens, 226  
 griseofulvin, 200  
 Carcinoid syndrome  
 bronchial carcinoid tumors, 709  
 somatostatin in treatment, 381  
 Carcinoid tumors  
 biomarkers for, 227  
 immunohistochemical stains for, 227  
 octreotide for, 410  
 stomach, 389  
 Carcinoma in situ  
 cervical dysplasia, 669  
 ductal, 674  
 neoplastic progression, 220  
 penis, 675  
 Carcinomas  
 carcinogens, 226  
 invasive, 220  
 metastases of, 220  
 metastasis of, 224  
 mucodipidermoid, 386  
 nomenclature of, 221  
 oncogenes, 227  
 thyroid, 351  
 vulvar, 668  
 Cardiac and vascular function curves, 295  
 Cardiac arrest  
 antacid adverse effects, 409  
 hypermagnesemia, 615  
 Cardiac cycle, 296  
 Cardiac depression, 326  
 Cardiac function curves, 294  
 Cardiac glycosides  
 mechanism and clinical use, 329  
 Cardiac looping, 288  
 Cardiac output  
 exercise and, 693  
 V/Q mismatch and, 693  
 Cardiac output equations, 294  
 Cardiac output variables, 293  
 Cardiac pressures (normal), 304  
 Cardiac tamponade, 320  
 aortic dissection and, 311  
 jugular venous pulse in, 296  
 MI, 317  
 shock, 320  
 Cardiac tumors, 324  
 Cardinal (transverse cervical) ligament, 649  
 Cardinal veins, 290  
 Cardiogenic shock, 320  
 Cardiomyopathy  
 Chagas disease, 158  
 dilated, 318  
 familial amyloid, 213  
 hypertrophic, 318  
 Pompe disease, 87  
 restrictive/infiltrative, 318  
 $\beta$ -blockers, 248  
 Cardiotoxicity  
 methylxanthines, 712  
 TCA adverse effects, 599  
 Cardiovascular agents and molecular targets, 325  
 Cardiovascular drugs  
 naming conventions for, 257  
 reactions to, 251  
 Cardiovascular system  
 anatomy, 292  
 cardiac output variables, 293  
 embryology, 290  
 pathology, 306  
 pharmacology, 324  
 physiology, 293  
 systemic sclerosis and, 487  
 Carditis  
 Lyme disease, 146  
 rheumatic fever, 322  
 Carfilzomib, 453  
 Carina (trachea), 687  
 Carmustine  
 CNS toxicity, 451  
 pulmonary fibrosis, 254  
 Carnitine acyltransferase fatty acid oxidation, 73  
 Carotid artery  
 atherosclerosis in, 310  
 emboli from, 557  
 embryonic development, 289  
 Carotid massage, 303  
 Carotid sinus, 303  
 baroreceptors, 303  
 Carpal bones, 459  
 Carpal tunnel syndrome, 470  
 lunate dislocation, 459  
 nerve injury, 457  
 rheumatoid arthritis, 478  
 Carteolol, 573  
 Cartilage  
 collagen in, 50  
 fluoroquinolone damage to, 253  
 Cartilage damage, 204  
 Carvedilol, 248, 331  
 Casal necklace, 67  
 Caseating granulomas  
 in tuberculosis, 140  
 Case-control study, 260  
 Case fatality rate, 262  
 Caseous necrosis, 209  
 Case series study, 260  
 Caspases, 208  
 Caspofungin  
 echinocandins, 200  
 Casts in urine, 618  
 Catabolism of amino acids, 82  
 Catalase, 210  
 Catalase-positive organisms, 128  
 Cataplexy, 591  
 Cataract, 554  
 Cataracts, 80  
 corticosteroid toxicity, 120  
 diabetes mellitus and, 354  
 muscular dystrophy, 61

- rubella, 182  
sorbitol, 81  
Catecholamines  
  amphetamines and, 245  
  ephedrine and, 245  
pacemaker action potential, 301  
pheochromocytoma and, 359  
Catecholamine synthesis/tyrosine catabolism, **83**  
Cation exchange resins  
  mechanism, use, and adverse effects, 365  
Cats (disease vectors)  
  Cat scratch disease, 149  
  *Campylobacter jejuni*, 145  
  *Pasteurella multocida*, 149  
  *Toxoplasma gondii*, 156, 182  
  Tinea corporis, 152  
Cauda equina, 524  
Cauda equina syndrome, 546  
Caudal regression syndrome, 638  
Caudate  
  basal ganglia, 513  
  Huntington disease, 538  
Cavernous sinus, **562**  
  thrombosis with mucormycosis, 153  
Cavernous sinus syndrome, 562  
CCR5 protein  
  HIV and, 175  
  maraviroc, 203  
  viral receptor, 166  
CD1a protein, 444  
CD4+ cell count  
  disease association by levels, 177  
  disease associations by levels, 177  
  prophylaxis for HIV/AIDS patients, 198  
CD4 protein, 99, 100  
  viral receptor, 166  
CD5 protein  
  in CLL, 442  
CD8 protein, 100  
CD16 protein, 101, 110  
CD20 protein, 110  
  in CLL, 442  
CD21 protein, 110  
  viral receptor, 166  
CD23 protein  
  in CLL, 442  
CD25 protein  
  cell surface protein, 110  
CD28 protein, 110  
CD34 protein, 110, 216  
  leukocyte extravasation and, 216  
CD40 protein, 103, 110  
CDKN2A gene, 225  
CEA tumor marker, 398  
  colorectal cancer, 397  
Cefazolin, 189, 196  
  mechanism and use, 189  
Cefepime  
  mechanism and use, 189  
Cefotaxime, 189  
Cefotetan  
  mechanism and use, 188  
Cefoxitin  
  mechanism and use, 189  
Cefpodoxime  
  mechanism and use, 188  
Ceftaroline  
  mechanism and use, 189  
  MRSA, 198
- Ceftazidime  
  *Pseudomonas aeruginosa*, 143  
  mechanism and use, 189  
Ceftriaxone, 180  
  for gonococci, 142  
  for *Haemophilus influenzae*, 142  
  gonococci treatment, 142  
  *Chlamydia* spp, 146  
  mechanism and use, 189  
  meningococci, 142  
  *Salmonella typhi*, 144  
Cefuroxime  
  mechanism and use, 189  
Celecoxib, 255  
  mechanism, use and adverse effects, 500  
Celiac artery/trunk  
  branches of, 374  
  structures supplied, 374  
Celiac disease  
  autoantibody, 115  
  dermatitis herpetiformis association, 495  
  HLA subtype, 100  
  IgA deficiency, 115  
  mechanism and associations, 391  
Celiac sprue, 391  
Cell cycle phases, **46**  
  regulation of, 46  
Cell envelope (bacteria), **124**  
Cell injury, 207  
  irreversible, 207  
Cell lysis  
  hyperkalemia with, 614  
Cell-mediated immunity, 101  
Cell membrane  
  exotoxin lysis of, 133  
Cell surface proteins  
  association and functions, 110  
  leukocyte adhesion deficiency, 117  
Cell trafficking, **47**  
Cell types  
  labile, 46  
  permanent, 46  
  stable (quiescent), 46  
Cellular biochemistry, 46  
Cellular injury  
  cellular adaptations, **206**  
  reversible, 207  
Cellulitis, 493  
  *Pasteurella multocida*, 149  
Cell wall  
  bacteria, 124  
Cemiplimab, 452  
Central clearing  
  nuclei, 351  
  rash, 152  
Central diabetes insipidus, 346  
Central/downward transtentorial herniation, 547  
Central nervous system  
  origins of, 504  
Central nervous system (CNS)  
  anesthetic principles for, 570  
  antiarrhythmic adverse effects, 331  
  antiarrhythmic effects on, 330  
  cancer epidemiology, 223  
  depression, 566  
  naming conventions for, 256  
  nitrosoureas effect on, 451  
  posterior fossa malformations, **506**  
  shock from injury, 320  
Central nervous system stimulants, **596**  
Central pontine myelinolysis, 542  
Central post-stroke pain syndrome, 533  
Central precocious puberty, 660  
Central retinal artery occlusion, 555, **557**  
Central sleep apnea, 703  
Central tendency measures, 267  
Central vertigo, 552  
Centriacinar emphysema, 698  
Cephalexin  
  mechanism and use, 189  
Cephalosporins  
  disulfiram-like reaction, 254  
  *Pseudomonas aeruginosa*, 143  
  mechanism and clinical use, **189**  
  mechanism and use, 189  
  pseudomembranous colitis, 252  
Ceramide trihexoside  
  in sphingolipidoses, 88  
Cerebellar degeneration  
  paraneoplastic, 229  
Cerebellar lesions  
  hemisphere, 528  
  lateral, 515  
  medial, 515  
  tonsillar herniation, 547  
  vermis, 528  
  vertigo with, 552  
Cerebellum  
  agenesis of vermis, 506  
  ectopia of tonsils, 506  
  herniation of, 506  
  input/output of, **515**  
Cerebral aqueduct of Sylvius, 520  
Cerebral artery distributions, 518  
Cerebral cortex  
  aphasia, 531  
  arterial distribution, **518**  
  dominant parietal lesion effects, 528  
  functional areas of, **517**  
  hemineglect, 532  
  nondominant parietal lesion effects, 528  
  visual field defects, 532  
Cerebral edema  
  therapeutic hyperventilation, 517  
Cerebral hemispheres  
  holoprosencephaly, 505  
Cerebral palsy  
  tizanidine, 572  
Cerebral perfusion pressure (CPP), 517  
“Cerebriform” nuclei, 439  
Cerebrospinal fluid (CSF)  
  albuminocytologic dissociation, 542  
  blood-brain barrier and, 511  
  circulation of, 511, 519, 520  
  findings in meningitis, 180  
  Guillain-Barré syndrome, 542  
  hydrocephalus, 540  
  multiple sclerosis, 541  
  neurodegenerative disorders, 538, 539  
  poliomyelitis, 549  
Cerebrovascular disease  
  diabetes mellitus, 354  
Certolizumab, 502  
Cervical cancer  
  epidemiology of, 667  
  hydronephrosis with, 623  
  oncogenic microbes and, 227  
Cervical pathology  
  dysplasia and carcinoma in situ, 669  
  invasive carcinoma, 669  
Cervical rib, 458  
Cervicitis  
  sexually transmitted infections, 184  
Cervix  
  epithelial histology, 650  
  lymphatic drainage of, 648  
  pathology of, 669  
  punctate hemorrhages, 158  
Cestode infections  
  diseases and treatment, 160  
Cetirizine, 710  
Cetuximab, 452  
cGMP, 303  
cGMP (cyclic guanosine monophosphate)  
  endocrine hormone messenger, 345  
  male sexual response, 651  
Chagas disease, 158  
  achalasia in, 386  
Chalk-stick fractures, 475  
Challenging patient scenarios, **276-277**  
Chancroid  
  clinical features and organisms, 184  
Chaperone protein, **45**  
Charcoal yeast extract agar, 126  
Charcoal yeast extract culture  
  *Legionella pneumophila*, 126, 143  
Charcot-Bouchard microaneurysm, 534  
Charcot-Bouchard microaneurysm), 531  
Charcot joints  
  syphilis, 147  
  tabes dorsalis and, 548  
Charcot-Leyden crystals, 698  
Charcot-Marie-Tooth disease, 542  
Charcot triad, 407  
Charging tRNA, 44  
Chédiak-Higashi syndrome  
  immunodeficiencies, 117  
Cheilosis, 67, 428  
Chelation  
  hemochromatosis, 405  
  lead poisoning, 429  
Chemokines, 108  
  delayed hypersensitivity, 112  
Chemoreceptors, 303  
Chemoreceptor trigger zone (CTZ), 511  
Chemotherapy  
  amelioration of adverse effects, **453**  
  cell types affected by, 46  
  MDRI and responsiveness to, 228  
  neutropenia with, 433  
  ondansetron, 410  
  Pseudo-Pelger-Hüet anomaly, 413  
Chemotoxicities, **454**  
Cherry hemangiomas, 492  
“Cherry red” epiglottis, 142  
Cherry-red spot (macula), 557  
  lysosomal storage disease, 88  
Chest pain  
  panic disorder, 586  
  pneumothorax, 706  
Chest wall  
  elastic properties, 689  
  in restrictive lungs disease, 699  
Chest X-rays  
  aortic dissections on, 311  
  balloon heart on, 318  
  eggshell calcification, 701  
  notched ribs on, 307  
  widened mediastinum on, 137  
Cheyne-Stokes respirations, 703  
  sleep apnea, 703  
Chiari malformations (I and II), 506

- Chickenpox  
rash, 183  
VZV, 165
- Chief cells (parathyroid), 340
- Chief cells (stomach), 382
- Chikungunya virus  
characteristics, 170
- Child abuse  
osteogenesis imperfecta and, 51  
types, signs and epidemiology, 579
- Childbirth  
brachial plexus injury in, 458  
death with preterm, 279  
Graves disease and, 350  
low birth weight, 658  
oxytocin and uterine contractions, 336, 659  
peripartum mood disturbances, 585  
progesterone levels after, 654  
Sheehan syndrome after, 347  
stress incontinence and, 623
- Childhood diseases/disorders  
behavioral, 580  
common fractures, 474  
hip dysplasia, 473  
leukocoria, 557  
musculoskeletal conditions, 473  
pathogens and findings in  
unvaccinated, 186  
primary brain tumors, 546
- Childhood/early-onset behavior disorders, 580
- Child neglect, 579
- Children  
causes of death, 279  
Chi-square ( $\chi^2$ ) test, 269  
*Chlamydia* spp, 148, 184  
macrolides, 193  
pneumonia, 707  
sexually transmitted infection, 184  
stains for, 125  
tetracyclines, 192  
*Chlamydia trachomatis*  
eosinophilia, 149  
pelvic inflammatory disease, 149  
pneumonia, 179  
prostatitis, 678  
serotypes, 149  
urinary tract infections, 624
- Chlamydophila pneumoniae*, 148  
pneumonia, 179
- Chlamydophila psittaci*  
atypical pneumonia, 148  
transmission, 149
- Chloramphenicol  
aplastic anemia and, 253  
gray baby syndrome, 253  
mechanism and clinical use, 192  
protein synthesis inhibition, 191
- Chlordiazepoxide, 566  
alcohol withdrawal, 596
- Chlorhexidine for sterilization/disinfection, 204
- Chloride channels  
cystic fibrosis, 60
- Chlorine for disinfection/sterilization, 204
- Chloroprocaine, 571
- Chloroquine, 157  
malaria, 157  
mechanism and clinical use, 200
- Chlorpheniramine, 710
- Chlorpromazine, 597
- Chlorpropamide, 363
- Chlorthalidone, 632
- Chocolate agar  
*Haemophilus influenzae*, 126, 142
- Cholangiocarcinoma, 407
- Cholangiocarcinomas  
*Clonorchis sinensis*, 160  
oncogenic microbes and, 227
- Cholangitis, 378, 392, 406
- Cholecalciferol, 70
- Cholecystectomy, 406, 407
- Cholecystitis, 406
- Cholecystokinin (CCK)  
source and action of, 381
- Choledocholithiasis, 406  
acute pancreatitis, 405  
Crohn disease, 406  
octreotide and, 410  
related pathologies, 406
- Cholera toxin  
lysogenic phage infection, 130  
mechanism, 132
- Cholestasis serum markers, 400
- Cholesteatoma, 552
- Cholesterol  
atherosclerosis, 310  
cholelithiasis and, 406  
in bile, 384  
lipid-lowering agents, 328  
synthesis of, 48, 74
- Cholesteryl ester transfer protein, 93
- Cholestyramine, 328
- Cholinergic agonists  
naming conventions for, 257
- Cholinergic effects  
cardiac glycosides, 329
- Cholinesterase inhibitors  
diarrhea with, 252  
neuromuscular blockade reversal, 571
- Cholinomimetic agents, 243  
glaucoma therapy, 573
- Chondrocalcinosis, 479
- Chondrocytes  
achondroplasia, 474  
bone formation, 468  
osteoarthritis, 478
- Chondroma, 476
- Chondrosarcoma  
epidemiology and characteristics, 477
- Chordae rupture, 300
- Chorea  
brain lesions, 528  
Huntington disease, 537  
movement disorders, 537
- Choriocarcinoma, 666, 677  
hCG in, 658  
metasis of, 224  
methotrexate for, 450  
testicular, 677  
theca-lutein cysts and, 670
- Chorionic villi  
hydatidiform moles, 666  
placenta, 640
- Chorioretinitis  
congenital toxoplasmosis, 182  
*Toxoplasma gondii*, 156
- Choristomas, 221
- Choroid layer (ophthalmology)  
inflammation, 553
- Choroid plexus (CNS), 520
- Christmas tree distribution, 496
- Chromaffin cells  
pheochromocytomas, 359
- Chromatin structure, 34
- Chromatolysis, 510
- Chromium carcinogenicity, 226
- Chromogranin, 227, 709  
tumor identification, 228
- Chromones for asthma, 712
- Chromosome abnormalities  
Familial adenomatous polyposis, 64
- Chromosomal translocations  
leukemias and lymphomas, 444
- chromosome 3p, 543
- Chromosome abnormalities  
gene associations with, 64  
hemochromatosis, 405  
hydatidiform mole, 666  
karyotyping for, 55  
nephroblastoma, 629  
nondisjunction (meiosis), 63  
omphaloceles, 368  
polyposis syndrome, 397  
renal cell carcinoma, 628
- Chromosome disorders  
sex chromosomes, 661
- Chronic bronchitis, 698
- Chronic disease, anemia of, 431
- Chronic gastritis  
causes of, 389
- Chronic granulomatous disease (CGD)  
immunodeficiencies, 117  
recombinant cytokines for, 121  
respiratory burst in, 109
- Chronic inflammation, 217
- Chronic ischemic heart disease, 312
- Chronic kidney disease  
erythropoietin in, 613
- Chronic lymphocytic leukemia (CLL), 442
- Chronic lymphocytic leukemia/small lymphocytic, 442
- Chronic mesenteric ischemia, 396
- Chronic mucocutaneous candidiasis, 116
- Chronic myelogenous leukemia (CML), 418, 442  
busulfan for, 451  
chromosomal translocations and, 444  
oncogenes and, 225
- Chronic myeloproliferative disorders  
RBCs/WBCs/platelets in, 442, 443
- Chronic obstructive pulmonary disease (COPD)  
albuterol for, 231
- Chronic pancreatitis, 407  
pancreatic insufficiency from, 391
- Chronic pyelonephritis, 624
- Chronic renal failure, 626  
hyperphosphatemia with, 352
- Chronic respiratory diseases  
death in children, 279  
pneumoconioses, 699  
with chronic inflammatory diseases, 707
- Chronic thromboembolic pulmonary hypertension, 703
- Chronic transplant rejection, 119, 120
- Chvostek sign, 615  
hypocalcemia, 615  
hypoparathyroidism, 352
- Chylomicrons, 94  
lipoprotein lipase in, 93
- Chylothorax, 705
- Chymotrypsin, 383
- Cidofovir  
mechanism and clinical use, 202
- Ciguatoxin, 250
- Cilastatin  
imipenem and, 190  
seizures with, 254
- Ciliary ganglia, 558
- Cilia structure, 49
- Ciliated cells, 686
- Cilostazol, 447
- Cilostazola, 249
- Cimetidine  
cytochrome P-450 and, 255  
histamine blockers, 409
- Cinacalcet  
mechanism, use, and adverse effects, 365
- Cinchonism  
antiarrhythmic causing, 330  
neurologic drug reaction, 254
- Cingulate gyrus  
limbic system, 514
- Cingulate (subfalcine) herniation, 547
- Ciprofloxacin  
cytochrome P-450 and, 255  
fluoroquinolones, 195  
for Crohn disease, 392  
meningococci, 142  
prophylaxis, 198
- Circadian rhythm  
hypothalamic control, 513  
sleep physiology, 512
- Circle of Willis, 519  
saccular aneurysms, 534
- Circulatory system  
fetal, 291
- Circumoral pallor  
group A streptococcal pharyngitis, 136
- Cirrhosis  
gynecomastia, 673  
hyperbilirubinemia in, 403  
portal hypertension and, 399
- Cisplatin, 451  
targets of, 452  
toxicities of, 254
- Citalopram, 599
- c-KIT gene, 225
- CK-MB  
cardiac biomarker, 312  
chronic ischemic heart disease, 312  
MI diagnosis, 314
- Cladribine, 450  
for hairy cell leukemia, 442  
mechanism and clinical use, 450
- clarithromycin, 193  
*Helicobacter pylori*, 146  
macrolides, 193
- Clasp knife spasticity, 547
- Class IA antiarrhythmics, 330
- Class IC antiarrhythmics, 330
- Classical conditioning, 576
- Class III antiarrhythmics, 331
- Classic galactosemia, 80
- Class II antiarrhythmics, 331
- Class III antiarrhythmics, 331
- Class IV antiarrhythmics, 332
- Class switching  
B cells, 103  
thymus-dependent antigens, 105
- Clathrin, 47
- Claudication  
atherosclerosis, 310  
Buerger disease, 484  
giant cell arteritis, 484
- Clavicle fractures, 470
- Clavulanate  
*Haemophilus influenzae*, 142

- Clavulanic acid, 189  
 Clawing (hand), 460  
   Klumpke palsy, 458  
 Clearance (CL) of drugs, 233  
 Clear cell adenocarcinoma, 668  
   DES and, 680  
 Cleavage in collagen synthesis, 50  
 Cleft lip and palate  
   development, 645  
   neural tube defects, 505  
   Patau syndrome, 63  
   Pierre Robin sequence, 644  
 Clevidipine, 326  
   for hypertensive emergency, 326  
 Clindamycin  
   bacterial vaginosis, 148  
   *Clostridium difficile* and, 138  
   mechanism and use, 192  
   metronidazole vs, 192  
   protein synthesis inhibition, 191  
   pseudomembranous colitis with, 252  
 Clinical reflexes/nerve roots, **527**  
 Clinical vignette strategies, 23  
 "Clock-face" chromatin, 419  
 Clock-face chromatin, 440  
 Clofazimine  
   *Mycobacterium leprae*, 141  
 Clomiphene  
   estrogen receptor modulators, 680  
   hot flashes with, 252  
 Clomipramine, 599  
 Clonidine, 246  
 Cloning methods (laboratory technique), 54  
*Clonorchis sinensis*  
   cholangiocarcinoma, 227  
   diseases and treatment, 160  
 Clopidogrel  
   acute coronary syndromes, 317  
   for ischemic stroke, 529  
   mechanism and clinical use, 447  
   thrombogenesis and, 421  
 Closed-angle glaucoma, 555  
   pilocarpine for, 243  
*Clostridium botulinum*, **138**  
   food poisoning, 178  
   therapeutic uses, 138  
   toxin production, 132  
*Clostridium difficile*  
   antibiotic use, 185  
   infection risk with proton pump inhibitors, 409  
   metronidazole, 195  
   nosocomial infection, 185  
 PPI association, 138  
   proton pump inhibitor use, 409  
   toxins and effects of, 138  
   vancomycin, 190  
   watery diarrhea, 179  
*Clostridium* spp, 138  
   anaerobic organism, 127  
   exotoxins, 138  
*Clostridium perfringens*, **138**  
   clindamycin, 192  
   exotoxin production, 133  
   food poisoning, 178  
   toxins produced, 138  
   watery diarrhea, 179  
*Clostridium tetani*, 138  
   toxin production, 132  
 Clotrimazole, 199  
 Clotting factors, 71  
 Clozapine, 597  
   agranulocytosis with, 253  
 Clubbing (digital), 699  
   cystic fibrosis, 60  
   Eisenmenger syndrome, 307  
   paraneoplastic syndromes, 229  
   pathophysiology, 704  
 Club cells, 685  
 Clue cells  
   bacterial vaginosis, 148, 181  
 Cluster A personality disorders  
   characteristics of, 588  
   paranoid, 588  
   schizoid, 588  
   schizotypal, 588  
 Cluster B personality disorders  
   antisocial, 588  
   borderline, 588  
   histrionic, 588  
   narcissistic, 588  
 Cluster C personality disorders  
   avoidant, 589  
   dependent, 589  
   obsessive-compulsive, 589  
 Cluster headaches  
   characteristics and treatment, 536  
   tryptans, 567  
 c-MYC gene, 225  
 CN III IV VI palsies, 561  
 CNS lymphomas  
   HIV-positive adults, 177  
   oncogenic microbes and, 227  
 Coagulation disorders, 435  
   defect in Chédiak-Higashi syndrome, 117  
   hemophilia, 435  
   mixed platelet/coagulation, 437  
   vitamin K and, 435  
 Coagulation pathways, **422**  
 Coagulative necrosis, 209  
   MI, 313  
 Coagulopathy  
   postpartum hemorrhage, 665  
   uterine bleeding with, 657  
 Coal workers' pneumoconiosis, 701  
 CoA production, 74  
   vitamin B<sub>5</sub> and, 67  
 Coarctation of aorta, 307, 308  
 Cobalamin, 69  
 Cocaine  
   overdose/intoxication treatment, 595  
   teratogenicity of, 638  
 Coccidi bacteria  
   antibiotic tests, 134  
*Coccidioides* spp  
   stain for, 125  
   treatment, 199  
 Coccidioidomycosis, 151  
   erythema nodosum and, 496  
 Cochlea  
   inner ear, 551  
   presbycusis, 551  
 Codeine, 572  
 Codominance, 56  
 Codons  
   amino acid specification by, 37  
   genetic code features, **37**  
   start and stop, **44**  
 Cofactors, 66  
   biotin, 66, 69  
   cobalamin, 67  
   copper, 51  
   Menkes disease, 51  
   pantothenic acid, 67  
   phenylketonuria, 84  
   pyridoxine, 67  
 pyruvate dehydrogenase complex, 76  
 thiamine, 66  
 vitamin K, 69  
 Cognitive behavioral therapy (CBT), 580  
   ADHD, 580  
   anxiety disorders, 586  
   bipolar disorder, 584  
   body dysmorphic disorder, 586  
   goals of, 596  
   obsessive-compulsive disorder, 586  
   panic disorder, 586  
   phobias, 586  
   postpartum depression, 585  
 Cohort study, 260  
 Coin lesion (X-ray)  
   x-ray signs, 709  
 Cola-colored urine, 620  
 Colchicine, 55  
   agranulocytosis, 253  
   calcium pyrophosphate deposition disease, 479  
   diarrhea with, 252  
   gout, 501  
   microtubules and, 48  
   myopathy with, 253  
 "Cold enrichment", 139  
 Colectomy  
   adenomatous polyposis, 397  
   inflammatory bowel disease, 392  
 Colesevelam, 328  
 Colestipol, 328  
 Colistin  
   *Pseudomonas aeruginosa*, 143  
   polymyxin E, 193  
 Colitis  
   *Clostridium difficile*, 138  
   oral vancomycin, 190  
   pseudomembranous, 179, 188  
 Collagen, **50**  
   decreased/faulty production, 50  
   epithelial cell junctions and, 488  
   osteoblast secretion of, 469  
   polyostotic fibrous dysplasia and, 57  
   scar formation, 219  
   synthesis and structure, **50**  
   types of, **50**  
   vitamin C in synthesis, 69  
   wound healing, 217  
 Collecting tubules  
   potassium-sparing diuretics and, 632  
 Colles fracture, 474  
 Colon  
   histology of, 372  
   ischemia in, 210  
 Colon cancer, 398  
   adenomatous polyposis and, 397  
   5-Fluorouracil, 450  
   incidence/mortality in, 223  
   *Staphylococcus galolyticus* and, 137  
   Lynch syndrome, 39  
   oncogenes and, 225  
   *S bovis* endocarditis, 137  
   serrated polyps and, 397  
   tumor suppressor genes and, 225  
 Colonic ischemia, 373, 396  
 Colonic polyps, 397  
   histologic types and characteristics, **397**  
   non-neoplastic, 397  
 Colony stimulating factor  
   clinical use, 121  
 Colorado tick fever, 167  
 Color blindness, 197  
 Colorectal cancer (CRC)  
   adenomatous polyposis progression, 397  
   diagnosis, presentation and risks, **398**  
   molecular pathogenesis of, 399  
 Colovesical fistulas, 393  
 Coma  
   hepatic encephalopathy, 400  
   herniation syndromes, 547  
   hyponatremia, 615  
   *Toxocara canis*, 159  
   *Trypanosoma brucei*, 156  
   rabies, 171  
   thyroid storm, 350  
 Combined contraception, 681  
 Comedones, 491  
 Commaless genetic code, 37  
 Comma-shaped rods, 145  
 Common bile duct, 371, 378  
 Common brain lesions  
   area and consequences of, **528**  
 Common cold, 167  
 Common (fibular) peroneal, 462  
 Common peroneal nerve, 462  
 Common statistical tests, **269**  
 Common vaginal infections, **181**  
 Common variable immunodeficiency (CVID), 116  
 Communicating hydrocephalus, 540  
 Communicating with patients with disabilities, **275**  
 Communication with patient, 272  
 Compartment syndrome, 472  
 Competitive antagonist, 237  
 Competitive inhibitors, 232  
 Complement  
   activation and function, **106**  
   eculizumab, 122  
   endotoxin activation, 133  
   immunodeficiency infections, **118**  
   innate immunity, 99  
   transplant rejection, 120  
 Complementation (viral), 162  
 Complement disorders, **107**  
 Complement protein C5  
   immunotherapy target, 122  
 Complement protein deficiencies, 107  
 Complement regulatory protein deficiencies, 107  
 Complete (third-degree) AV block, 316  
 Complex partial seizures, 535  
 Complex renal cysts vs simple cysts, 627  
 Compliance (lung and chest wall), 689  
 Comprehensive Basic Science Examination (CBSE), 11  
 Comprehensive Basic Science Self-Assessment (CBSSA), 11  
 Computer-Based Test (CBT)  
   environment of, 3–4  
   exam schedule for, 7–8  
   structure of, 3  
 COMT inhibitors, 569  
 Conduct disorder, 580  
 Conducting zone (respiratory tree), 686  
 Conduction aphasia, 534  
 Conductive hearing loss, 552  
 Condyloma acuminatum  
   HPV and, 491  
 Condylomata acuminata  
   sexual transmission, 184

- Condylomata lata  
syphilis, 147, 184
- Confidence intervals, **269**
- Confidentiality, 270  
behavioral science ethics, 270  
exceptions to, 273  
in abuse, 273
- Confluence of the sinuses, 520
- Confounding bias, 266
- Congenital adrenal hyperplasias, 343
- Congenital heart diseases, 306  
atrial septal defect (ASD), 307  
coarctation of the aorta, 307  
defect associations, 308
- D-transposition of great vessels, 306
- Ebstein anomaly, 306
- Eisenmenger syndrome, 307
- patent ductus arteriosus, 307
- persistent truncus arteriosus, 306
- phenylketonuria, 84
- pulmonary arterial hypertension, 703  
right-to-left shunts, 306
- rubella, 182
- Tetralogy of Fallot, 306
- total anomalous pulmonary venous return, 306
- tricuspid atresia, 306
- ventricular septal defect, 307
- Congenital hypothyroidism, 349
- Congenital long QT syndrome, 315
- Congenital lung malformations, **684**
- Congenital malformation mortality, 279
- Congenital megacolon, 394
- Congenital nevus, 489
- Congenital penile abnormalities, **647**
- Congenital rubella  
cardiac defect associations, 308  
heart murmur, 300  
presentation of, 169
- Congenital solitary functioning kidney, 603
- Congenital syphilis, 147
- Congestion (respiratory)  
with lobar pneumonia, 707
- Congo red stain  
amyloid deposits, 213  
medullary carcinoma, thyroid, 351
- Conivaptan, 364  
SIADH, 364
- Conjugated (direct)  
hyperbilirubinemia, 403
- Conjugate vaccines, 127
- Conjugation (bacterial genetics), 130
- Conjunctival suffusion/injection eye disorders, 147
- Conjunctivitis, 148  
causes of, 553  
chlamydia, 184  
gonococcal prophylaxis, 198
- Haemophilus influenzae*, 142
- Loa loa, 159  
reactive arthritis, 481
- rubeola, 170, 183
- Zika virus, 172
- Connective tissue  
drug reactions, **253**  
tumor nomenclature, 221
- Connective tissue diseases  
aortic dissection and, 310  
aortic dissection, 311  
pulmonary arterial hypertension, 703  
thoracic aortic aneurysms and, 310
- Consensual light reflex, 558
- Consent  
healthcare proxy, 277  
informed, 271
- Consolidation (lung)  
lobar pneumonia, 707  
physical findings, 704
- Constipation  
anal fissures, 376  
calcium channel blockers, 326
- Hirschsprung disease, 394  
irritable bowel syndrome, 394
- laxative treatments, 411
- loperamide, 410
- ondansetron, 410
- ranolazine, 327
- vincristine, 451
- Constrictive pericarditis  
jugular venous pulse in, 296
- Contact dermatitis  
Type IV hypersensitivity, 113
- Continuous heart murmurs, 300
- Contraception  
methods for, 681  
parental consent for minors and, 272
- progestins for, 681
- Contractility, 293
- Contraction alkalosis, 632
- Conversion disorder, 589
- Coombs test, 420, 433
- Cooperative kinetics, 232
- COPD (chronic obstructive pulmonary disease)  
organisms causing pneumonia, 179
- COPI/COPII proteins, 47
- Copper  
deficiency, 429  
toxicity, 251
- Copper intrauterine device, 681
- Copper metabolism  
Wilson disease, 405
- Coprolalia, 580
- Cord factor, 140
- Cori disease, 87
- "Corkscrew" esophagus, 387
- Corkscrew fibers, 546
- "Corkscrew" hair, 69
- Cornea  
astigmatism, 553  
collagen in, 50
- Corneal arcus  
familial hypercholesterolemia, 94  
hyperlipidemia, 309
- Corneal reflex, 523
- Corneal squamous metaplasia, 66
- Corneal vascularization, 67
- Coronary arteries  
atherosclerosis in, 310
- Coronary artery disease  
atrial fibrillation and, 316  
diabetes mellitus and, 354  
hormonal contraception with, 681  
sudden cardiac death, 312
- Coronary blood supply, 292
- Coronary sinus  
anomalous pulmonary return, 306  
development, 290
- Coronary steal syndrome, **312**
- Coronary vasospasm, 251  
triptans and, 567
- Coronaviruses  
characteristics and medical importance, 167
- genomes of, 163
- Cor pulmonale  
heart failure, 319
- pneumoconioses, 701
- pulmonary hypertension, 702
- Corpus cavernosum  
lymphatic drainage of, 648
- Corpus luteum  
hCG and, 658  
progesterone production, 654
- Corrected reticulocyte count, 427
- Correlation coefficient (*r*), 270
- Cortical signs, 532
- Corticopapillary osmotic gradient, 612
- Corticosteroid-binding globulin, 344
- Corticosteroids  
avascular necrosis of bone, 475
- cataracts, 554
- Crohn disease, 392
- Cushing syndrome, 356  
giant cell arteritis, 484
- hyperglycemia with, 252
- lymphopenia, 433
- lymphopenia with, 433
- microscopic polyangiitis, 485
- osteoporosis with, 253
- pancreatitis with, 252
- polymyalgia rheumatica treatment, 483
- Takayasu arteritis, 484
- thyroid storm, 350
- Corticotropin-releasing hormone (CRH)  
cortisol regulation, 344
- function of, 336
- signaling pathways of, 345
- Cortisol  
in Cushing syndrome, 356
- signaling pathways for, 345
- source, function, and regulation, 344
- Corynabacterium diphtheriae, 186
- Corynebacterium diphtheriae*, **139**  
culture requirements, 126
- culture requirements for, 126
- exotoxin effects, 139
- exotoxin production, 132
- Costovertebral angle tenderness, 624  
acute interstitial nephritis, 625
- kidney stones, 622
- urinary catheterization, 185
- urinary tract infections, 181
- Cough  
ACE inhibitors, 254
- chronic bronchitis, 698
- from ACE inhibitors, 633
- gastroesophageal reflux disease, 387
- hypersensitivity pneumonitis, 699
- lung cancer, 709
- nonproductive, 140
- staccato, 149
- whooping, 132, 143
- Cough reflex, 523
- Councilman bodies  
yellow fever, 171
- Countertransference, 576
- Courvoisier sign, 378, 408
- Covalent alterations, 45
- COVID-19  
antiviral therapy, 201
- characteristics, **172**
- RNA viruses, 167
- Cowpox, 164
- COX-2 gene  
colorectal cancer and, 399
- Coxiella burnetii*  
animal transmission, 149
- Q fever, 149
- Coxsackievirus  
acute pericarditis, 323
- picornavirus, 183
- presentation, 168
- rashes of childhood, 183
- C-peptide  
insulin and, 342
- with insulinomas, 361
- CpG island methylator phenotype (CIMP), 397
- Crackles (physical findings), 704
- Cranial nerve palsies  
CN III, 561
- CN III, IV, VI, **561**
- CN IV, 561
- CN VI, 561
- osteopetrosis, 475
- Cranial nerve reflexes  
afferent/efferents for, **523**
- Cranial nerves  
common lesions, **550**
- function and type, **523**
- location of nuclei, 521
- pharyngeal arch derivation, **644**
- reflexes of, 521
- ventral brain stem view, 520
- Craniopharyngioma, 637  
description and histology, 546
- hypopituitarism with, 347
- Craniotubes, 475
- C-reactive protein (CRP), 214
- Creatine kinase, 203
- Creatinine  
ACE inhibitor effects, 633
- clearance of, 606
- Creatinine clearance  
glomerular filtration rate and, 606
- Cremasteric reflex, 462, 527
- Crepitus  
esophageal perforation, 387
- necrotizing fasciitis, 493
- soft tissue, 138
- Crescentic glomerulonephritis, 620
- CREST syndrome  
autoantibody, 115
- Raynaud syndrome and, 486
- sclerodermal esophageal dysmotility, 387
- Creutzfeldt-Jakob disease  
myoclonus with, 537
- prion disease, 178
- symptoms and histologic findings, 539
- "Crew cut" (skull X-ray), 432
- Cricothyroid muscle, 644
- Cri-du-chat syndrome, **64**
- Crigler-Najjar syndrome, 404  
hyperbilirubinemia in, 403
- Crimean-Congo hemorrhagic fever, 167
- CRISPR/Cas9, **53**
- Crohn disease  
azathioprine, 120
- natalizumab, 122
- sulfasalazine for, 410
- therapeutic antibodies for, 122
- ulcerative colitis comparison, 392
- vitamin B<sub>12</sub> deficiency, 69
- Cromolyn, 712
- Cross-linking in collagen synthesis, 50
- Cross-sectional study, 260

- Croup, 169  
 acute laryngotracheobronchitis, **170**  
 paramyoviruses, 167, 169  
 pulsus paradoxus in, 320
- Crust (skin)  
 basal cell carcinoma, 498  
 characteristics, 489  
 impetigo, 493  
 varicella zoster virus, 493
- Cryoprecipitate  
 transfusion of, 438
- Cryptococcal meningitis, 199
- Cryptococcosis, 153
- Cryptococcus* spp  
 in immunodeficiency, 118  
 meningitis, 180  
 treatment, 199  
 urease-positive, 127
- Cryptococcus neoformans*, 153  
 HIV-positive adults, 177  
 stains for, 125
- Cryptogenic organizing pneumonia, 707
- cryptorchidism, 675
- Cryptorchidism, **675**
- Cryptosporidium* spp, 155  
 in HIV positive adults, 177  
 stains for, 125  
 watery diarrhea, 179
- Crypts of Lieberkühn, 372
- C-section deliveries  
 neonatal flora, 178  
 risk factors after, 664
- Culture requirements, **126**
- "Currant jelly" stools, 396  
 acute mesenteric ischemia, 395  
 intussusception, 395
- Curschmann spirals, 698
- Cushing disease, 356
- Cushing-like symptoms, 201
- Cushing reflex, 303, 517
- Cushing syndrome, 229  
 anovulation with, 669  
 corticosteroids, 120  
 eosinopenia, 433  
 etiology and diagnosis, 356  
 small cell lung cancer, 709
- Cushing ulcers  
 gastritis, 389
- Cutaneous anthrax, 137
- Cutaneous flushing  
 drug reaction and, 251  
 drugs causing, 251
- Cutaneous larva migrans, 158
- Cutaneous leishmaniasis, 158
- Cutaneous mycoses, 152
- Cutaneous paraneoplastic syndromes, 229
- Cutaneous small-vessel vasculitis, 484
- Cutis aplasia  
 Patau syndrome, 63
- CXCR4/CCR5 protein  
 presence on cells, 110  
 viral receptor, 166
- Cyanide toxicity  
 blood oxygen in, 690  
 nitroprusside, 326  
 oxygen deprivation, 693  
 treatment for, 251  
 vs carbon monoxide poisoning, **691**
- Cyanosis  
 "blue kids", 306
- Eisenmenger syndrome, 307
- esophageal atresia, 369
- methemoglobinemia, 690
- patent ductus arteriosus, 307  
 tetralogy of Fallot, 306
- Cyclin-CDK complexes, **46**
- Cyclin-dependent kinases, 46
- Cyclobenzaprine, 572
- Cyclooxygenase  
 aspirin effect on, 421
- Cyclooxygenase inhibition  
 irreversible, 500  
 reversible, 499  
 selective, 500
- Cyclophosphamide  
 hemorrhagic cystitis with, 254  
 mechanism, use and adverse effects, 451  
 SIADH with, 252  
 transitional cell carcinoma and, 629
- Cyclopia, 505
- Cycloplegia  
 atropine, 244  
 muscarinic antagonists for, 244
- Cyclosporine  
 gingival hyperplasia, 253  
 gout, 253  
 immunosuppression, 120
- Cyclothymic disorder, 584
- Cystathione  
 vitamin B<sub>6</sub> and, 67
- Cystathione synthase deficiency, 85
- Cyst disorders (renal), 627
- Cystic duct, 378
- Cysticercosis, 160
- Cystic fibrosis, **60**  
*Aspergillus fumigatus*, 153  
 meconium ileus and, 396  
 organisms causing pneumonia in, 179  
 pancreatic insufficiency, 391  
 vitamin deficiencies and, 65
- Cystine  
 kidney stones, 622
- Cystinuria, **85**
- Cystitis  
 acute bacterial, 624
- Cytarabine  
 mechanism and clinical use, 450
- Cytochrome C, 208
- Cytochrome P-450  
 azoles, 199  
 drug interactions with, **255**  
 griseofulvin, 200  
 macrolides, 193  
 phenobarbital effect on, 564  
 rifamycins, 196  
 ritonavir, 203
- Cytokeratin, 228, 702
- Cytokines, **108**  
 acute, 108  
 corticosteroids and, 120  
 Graves disease and, 350  
 rejection reactions, 119, 120  
 Type IV hypersensitivity, 113
- Cytokinesis, 46
- Cytomegalovirus (CMV)  
 AIDS retinitis, 165  
 cholecystitis and, 406  
 clinical significance, 165  
 esophagitis, 387  
 HIV-positive adults, 177  
 immunodeficient patients, 117, 118  
 in HIV positive adults, 177  
 pneumonia, 707  
 TORCH infection, 182  
 transmission and clinical significance, 165  
 treatment, 202
- Cytoplasm  
 cell cycle phase, 46  
 cytoskeletal elements, 48  
 glycolysis, 76  
 metabolism in, 74
- Cytoplasmic ANCA (c-ANCA)  
 autoantibody, 115
- Cytoplasmic membrane (bacteria), 124
- Cytoplasmic processing bodies (P-bodies), 41
- Cytoskeletal elements, **48**
- Cytotoxic T cells, **102**  
 cell surface proteins, 110  
 MHC I and II, 100
- Cytotrophoblast, 640
- D**
- Dabigatran, 446  
 reversal of, 447
- Dabrafenib, 453
- Dacrocytes  
 associated pathology, 424
- Dactinomycin  
 RNA polymerase inhibition, 42
- Dactinomycin (actinomycin D)  
 mechanism and clinical use, 449
- Dactylitis  
 seronegative spondyloarthritis, 481  
 sickle cell anemia, 432
- Dalfopristin  
 VRE, 198
- Danazol, **682**  
 pseudotumor cerebri, 540  
 "Dancing eyes dancing feet", 229
- Dandy-Walker malformation, 506
- Dantrolene, 570  
 malignant hyperthermia treatment, 570  
 mechanism and use, 572
- Dapagliflozin, 363
- Dapsone  
 hemolysis in G6PD deficiency, 253  
*Mycobacterium leprae*, 196  
*Pneumocystis jirovecii*, 154  
 Leprosy treatment, 141  
 mechanism and use, **194**
- Daptomycin  
 mechanism and clinical use, **195**  
 MRSA, 198
- Darkfield microscopy  
 for Treponema, 146
- Darunavir  
 HIV therapy, 203
- Dasatinib, 453
- Datura, 244
- Daunorubicin  
 dilated cardiomyopathy, 251
- DCC gene, 225
- D cells  
 somatostatin production, 381
- Deacetylation  
 histones, 34
- Deafness  
 Alport syndrome, 620  
 congenital long QT syndromes, 315  
 congenital syphilis, 147  
 rubella, 182  
 syphilis, 182
- Deamination  
 base excision repair, 39
- Death  
 children explaining to, 277  
 common causes by age, **279**  
 diabetes mellitus, 354  
 sudden cardiac death, 312  
 thyroid storm, 350
- Debranching enzyme  
 glycogen metabolism, 87
- Decay-accelerating factor (DAF), 106
- Deceleration injury, 311
- Decerebrate (extensor) posturing, 528
- Decidua basalis, 640
- Decision-making capacity, **271**  
 surrogate for, 272
- Decorticate (flexor) posturing, 528
- Decussation  
 in spinal tracts, 526
- Deep brachial artery, 465
- Deeper injury burn, 497
- Deep inguinal lymph nodes, 648
- Deep partial-thickness burn, 497
- Deep venous thrombosis, **695**  
 direct factor Xa inhibitors for, 446  
 glucagonomas and, 361  
 tamoxifen/raloxifene and, 452
- Defense mechanisms  
 immature, 576  
 mature, 577
- Defensins, 99
- Deferasirox, 251
- Deferiprone, 251
- Deferoxamine, 251
- Deformation (morphogenesis), 637
- Degarelix, **680**
- Degenerate/redundant genetic code, 37
- Degmacytes  
 associated pathology, 424
- Dehydration  
 gout exacerbation, 479  
 loop diuretics and, 631  
 osmotic laxatives, 411  
 salivary stones with, 386  
 shock, 320
- Dehydrogenase, 73
- Delavirdine  
 HIV therapy, 203
- Delayed hemolytic transfusion reaction, 114
- Delirium, **581**  
 barbiturate withdrawal, 594  
 PCP, 595  
 thyroid storm, 350
- Delirium tremens (DTs)  
 alcohol withdrawal, 593
- Delivering bad news, **274**
- δ cells  
 pancreatic tumors, 361
- Delta virus  
 characteristics and medical significance, 167
- Deltoid muscle  
 Erb palsy, 458
- Delusional disorder, 583
- Delusions  
 mesolimbic pathway, 514  
 types of, 582
- Demeclocycline, 364  
 diabetes insipidus and, 252, 346
- Dementia  
 HIV-positive adults, 177  
 metachromatic leukodystrophy, 88  
 neurodegenerative disorders, 538  
 prion disease, 178  
 vitamin B<sub>3</sub> deficiency, 67
- Demyelinating/dysmyelinating disorders, **542**  
 acute disseminated (postinfectious) encephalomyelitis, 542
- Charcot-Marie-Tooth disease, 542

- Demyelinating (*continued*)  
 lead poisoning (adult), 434  
 metachromatic leukodystrophy, 88  
 multiple sclerosis, 541  
 osmotic demyelination syndrom, 542  
 progressive multifocal leukoencephalopathy, 542  
 vitamin B<sub>12</sub> deficiency, 548
- Dendritic cells, **418**  
 IL-10, 108  
 in innate/adaptive immunity, 418  
 innate immunity, 99  
 T- and B-cell activation, 99
- Dengue virus, 167  
 characteristics, **171**
- Denial, 576
- Denosumab  
 for osteoporosis, 474  
 target and clinical use, 122
- De novo pyrimidine synthesis  
 Carbamoyl phosphate synthetase in, 73
- De novo synthesis  
 pyrimidine and purine, **36**
- Dense deposit disease, 620
- Dental plaque  
 normal flora, 178  
 viridans streptococci, 128
- Dentate line, 376
- Dentate nucleus, 515
- Dentin  
 collagen in, 50  
 osteogenesis imperfecta, 51
- Dentinogenesis imperfecta, 51
- Denys-Drash syndrome, 629
- Dependent personality disorder, 589
- Depersonalization/derealization disorder, 581  
 panic disorder, 586
- Depolarizing neuromuscular blocking drugs, 571
- Depressants  
 intoxication and withdrawal, 594
- Depressants intoxication and withdrawal, 594
- Depression  
 atypical features in, **584**  
 benzodiazepine withdrawal, 593, 594  
 drug therapy, 595  
 electroconvulsive therapy, 584  
 metoclopramide, 410  
 neurotransmitter changes with, 510  
 postpartum, 585  
 seasonal pattern with, 584  
 serotonin-norepinephrine reuptake inhibitors (SNRIs) for, 599  
 SSRIs for, 599
- De Quervain tenosynovitis, 472
- Dermatitis  
 B-complex deficiency, 65  
 Type IV hypersensitivity reaction, 113  
 vitamin B<sub>5</sub> deficiency, 67  
 vitamin B<sub>7</sub> deficiency, 67
- Dermatitis herpetiformis, 391  
 characteristics and treatment, 495
- Dermatologic terms  
 macroscopic, 489–502  
 microscopic, **489**
- Dermatome landmarks, **527**
- Dermatomyositis/polymyositis, **483**  
 autoantibody, 115  
 paraneoplastic syndrome, 229
- Dermatophytes, 152
- Dermis, 487
- Descending colon, 370
- Descent of testes and ovaries, **648**
- Desert bumps, 151
- Desflurane, 570
- Desipramine, 599
- Desloratadine, 710
- Desmin, 48  
 tumor identification, 228
- Desmopressin, 364  
 central DI, 337  
 DI treatment, 346  
 for hemophilia, 435
- Desmosome, 488
- Desquamation  
 staphylococcal toxic shock syndrome, 135
- Desvenlafaxine, 599
- Developmental delay  
 fetal alcohol syndrome, 639  
 renal failure and, 626
- Dexamethasone  
 Cushing syndrome diagnosis, 356
- Dexlansoprazole, 409
- Dexrazoxane, 449, 453
- Dextroamphetamine, 596
- Dextrocardia, 288
- Dextromethorphan, 593, **711**
- DHT (dihydrotestosterone), 646
- Diabetes insipidus  
 lithium, 598  
 lithium toxicity, 593  
 potassium-sparing diuretics for, 632  
 thiazides for, 632
- Diabetes insipidus (DI)  
 antiidiuretic hormone in, 335  
 drug reaction and, 252
- Diabetes mellitus  
 atherosclerosis and, 310  
 hypoglycemia in, 356  
 manifestations and complications, **354**  
 Type 1 vs Type 2, **355**
- Diabetes mellitus therapy, **362**  
 decrease glucose absorption, 363  
 increase glucose-induced insulin secretion, 363  
 increase insulin secretion, 363  
 increase insulin sensitivity, 363  
 insulin preparations, 362
- Diabetes mellitus Type 1  
 autoantibody, 115  
 HLA subtype, 100  
 localized amyloidosis in, 213
- Diabetic glomerulonephropathy, 621
- Diabetic ketoacidosis (DKA)  
 ketone bodies, 90  
 signs, symptoms, and treatment, 355
- Diabetic nephropathy  
 ACE inhibitors for, 633
- Diabetic neuropathy, 599
- Diabetic retinopathy, **556**
- Diagnosis errors, 281
- Diagnostic criteria, psychiatric  
 panic disorder, 586  
 symptom duration and, **587**
- Diagnostic test evaluation  
 terminology and computations, **264**
- Diagnostic tests/maneuvers  
 wrist and hand injury, 470
- Dialectical behavioral therapy, 588, 596
- Dialysis-related amyloidosis, 213
- Diamond-Blackfan anemia, 430
- Diaper rash  
*Candida albicans*, 153  
 nystatin, 199
- Diaphoresis, 313, 347  
 in MI, 313
- Diaphragmatic hernia, 380
- Diarrhea, 144, 328, 391, 409  
 amebiasis, 155  
 as laxative adverse effect, 411  
 B-complex deficiency, 65  
 bismuth/sucralfate for, 409  
 cholera toxin, 132  
 clindamycin, 192  
 drug reaction and, 252  
 graft-versus-host disease, 119  
 HIV-positive adults, 177  
*Campylobacter jejuni*, 145  
*Clostridium difficile*, 138  
*Cryptosporidium*, 155  
 inflammatory bowel diseases, 392  
 irritable bowel syndrome, 393  
*Salmonella*, 144  
*Shigella*, 144  
*Vibrio cholerae*, 146  
 lactase deficiency, 81  
 lactose intolerance, 391  
 leflunomide, 500  
 loperamide for, 410  
 malabsorption syndromes, 391  
 metoclopramide, 410  
 misoprostol, 409  
 opioids for, 572  
 organisms causing, **179**  
 rice-water, 132  
 rotavirus, 167  
 thyroid storm and, 348  
 VIPomas, 381  
 viruses causing, 179  
 vitamin C toxicity, 69  
 watery, 132  
*Yersinia enterocolitica*, 144
- Diastole  
 cardiac cycle, 296  
 heart murmurs of, 300  
 heart sounds of, 296
- Diastolic heart murmurs, 300
- Diazepam, 566  
 alcohol withdrawal, 596
- Diclofenac, 500
- Dicloxacillin  
 mechanism and use, 188
- Dicyclomine, 244
- Didanosine  
 pancreatitis, 252
- Diencephalon, 504
- Diethylcarbamazine  
 antihelminthic, 200  
 nematode infections, 159
- Diethylstilbestrol (DES), 680
- Differential media, 126
- Differentiation  
 of T cells, 102
- Diffuse axonal injury, **533**
- Diffuse cortical necrosis, **626**
- Diffuse gastric cancer, 389
- Diffuse glomerular disorders, 618
- Diffuse proliferative glomerulonephritis (DPGN), 620
- Diffuse scleroderma, 487
- Diffuse stomach cancer, 389
- Diffusion-limited gas exchange, 692
- DiGeorge syndrome, 352  
 lymph node paracortex in, 96  
 thymic aplasia, 116  
 thymic shadow in, 96, 98
- Digestion  
 bile functions in, 384  
 carbohydrate absorption, 383  
 malabsorption syndromes, 391  
 vitamin and mineral absorption, 384
- Digestive tract  
 anatomy, **372**  
 basal electric rhythm, 372  
 histology, **372**
- Digital Clubbing, 704
- Digoxin, 237  
 arrhythmias induced by, 330  
 contractility effects of, 294  
 for dilated cardiomyopathy, 318  
 mechanism and clinical use, 329  
 sodium-potassium pump inhibition, 49  
 toxicity treatment, 332
- Dihydroergotamine, 536
- Dihydroorotate dehydrogenase leflunomide effects, 36
- Dihydropyridine calcium channel blockers, 257
- Dihydropyridine receptor, 466
- Dihydrorhodamine (flow cytometry) test, 117
- Dihydrotestosterone (DHT)  
 5α-reductase deficiency, 659  
 function, 659  
 sexual determination, 646
- Dilated cardiomyopathy, 318  
 balloon heart in, 318  
 doxorubicin, 449  
 drug reaction and, 251  
 heart failure with, 319  
 hemochromatosis, 405  
 muscular dystrophy, 61  
 systolic dysfunction, 318  
 wet beriberi, 66  
 with myocarditis, 323
- Diltiazem, 326
- Dimenhydrinate, 710
- Dimercaprol  
 for arsenic toxicity, 251  
 for lead poisoning, 251  
 for mercury poisoning, 251
- Dinitrophenol, 78
- DIP, 460
- Diphenhydramine, 710
- Diphenoxylate, 572
- Diphtheria  
 exotoxins, 131, 132  
*Corynebacterium diphtheriae*, 139  
 vaccine for, 139
- Diphtheria toxin  
 immunity, 110
- Diphyllobothrium latum*  
 disease and treatment, 160  
 vitamin B<sub>12</sub> deficiency, 69
- Diplopia  
 brain stem/cerebellar syndromes, 541  
 central vertigo, 552  
 drug toxicity, 564  
 intracranial hypertension, 540  
 myasthenia gravis, 486  
 osmotic demyelination syndrome, 542
- Dipyridamole  
 for coronary steal syndrome, 312  
 mechanism and clinical use, 447
- Dipyridamoleb, 249
- Direct bilirubin, 385
- Direct cholinomimetic agonists, 243
- Direct coagulation factor inhibitors  
 mechanism and clinical use, **446**

- Direct (conjugated)  
  hyperbilirubinemia, 403
- Direct Coombs test, 420  
  Type II hypersensitivity, 112
- Direct factor Xa inhibitors  
  reversal of, 447
- Direct fluorescent antibody (DFA)  
  microscopy  
    for Treponema, 146
- Direct inguinal hernia, 380
- Direct light reflex, 558
- Direct sympathomimetics, 245
- Discolored teeth, 204
- Discounted fee-for-service, 277
- Disease prevention, 278
- Disease vectors  
  armadillos, 149  
  birds, 149  
  dogs, 144, 145, 149  
  fleas, 150  
  flies, 144, 149  
  Aedes mosquitoes, 171  
  Anopheles mosquito, 157  
  Ixodes ticks, 146  
  pigs, 145  
  rodents, 167  
  ticks, 146, 150
- Disinhibited behavior  
  Klüver-Bucy syndrome, 528
- Disinhibited social engagement, 579
- Disopyramide, 287
- Disorganized thought, 582
- Dispersion measures, 267
- Displacement, 576
- Disruption (morphogenesis), 637
- Disruptive mood dysregulation disorder, 580
- Disseminated candidiasis, 153
- Disseminated gonococcal infection, 480
- Disseminated intravascular coagulation (DIC), 437, 442  
  acute myelogenous leukemia, 442
- Ebola, 171
- endotoxins, 131
- meningococci, 142
- microangiopathic anemia, 433
- Dissociative amnesia, 581
- Dissociative disorders, 576, **581**  
  identity disorder, 581
- Distal esophageal spasm, 387
- Distal humerus, 465
- Distal renal tubular acidosis (RTA type 1), 617
- Distributive shock, 320
- Disulfiram  
  alcoholism treatment, 595  
  disulfiram-like reaction, 254
- Disulfiram-like reaction  
  griseofulvin, 200  
  metronidazole, 195
- Diuresis  
  atrial natriuretic peptide, 303  
  for shock, 320
- Diuretics  
  dilated cardiomyopathy, 318  
  electrolyte changes, 632  
  for SIADH, 346  
  glaucoma therapy, 573  
  hypertension treatment, 324  
  pancreatitis, 252
- Diuretic sites of action, **630**
- Diverticula (GI tract), **393**
- Diverticulitis, 393
- Diverticulosis, 393  
  GI bleeding association, 390
- Diverticulum, 393
- Dizygotic ("fraternal") twins, 641
- Dizziness  
  AChE inhibitors, 569  
  calcium channel blockers, 326  
  dihydropyridine, 326  
  nitrates, 326  
  ranolazine, 326  
  sacubitril, 327  
  vertigo and, 552
- DMD gene, 61
- DMPK gene, 61
- DNA, 210  
  cloning methods, 55  
  laddering in apoptosis, 208  
  methylation in, 34  
  mutations in, **40**  
  plasmid transfer, 130  
  repair of, 39
- DNA ligase  
  action of, 38
- DNA polymerase  
  action of, 38
- DNA polymerases  
  action of, 38
- DNA repair, **39**  
  double strand, 39  
  single strand, 39
- DNA replication, **38**
- DNA topoisomerases, 38
- DNA transcription  
  deacetylation, 34
- DNA viral genomes, **163**
- DNA viruses  
  characteristics, **163**  
  Herpesviruses, 164
- Dobutamine, 245
- Döhle bodies, 416
- dominant, 437
- Dominant inheritance, 59
- Dominant negative mutations, 57
- Donepezil, 243, 569
- Do not resuscitate (DNR) order, 272
- Dopamine, 599  
  basal ganglia, 516  
  changes with disease, 510  
  function of, 336  
  Huntington disease, 538  
  kidney functions and, 613  
  L-DOPA, 568  
  PCT secretion of, 613  
  pheochromocytoma secretion, 359  
  sympathomimetic effects, 245  
  vitamin B<sub>6</sub> and, 67
- Dopamine agonists  
  acromegaly treatment, 347  
  Parkinson disease therapy, 568
- Dopaminergic pathways  
  symptoms of altered activity, **514**
- Dopamine  $\beta$ -hydroxylase  
  vitamin C and, **69**
- Dornase alfa (DNase), 60
- Dorsal columns (spinal cord), 513  
  thalamic relay for, 513
- Dorsal column tract, 526
- Dorsal interossei muscle, 460
- Dorsal midbrain  
  lesion effects, 528
- Dorsal motor nucleus  
  function and cranial nerves, 521
- Dorsal optic radiation, 562
- Dorsiflexion  
  common peroneal nerve injury, 462
- Double duct sign, 378
- Double stranded viruses, 163
- Double Y males, 661
- "Down-and-out" eye", 534
- Down syndrome, 62  
  ALL and AML in, 442  
  cardiac defect association, 307  
  chromosome association, 64  
  hCG in, 658  
  Hirschsprung disease and, 394
- Doxazosin, 247
- Doxepin, 599
- Doxorubicin  
  toxicities, 318
- Doxycycline, 198  
  chlamydiae, 127  
  *Mycoplasma pneumoniae*, 150  
  lymphogranuloma venereum, 149  
  rickettsial/vector-borne disease, 150  
  tetracyclines, 192
- Doxylamine, 710
- DPP-4 inhibitors, 363
- Dressler syndrome, 313, 317, 323
- Drooling treatment, 244
- "Drop metastases", 546
- "Drop" seizures, 535
- Drug dosages, 233, **234**  
  calculations, **233**  
  geriatric patients, 234  
  lethal median, 237  
  median effective, 237  
  toxic dose, 237
- Drug-induced long QT  
  torsades de pointes with, 315
- Drug-induced lupus, 253  
  autoantibody, 115  
  isoniazid, 197
- Drug interactions  
  additive type, 238  
  antagonistic type, 238  
  permissive type, 238  
  potentiation type, 238  
  synergistic type, 238
- Drug interaction types, **238**
- Drug name conventions, **256**  
  second generation histamine blockers, 710
- Drug overdoses  
  of weak acids, 235  
  of weak bases, 235
- Drug reactions  
  cardiovascular, 251  
  endocrine/reproductive, 251  
  gastrointestinal, 252  
  hematologic, 252, **253**  
  multiorgan, **254**  
  musculoskeletal, **253**  
  neurologic, 254  
  renal/genitourinary, **254**  
  respiratory, 254
- Drug reaction with eosinophilia and systemic symptoms (DRESS), 253
- Drug-related myocarditis, 323
- Drug resistance  
  plasmids in, 131
- Drugs, 233, **234**  
  cholinomimetic agents, 243  
  dilated cardiomyopathies and, 318  
  efficacy vs potency, 236  
  patient difficulty with, 276  
  phase I metabolism, 234  
  reactions to, 251  
  therapeutic index, 237  
  toxicities and treatments, 251  
  urine pH and, 235
- Drug safety  
  therapeutic index measurement, 237
- Drug trial phases, 261
- Drunken sailor gait, 528
- Drusen, 556
- Dry beriberi, 66
- Dry mouth  
  Lambert-Eaton myasthenic syndrome, 486
- Dry skin, 66
- D-transposition of great vessels, 306
- Dubin-Johnson syndrome, **404**  
  hyperbilirubinemia in, 403
- Duchenne muscular dystrophy inheritance, 61
- Ductal adenocarcinomas, 378
- Ductal carcinoma in situ, 674
- Ductal carcinomas (invasive), 674
- Ductus arteriosus, 289, 291
- Ductus deferens, 645
- Ductus venous, 291
- Duloxetine, 599
- Duodenal atresia, 369
- Duodenal ulcer, 390  
  hemorrhage, 390
- Duodenum, 370  
  histology, 372  
  location, 368
- Duplex collecting system, 603
- Dural venous sinuses, **519**
- Dura mater, 511
- Durvalumab, 452
- Dwarfism  
  achondroplasia, 474
- d-xylose test, 383, 391
- Dynein  
  movement of, 48
- Dynein motors, 171
- Dysarthria  
  amyotrophic lateral sclerosis, 548  
  osmotic demyelination syndrome, 542
- Dysbetalipoproteinemia  
  familial dyslipidemias, 94
- Dysdiadochokinesia, 515
- Dysentery  
  *Entamoeba histolytica*, 179  
  *Escherichia coli*, 145  
  *Shigella* spp., 132, 144, 179
- Dysfunctional uterine bleeding, 657
- Dysgerminoma, 670, 671
- Dysgeusia, 71
- Dyskeratosis  
  characteristics, 489
- Dyskinesia  
  tardive, 254
- Dyslipidemia  
  vitamin B<sub>3</sub> effects, 67
- Dyslipidemias  
  familial, 94
- Dysmenorrhea  
  copper IUD, 681  
  primary, 670
- Dysmetria  
  central vertigo, 552  
  with strokes, 532
- Dyspareunia, 590
- Dysphagia  
  achalasia, 386  
  esophageal pathologies and, 387  
  osmotic demyelination syndrome, 542
- Plummer-Vinson syndrome, 428  
  stroke effects, 533
- Zenker diverticulum, 394
- Dysplasia, 206  
  bronchopulmonary, 210  
  cervical, 669  
  neoplastic progression, 220

- Dysplasia of hip, 473  
 Dysplastic kidney  
     multicystic, 602  
 Dyspnea  
     heart failure, 319  
     left heart failure, 319  
     pneumothorax, 706  
 dystonia, 514  
 Dystonia  
     acute, 244  
     antipsychotics/antiepileptics, 593  
     benztropine for, 244  
     Lesch-Nyhan syndrome, 37  
     movement disorders, 537  
     treatment of, 244  
 Dystrophic calcification  
     characteristics of, 212  
 Dystrophin (*DMD*) gene, 61  
 Dysuria  
     cystitis, 181  
     prostatitis, 678  
     urinary catheterization, 185  
     urinary tract infections, 624
- E**
- Ear  
     pharyngeal pouch derivation, 644  
 Early complement deficiencies (C1-C4), 107  
 Early fetal development timeline, **636**  
 Eating disorders  
     anorexia nervosa, 590  
     anovulation and, 669  
     binge-eating disorder, 590  
     characteristics and types of, **590**  
     pica, 590  
 Eaton agar, 126  
 Ebola virus  
     characteristics, **171**  
     filoviruses, 167  
 Ebstein anomaly, 306  
 E-cadherin, 220  
     tissue invasion in cancer, 222  
 Echinocandins  
     mechanism and clinical use, 200  
     opportunistic fungal infections, 153  
*Echinococcus granulosus*  
     disease association and treatment, 160  
 Echinocytes  
     associated pathology, 424  
 Echothiophate, 573  
 Echoviruses  
     picornavirus, 123  
 Eclampsia, 308, 667  
 Ecological study, 260  
*Ectyphyma gangrenosum*, 143  
     *Pseudomonas* spp, 143  
 Ectocervix  
     epithelial histology, 650  
 Ectoderm  
     derivatives, 637  
     pharyngeal (branchial) clefts, 643  
 Ectoparasites, 161  
     infections, 161  
 Ectopic pregnancy, 665  
     hCG in, 657  
     *Chlamydia trachomatis*, 149  
 Kartagener syndrome, 49  
     methotrexate for, 450  
     salpingitis and, 185  
 Eculizumab  
     for paroxysmal nocturnal hemoglobinuria, 432  
     target and clinical use, 122
- Eczema  
     eczematous dermatitis, 489  
     phenylketonuria, 84  
     skin scales in, 489  
     Wiskott-Aldrich syndrome, 117
- Edema  
     acute poststreptococcal glomerulonephritis, 620  
     Arthus reaction, 113  
     calcium channel blockers, 326  
     capillary fluid exchange and, 305  
     danazol, 682  
     fludrocortisone, 364  
     heart failure and, 319  
     immunosuppressants, 120  
*Trichinella spiralis*, 159  
 Kawasaki disease and, 484  
 kwashiorkor, 71  
     loop diuretics for, 631  
     periorbital, 159  
     peripheral, 319  
     pitting, 319  
     pseudoephedrine/phenylephrine, 711  
     trichinosis, 159  
     vasogenic, 511  
     wet beriberi, 66  
     with hyperaldosteronism, 358
- Edinger-Westphal nuclei, 558  
 Edoxaban, 446  
 Edrophonium, 243  
 Edwards syndrome, 63  
     chromosome association, 64  
 favipravir, 203  
 Effective refractory period  
     Class I antiarrhythmic effect, 330  
     Class IC antiarrhythmic effect, 330  
 Effective renal plasma flow, **606**  
 Efficacy vs potency of drugs, **236**  
 EGFR gene, 709  
     “Eggshell” calcification, 701  
 Eggshell calcification, 483  
 Ego defenses  
     immature defenses, 576–600  
     mature, 577  
 Ego-dystonic behavior, 586  
 Egophony, 704  
 Ego-syntonic behavior, 588  
 Ehlers-Danlos syndrome  
     aneurysm association with, 534  
     collagen in, **51**  
     heart murmur with, 300  
*Ehrlichia* spp  
     animal transmission, 149  
     Gram stain, 125  
     *Ehrlichia chaffeensis*, 149  
     rickettsial/vector-borne, 150  
 Ehrlichiosis  
     transmission, 150  
 Eisenmenger syndrome, 307  
 Ejaculation  
     innervation of, 651  
     sperm pathway, 650  
 Ejaculatory ducts  
     embryology of, 645  
 Ejection fraction  
     equation for, 294  
 Elastase, 383  
     activity in emphysema, 698  
 Elastic recoil, 689  
 Elastin  
     characteristics of, **52**  
 Elbow  
     overuse injuries, 469
- Electrocardiograms (ECGs), **302**  
     acute pericarditis on, 323  
     cardiac tamponade on, 320  
     hyperkalemia, 615  
     low-voltage, 318, 320  
     MI diagnosis with, 314  
     STEMI localization, 314  
     STEMI-NSTEMI comparison, 312  
     tracings of, **316**
- Electroconvulsive therapy  
     adverse effects, 585
- Electroconvulsive therapy (ECT)  
     adverse effects, 584  
     MDD with psychotic features, 584  
     postpartum psychosis, 584, 585
- Electroencephalogram (EEG)  
     Creutzfeldt-Jakob disease, 539  
     sleep stages, 512
- Electrolytes  
     diuretic effects on, **632**  
     high/low serum concentrations of, 615
- Electron acceptors (universal), 75  
 Electron transport chain  
     inhibitors of, 78  
     oxidative phosphorylation, 78
- Electrophoresis  
     hemoglobin, 420
- Elek test, 139  
 Elementary bodies (chlamydiae), 148  
 Elephantiasis, 159  
 11 $\beta$ -hydroxylase, 343  
 11-deoxycorticosterone, 343  
 Elfin facies, 64  
 Elliptocytes  
     associated pathology, 424
- Elongation Factor  
     *Corynebacterium diphtheriae*, 139
- Elvitegravir, 203  
 Emancipated minors, 272  
 EMB agar, 126  
     *Escherichia coli*, 126  
     lactose-fermenting enterics, 144
- Emboli  
     atherosclerosis, 310  
     atrial fibrillation, 316  
     atrial septal defect, 307  
     paradoxical, 307  
     pulmonary, 321  
 Embolic stroke, 529  
 Emboliform nucleus, 513, 515  
 Embryogenesis  
     gene location and function, **636**  
     intrinsic pathway and, 208
- Embryology  
     development, 636  
     erythropoiesis, 414  
     hematology/oncology, 414  
     neurological, 503  
     pancreas and spleen, 370  
     renal, 602  
     reproductive, 636  
     respiratory, 684  
 Embryonal carcinoma, 677  
 Emicizumab  
     target and clinical use, 122  
 Emission  
     innervation of, 651  
 Emission—, 651  
 Emollients  
     laxative, 411  
 Emotion  
     neural structures and, 514
- Emotional/social development  
     neglect and deprivation effects, 579
- Empagliflozin, 363  
 Empathy, expression of, 274  
 Emphysema, 696, 698  
     diffusion-limited gas exchange, 692  
     panacinar, 403  
      $\alpha_1$ -antitrypsin deficiency, 698
- Empty/full can test, 456  
 Empty sella syndrome, 347  
 Emtricitabine, 203  
 Enalapril, 633  
 Encapsulated, 118  
 Encapsulated bacteria, **127**  
     infections with immunodeficiency, 118
- Encapsulated bacteria vaccines, **127**
- Encephalitis  
     anti-NMDA receptor, 229  
     guanosine analogs, 202  
     herpesviruses, 164, 180  
     HSV identification, 166  
     *Cryptococcus neoformans*, 153  
     Lassa fever, 167  
     measles virus, 170  
     neonatal, 182
- Encephalomyelitis  
     paraneoplastic syndrome, 229
- Encephalopathy  
     hepatic, 375, 400  
     hypertensive emergency, 308  
     lead poisoning, 429  
     Lyme disease, 146  
     prion disease, 178
- Encephalotrigeminal angiomas, 543
- Encorafenib, 453
- Endemic typhus, 149
- Endocannabinoids  
     appetite regulation, 344
- Endocardial cushion, 288
- Endocardial fibroelastosis, 318
- Endocarditis  
     bacterial, **321**  
     coarctation of aorta, 307  
     culture-negative, 150  
     daptomycin, 195  
     enterococci, 137  
     heart murmurs, 300  
     heroin addiction and, 600  
     *Candida albicans*, 153  
     *Coxiella burnetii*, 149  
     *Staphylococcus aureus*, 135  
     *Streptococcus bovis*, 137  
     Löffler, 318  
     native valve etiology, 321  
     nonbacterial, 482  
     nonbacterial thrombotic, 229  
     prophylaxis, 198
- Endocervix  
     epithelial histology, 650
- Endochondral ossification, **468**
- Endocrine pancreas cell types, **335**
- Endocrine/reproductive drug reactions, **252**
- Endocrine system  
     anatomy, 335  
     embryology, 334  
     hormones acting on kidney, 614  
     pathology, 346  
     pharmacology, 362  
     physiology, 336  
     steroid hormone signaling pathways, 345

- Endoderm  
derivatives, 637, 643  
pharyngeal (branchial) pouch  
derivation, 643
- Endodermal sinus tumor, 671, 677
- Endometrial carcinoma, 672  
epidemiology of, 667  
estrogens and, 680
- Endometrial hyperplasia, 672  
follicular cysts, 669, 670
- Endometrial polyps  
uterine bleeding with, 657
- Endometriosis  
characteristics and treatment, 672  
danazol for, 682
- Endometritis, 672
- Endometrium  
abnormal uterine bleeding, 657  
maintenance of, 656
- Endoplasmic reticulum, **47**  
rough, 47  
smooth, **47**
- Endosomes, 47
- Endothelial cells  
in wound healing, 217  
leukocyte extravasation and, 216
- Endothelin receptor antagonist  
naming conventions for, 257  
pulmonary hypertension treatment,  
711
- Endothelium-derived relaxing factor  
(EDRF), 345
- Endotoxins  
effects of, **133**  
features of, **131**
- Enflurane, 254, 570  
mechanism and effects, 570  
seizures with, 254
- Enfuvirtide, 203
- Enhancer (gene expression), 41
- Enoxacin, 195
- Entacapone, 568
- Entamoeba histolytica*  
amebiasis, 155  
bloody diarrhea, 179  
metronidazole, 195
- Enteric nerves, 411
- Enteritis  
vitamin B<sub>5</sub> deficiency, 67  
vitamin B<sub>7</sub> deficiency, 67  
vitamin B<sub>12</sub> deficiency, 69
- Enterobacter aerogenes*, 189
- Enterobacter* spp  
nosocomial infection, 185
- Enterobius* spp  
diseases association, 161  
infection routes, 158
- Enterobius vermicularis*  
intestinal roundworms, 159
- Enterochromaffin-like (ECL) cells, 383
- Enterococci, **137**  
penicillins for, 188  
vancomycin, 190  
vancomycin-resistant (VRE), 137
- Enterococcus faecium*, 137
- Enterococcus* spp  
UTIs, 181
- Enterocolitis  
necrotizing, 396  
vitamin E excess, 70
- Enterohemorrhagic *Escherichia coli*  
(EHEC), 132, 145, 179
- Enteroinvasive *Escherichia coli*  
(EIEC), 145, 179
- Enterokinase/enteropeptidase, 383
- Enteropathogenic, 145
- Enterotoxigenic *E. coli*, 144
- Enterotoxigenic *Escherichia coli*  
(ETEC), 132, 179
- Enterotoxins, 131  
*Vibrio cholerae*, 146
- Enterovirus meningitis, 180
- Enthesitis, 481
- Entorhinal cortex, 514
- Enuresis  
characteristics/treatment, 591  
sleep stages and, 512  
TCA use for, 599
- env* gene, 175
- Environs (viral), **163**
- Enzyme kinetics  
partial agonists, 237
- Enzyme-linked immunosorbent  
assay, **54**
- Enzymes  
lipid transport and, 92, 93  
rate-determining, 73  
terminology for, **73**
- Eosinopenia  
cell counts and causes, 433
- Eosinophilia  
drug reaction and, 253  
*Aspergillus fumigatus*, 153  
*Chlamydia trachomatis*, 149  
macrolides, 193
- Eosinophilic esophagitis, 387
- Eosinophilic granuloma, 699
- Eosinophilic granulomatosis  
autoantibody, 115
- Eosinophils, **418**  
corticosteroid effects, 433  
in esophagus, 387
- Ependymal cells, 507
- Ependymoma, 546
- Ephedrine, 245
- Epicanthal folds  
cri-du-chat syndrome, 64  
Down syndrome, 63
- Epidemic typhus, 149
- Epidemiology  
cancer, 223
- Epidemiology and biostatistics,  
259–281
- Epidermal growth factor (EGF)  
in wound healing, 217
- Epidermis, 487  
embryologic derivatives, 637
- Epidermophyton*, 152
- Epидидим  
embryology of, 645
- Epididymitis, 184, 678
- Epididymitis and orchitis, **678**
- Epidural hematomas, 531
- Epidural space, 511
- Epigastric pain  
chronic mesenteric ischemia, 396  
Ménétrier disease, 389  
pancreatitis, 407
- Epigastric veins, 375
- Epiglottitis  
*Haemophilus influenzae*, 142  
unvaccinated children, 186
- Epilepsy  
gustatory hallucinations in, 582  
seizures, 535
- Epilepsy therapy  
drugs and side effects, **564**
- Epinephrine, 245  
glaucoma treatment, 573  
glycogen regulation by, 86
- pheochromocytoma secretion, 359  
unopposed secretion of, 354  
vitamin B<sub>6</sub> and, 67
- Epiphysis  
slipped capital femoral, 473, 475  
tumors in, 475  
widening of, 475
- Episcleritis  
inflammatory bowel disease, 392
- Epispadias, 647
- Epistaxis, **695**  
hereditary hemorrhagic  
telangiectasia, 324
- Epithelial cell junctions, 488
- Epithelial cells  
tumor nomenclature of, 221
- Epithelial histology (female), **650**
- Epithelial hyperplasia, 674
- Eplerenone, 632
- Epley maneuver, 552
- Epoetin alfa, 121, 453
- Epstein-Barr virus (EBV), 166  
aplastic anemia, 431  
Burkitt lymphoma, 439  
hairy leukoplakia and, 493  
head and neck cancer, 695  
HIV-positive adults, 177  
Hodgkin lymphoma, 438  
in HIV positive adults, 177  
in immunodeficient patients,  
118
- nasopharyngeal carcinomas,  
165
- oncogenicity, 227
- paracortical hyperplasia in, 96
- Epstein-Barr virus (HHV-4)  
transmission and clinical  
significance, 165
- Eptifibatide  
antiplatelet activity, 447  
mechanism and clinical use, 447  
thrombogenesis and, 421
- Erb palsy  
injury and deficits, 458
- Erectile dysfunction, 590
- Erection  
autonomic innervation, 651  
ischemic priapism, 675
- Ergocalciferol, 70
- Ergosterol synthesis inhibitors, 256
- Ergot alkaloids  
coronary vasospasm, 251
- Erlotinib, **453**
- Erosions (gastrointestinal), 372, 389
- Errors (medical), 281
- Erysipelas, 493  
*Streptococcus pyogenes*, 136  
*Streptococcus pyogenes*, 493
- Erythema  
complicated hernias, 380  
in Lyme disease, 146  
Kawasaki disease, 484
- Erythema marginatum, 322
- Erythema migrans  
in Lyme disease, 146
- Erythema multiforme  
causes of, 495  
coccidioidomycosis, 151
- Erythema nodosum, 496  
inflammatory bowel disease, 392
- Erythroblastosis fetalis, 415
- Erythrocyte casts in urine, 618
- Erythrocytes, **417**  
blood types, 415  
hereditary spherocytosis, 432
- myeloproliferative disorders, 442  
transfusion of, 438
- Erythrocyte sedimentation rate  
(ESR), **215**  
fibrinogen and, 214  
subacute granulomatous thyroiditis,  
349
- Erythrocytosis, 417  
oxygen-hemoglobin dissociation  
curve, 690
- Erythrogenic exotoxin A, 133
- Erythrogenic toxin, 136
- Erythromelalgia, 443
- Erythromycin  
macrolides, 193  
prophylaxis, 198  
protein synthesis inhibition, 191  
reactions to, 252
- Erythroplasia of Queyrat, 675
- Erythropoiesis, 703  
fetal, 414
- Erythropoietin  
anemia of chronic disease, 431  
aplastic anemia, 431  
clinical use, 121  
high altitude response, 694  
in renal failure, 626  
polycythemia and, 229  
release of, 613  
signaling pathways for, 345  
with pheochromocytoma, 359
- Eschar, 132  
in cutaneous anthrax, 137  
with mucormycosis, 153
- Escherichia coli*, 145  
cephalosporins, 189  
culture requirements, 126  
encapsulation, 127  
galactosemia, 80  
*lac* operon, 40  
lactose fermentation, 144  
meningitis, 181
- Escherichia coli* serotype O157:H7  
food poisoning, 178  
Shiga toxin production, 179  
thrombotic microangiopathies  
and, 436  
toxin production, 145
- Escitalopram, 599
- E-selectin, 216
- Esmolol, 248
- Esomeprazole, 409
- Esophageal adenocarcinoma, 388
- Esophageal atresia, 369
- Esophageal cancer  
achalasia and, 386  
location and risk factors, 388
- Esophageal dysmotility  
CREST syndrome, 487
- Esophageal pathologies, **387**  
perforation, 387  
varices, 375
- Esophageal reflux  
*H<sub>2</sub>* blockers for, 409  
proton pump inhibitors for, 409
- Esophageal strictures, 387
- Esophageal varices, 387
- Esophageal webs, 387

Esophagitis, 387  
bisphosphonates, 500  
drug reaction and, 252  
HIV-positive adults, 177

**Esophagus**  
blood supply and innervation, 374  
diaphragm, 687  
pathologies of, 387  
portosystemic anastomosis, 375

**Essential amino acids**, 81

**Essential fatty acids**, **65**

**Essential fructosuria**, 80

**Essential mixed cryoglobulinemia**, 174

**Essential thrombocythemia**, 443

**Essential tremor**, 537

**Esters (local anesthetics)**, 571

**estrogen**, 663

**Estrogen**  
androgen conversion to, 659  
androgen insensitivity syndrome, 662  
bone formation, 468, 469  
epiphyseal plate closure, 659  
gynecomastia (males), 673  
mechanism, use and adverse effects, 680  
menopause, 659  
menstrual cycle, 656  
ovulation, 655  
premature ovarian failure, 659, 669  
prolactin suppression of, 336  
signaling pathways for, 345  
source and function of, **654**  
Turner syndrome, 661

**Estrogen receptor modulators (selective)**, 680

**Etanercept**, 502

**Ethacrynic acid**, 631

**Ethambutol**, 196  
mechanism and clinical use, **197**

**Ethanol**  
carcinogenicity, 226  
lactic acidosis and, 72  
metabolism, **72**  
NADPH (nicotinamide adenine dinucleotide phosphate), 72

**Ethics**  
advanced directives, 272  
consent, 271  
core principles of, 270  
religious beliefs and, 277

**Ethinyl estradiol**, 680, 681

**Ethoxysuimide**  
absence seizures, 564  
epilepsy therapy, 564

**Ethylenediaminetetraacetic (EDTA)**, 251

**Ethylene glycol**  
toxicity treatment, 251

**Ethylene oxide sterilization/ disinfection**, 204

**Etonogestrel**, 681

**Etoposide**, 452

**Etoposide/teniposide**  
teniposide, 38

**Euchromatin**, 34

**Eukaryotes**  
mRNA start codons, 44  
ribosomes in, 45  
RNA polymerase in, 42  
RNA processing, **41**

**Eukaryotic gene**  
functional organization, **41**

**Eukaryotic initiation factors**, 45

**Eukaryotic release factors**, 45

**Eustachian tubes**  
embryonic derivation, 644

**Euthyroid sick syndrome**, 349

**Evasion of apoptosis**, 222

**Eversion (foot)**, 462

**Evolocumab**, 328

**Ewing sarcoma**  
dactinomycin for, 449  
epidemiology and characteristics, 477

**Exanthem subitum**  
HHV-6/7, 165  
“Excision” event, 130

**Excitatory pathway**, 516

**Exclusive provider organization plan**, 278

**Exemestane**, 680

**Exenatide**, 363

**Exercise**  
blood flow autoregulation, 304  
peripheral resistance, 295  
respiratory response, **694**  
syncope with, 318  
Tetralogy of Fallot, 306

**Exercise-induced amenorrhea**, 669

**Exocrine glands**, 239

**Exocytosis**, 50

**Exogenous corticosteroids**, 344

**Exons**  
deletions in muscular dystrophies, 61  
vs introns, 43

**Exotoxins**  
bacterial, **132–133**  
features of, **131**  
*Pseudomonas aeruginosa*, 132  
*Streptococcus pyogenes*, 133  
organisms with, 132

**Expiratory reserve volume (ERV)**, 688

**Extension**  
hip, 461

**External hemorrhoids**, 376

**External rotation**  
hip, 461

**Extinction (conditioning)**, 576

**Extracellular fluid (ECF)**  
volume regulation, 612

**Extragonadal germ cell tumors**, **676**

**Extrahepatic manifestations of hepatitis B and C**, **174**

**Extramammary Paget disease**, 668

**Extravascular hemolysis**  
causes and findings with, 431  
HbC disease, 432  
hereditary spherocytosis, 432  
pyruvate kinase deficiency, 432

**Extrinsic (death receptor) pathway**  
mechanism and regulation, 208

**Extrinsic hemolytic anemia**  
causes and findings, 433

**Extrinsic pathway**, 208  
warfarin and, 446

**Exudate**  
“anchovy paste”, 155  
pleural effusion, 705

**Ex vacuo ventriculomegaly**, 540

**Eye disorders**  
Alport syndrome, 620

**Eye movements**, 532  
cranial nerve palsies, 561  
medial longitudinal fasciculus, 563  
with stroke, 532

**Eyes**  
anatomy of, 553  
aqueous humor pathway, 554

**Ezetimibe**, 328

diarrhea, 252

**F**

**Fabry disease**, 61

**Facial nerve (CN VII)**, 146  
functions of, **523**  
inflammatory demyelinating polyradiculopathy, 542

**lesions of**, **550**  
pharyngeal arch derivation, 644

**Facies**  
coarse, 116  
congenital syphilis, 147  
elfin, 64  
epicanthal folds, 63  
“facial plethora”, 710  
flat, 63  
in fetal alcohol syndrome, 639  
leonine (lion-like), 141  
moon, 356  
risus sardonicus, 138  
twisted face, 602

**Factitious disorder**, **589**  
characteristics of, 589  
on another, 589  
on self, 589  
vs malingering and somatic symptom disorders, 589

**Factor IXa and X**  
immunotherapy, 122

**Factor VIII concentrate**, 435

**Factor V Leiden**, 423  
description of, 437  
venous sinus thrombosis and, 519

**Factor Xa**  
inhibitors of, 423

**Factor XI concentrate**, 435

**Facultative anaerobes**, 127

**Facultative intracellular bacteria**, 127

**FADH (flavin adenine dinucleotide)**, 75  
in TCA cycle, 75

**Failure mode and effects analysis**, 281

**Failure to thrive**  
galactosemia, 80  
SCID, 117

**Falciform ligament**, 371

**Fallopian tubes**  
anatomy, 649  
epithelial histology, 650

“False” diverticulum, 393

**False-negative rate**, 264

**Famciclovir**, 202

**Familial adenomatous polyposis**, 397  
chromosome association, 64

**Familial amyloid cardiomyopathy**, 213

**Familial amyloid polyneuropathies**, 213

**Familial dyslipidemias**, **94**

**Familial hypercholesterolemia**, 60, 94

**Familial hypocalciuric hypercalcemia**, 353

**Familial hypocalciuric hypercalcemia**, 353

**Famotidine**, 409

**Fanconi anemia**, 431  
DNA repair in, 39  
nonhomologous end joining and, 39

**Fanconi syndrome**  
drug reaction and, 252  
renal tubular defects, 610

**Fascia**  
collagen in, 50

**Fasted vs fed state**, **90**

**Fastigial nucleus**, 515

**Fasting and starvation**, 91

**Fasting plasma glucose test**  
diabetes mellitus diagnosis, 354

**Fasting state**, 76, 91  
migrating motor complexes production in, 381

**Fat emboli**, 696

**Fatigue**, 281  
heart failure and, 319  
medical errors and, 279  
MI signs, 313

**Fat necrosis**, 209, 673

**Fat redistribution**, 253

**Fat-soluble vitamins**, 65  
absorption with orlistat, 411

**Fatty acid oxidation**  
Carnitine acyltransferase in, 73

**Fatty acids**  
metabolism of, 74, 89  
oxidation of, 72, 74  
synthesis, 72

**Fatty acid synthase**  
vitamin B<sub>5</sub> and, 67

**Fatty acid synthesis**  
Acetyl-CoA carboxylase in, 73

**Fatty casts**, 618

**Fatty liver disease**  
hepatocellular carcinoma and, 401  
nonalcoholic, 401

**FBNI gene mutation**  
dominant negative mutation, 51

**Fear**  
anxiety disorder and, 585  
panic disorder and, 586  
phobias and, 586

**Febrile nonhemolytic transfusion reaction**, 114

**Febrile pharyngitis**, 164

**Febrile seizures**, 534

**Febuxostat**, 501  
Lesch-Nyhan syndrome, 37

**Fecal elastase**, 391

**Fecal immunochemical testing (FIT)**, 398

**Fecalith obstruction**, 393

**Fecal microbiota transplant**, 138

**Fecal occult blood testing (FOBT)**, 398

**Fecal retention**, 581

**Feces**  
explosive expulsion of, 394

**Federation of State Medical Boards (FSMB)**, 2

**Fed state**, 76, 91

**Fee-for-service**, 277

**Felty syndrome**, 478

**Female genital embryology**, 645

**Female/male genital homologs**, **647**

**Female reproductive anatomy**  
ligaments and structure, **649**

**Female reproductive epithelial histology**, **650**

**Femoral epiphysis, slipped**, 473

**Femoral head**  
avascular necrosis of, 475

**Femoral hernia**, 380

**Femoral neck fracture**, 474

**Femoral nerve**, 462

**Femoral region**, **378**

**Femoral sheath**, 378

**Femoral triangle**, 378

**Fenestrated capillaries**, 511

**Fenofibrate**, 328

**Fenoldopam**, 245, 326

**Fentanyl**, 572

**ferritin**, 431

- Ferritin  
acute phase reactants, 214  
iron deficiency anemia, 428  
iron study interpretation, 429  
lab values in anemia, 429
- Ferrochelatase, 434
- Fertility  
double Y males, 661  
menstrual cycle, 656
- Fertilization, 655, 657
- Fetal alcohol syndrome  
developmental effects in, 639  
heart defects in, 308  
holoprosencephaly in, 505
- Fetal circulation, 291  
umbilical cord, 642
- Fetal erythropoiesis, 414
- Fetal hemoglobin, 690
- Fetal lung maturity, 681
- Fetal movement, 636
- Fetal-postnatal derivatives, 291
- Fetal tissue  
collagen in, 50
- Fever, 199  
childhood rashes, 183  
clindamycin, 192  
complicated hernias, 380  
endotoxins, 131  
epiglottitis, 186  
exotoxins, 133  
genital herpes, 184  
high fever, 165, 171, 183  
*Rickettsia rickettsii*, 149  
*Salmonella* spp, 149  
*Trichinella spiralis*, 159
- Jarisch-Herxheimer reaction, 148
- Legionnaires' disease, 143  
low-grade, 143, 172  
malaria, 157  
mononucleosis, 165  
neuroleptic malignant syndrome, 593  
pathophysiology and management, 534  
pulmonary anthrax, 137  
recurring, 156  
spiking, 158
- Tetralogy of Fallot, 306
- thyroid storm causing, 350
- toxic shock syndrome, 135
- undulant, 143
- vasculitides, 484
- vs heat stroke, 534
- Waterhouse-Friderichsen syndrome, 142
- Weil disease, 147
- with inflammation, 214
- with meningococci, 142
- Fever vs heat stroke, 534
- Fexofenadine, 710
- Fibrates, 328  
hepatitis and, 252  
myopathy and, 253
- Fibrinogen, 215, 417  
ESR and, 214  
in cryoprecipitate, 438
- Fibrinoid necrosis, 209
- Fibrinous pericarditis, 313
- Fibroadenoma, 673
- Fibroblast growth factor (FGF)  
in wound healing, 217  
signaling pathways for, 345
- Fibroblast growth factor (FGF) gene, 636
- Fibroblast growth factor receptor (FGFR3), 474
- Fibroblasts  
cortisol and, 344  
in wound healing, 217
- Fibrocystic, 673  
“Fibro fog”, 483
- Fibroid (leiomyoma)  
leuprolide for, 680
- Fibroma, 221
- Fibromas, 670  
nomenclature for, 221
- Fibromuscular dysplasia, 308
- Fibromyalgia, 483, 599
- Fibronectin  
in cryoprecipitate, 438  
thrombocytes, 417
- Fibrosarcomas, 221
- Fibrosis  
silicosis, 701
- Fibrous plaque in atherosclerosis, 310
- Fibular neck fracture, 462
- Fick principle, 294
- Fidaxomicin  
*Clostridium difficile*, 138
- Field cancerization, 695
- Field defect (morphogenesis), 637
- Fifth disease  
rash, 183
- 50S inhibitors, 191
- Filgrastim, 453
- Filgrastim (G-CSF), 121
- Filoviruses  
characteristics and medical importance, 167  
negative-stranded, 168
- Filtration, 607
- Fimbria pilus, 124
- Financial considerations in treatment, 277
- Finasteride, 682  
benign prostatic hyperplasia, 678  
reproductive hormones and, 659
- Finger agnosia, 528
- Finger drop, 456
- Finger movements, 456
- Finger-to-nose test, 515
- Finkelstein test, 472
- First-degree AV block, 316
- First-order elimination, 233, 234
- First-order kinetics, 233
- Fisher's exact test, 269
- Fish oil/marine omega-3 fatty acids, 328
- Fitz-Hugh-Curtis syndrome, 142, 185
- 5 $\alpha$ -reductase inhibitors  
inhibitors for BPH, 678
- 5 $\alpha$ -reductase deficiency, 663  
sexual differentiation, 646
- 5 $\alpha$ -reductase, 659  
hypospadias, 647
- 5-aminosalicylic drugs, 410
- 5-fluorouracil (5-FU)  
mechanism and clinical use, 450  
pyrimidine synthesis and, 36
- 5-HT  
MAO inhibitor effect on, 599  
opioid effects, 572  
trazodone effects, 600  
vilazodone effects, 600  
vortioxetine effects, 600
- 5-HT<sub>1B/1D</sub> agonists, 256
- Fixation, 577
- Fixed splitting, 298
- Flaccid paralysis  
botulinum toxin, 138  
LMN lesion, 548  
motor neuron signs, 547
- Flagellin, 99
- Flagellum, 124
- Flask-shaped ulcers, 155
- Flavin nucleotides, 75
- Flaviviruses, 163
- Fleas, 149
- Fleas (disease vectors), 149
- Flexion  
foot, 463  
hip, 461
- Flexor digiti minimi muscle, 460
- Flexor pollicis brevis muscle, 460
- Flies (disease vectors), 144
- Floppy baby”, 548
- Floppy baby syndrome  
*Clostridium botulinum*, 138
- Flow cytometry, 54
- Flow volume loops, 697
- Fluconazole, 151  
*Cryptococcus neoformans*, 153  
mechanism and use, 199  
opportunistic fungal infections, 153
- Flucytosine  
*Cryptococcus neoformans*, 153  
mechanism and clinical use, 199  
with/without amphotericin B, 199
- Fludrocortisone  
mechanisms, use and adverse effects, 364
- Fluid compartments, 605
- Flumazenil  
benzodiazepine overdose, 251, 594
- Fluorescence in situ hybridization, 55
- Fluorescent antibody stain, 125
- Fluoroquinolone  
*Salmonella typhi*, 144
- Fluoroquinolones  
*Mycoplasma pneumoniae*, 150  
mechanism and clinical use, 195  
pregnancy contraindication, 204  
tendon/cartilage damage with, 253  
teratogenicity of, 638  
TOP II (DNA gyrase) and TOP IV inhibition in prokaryotes, 38
- Fluoxetine, 599
- Fluphenazine, 596, 597  
Tourette syndrome, 596
- Flutamide, 682
- Fluticasone, 712
- Fluvoxamine, 599
- FMRI gene, 61
- Foam cells  
Niemann-Pick disease, 88
- Focal glomerular disorders, 618
- Focal hepatic necrosis, 252
- Focal necrotizing vasculitis, 485
- Focal neurological deficits  
pituitary apoplexy, 347
- Focal nodular hyperplasia, 402
- Focal segmental glomerulosclerosis, 621
- Folate antagonist  
teratogenicity, 638
- Folate deficiency  
anemia with, 430  
neural tube defects, 505
- Folate synthesis  
inhibition/block, 194
- Folic acid  
folate, 68
- Follicles (lymph node), 96
- Follicles (spleen), 98
- Follicle-stimulating hormone (FSH)  
clomiphene effect, 680  
hCG and, 658
- PCOS, 669  
premature ovarian failure, 659
- Follicular conjunctivitis  
*Chlamydia trachomatis*, 149
- Follicular cysts (ovary), 670
- Follicular lymphoma  
occurrence and genetics, 439
- Follicular lymphomas, 444
- Follicular phase (menstrual cycle), 656
- Follicular thyroid carcinoma  
causes and findings, 351
- Fomepizole, 251
- Food-borne illness causes, 178
- Food poisoning  
causes of, 178  
*Bacillus cereus*, 138, 178  
*Staphylococcus aureus*, 135, 178  
toxic shock syndrome toxin, 133
- Foot drop, 462  
lead poisoning, 429
- Foramen cecum, 334
- Foramen of Magendie, 520
- Foramen of Monro, 520
- Foramen ovale  
atrial septal defect, 307  
embryology, 288  
fetal circulation, 288  
retained patency of, 306
- Foramina of Luschka, 520
- Forced expiratory volume (FEV)  
obstructive lung disease, 697  
restrictive lung disease, 699
- Forebrain, 505
- Foregut  
blood supply/innervation of, 374  
development of, 368
- Foreign body inhalation, 687
- Formoterol, 712  
46,XX DSD, 662  
46XX/46 XY DSD, 662
- Fosamprenavir  
HIV-positive adults, 202
- Fosaprepitant, 453
- Foscarnet  
mechanism and clinical use, 202  
retinitis in immunosuppressed patients, 202
- Fosphenytoin, 564
- Fossa ovalis, 291
- Fovea  
cherry-red spot, 557
- FOXP3 protein, 102
- Fractures  
chalk-stick, 475  
Colles, 474  
common pediatric, 474  
femoral neck, 474  
in child abuse, 579  
pathologic, 477  
scaphoid, 459  
vertebral compression, 474
- Fragile X syndrome, 62  
chromosome association, 62
- Frameshift mutation, 40  
muscular dystrophy and, 61
- Francisella* spp  
culture requirements, 126  
intracellular organism, 127
- Francisella tularensis*  
animal transmission, 149  
transmission, 149
- Frataxin, 549
- Free fatty acids  
fast/starvation states, 91  
lipid transport and, 92

- Free light chain (FLC) assay  
  plasma cell dyscrasias, 440
- Free nerve endings, 509
- Free radical injury, 210
- Fremitus (tactile), 704
- Fresh frozen plasma, 438
- Fresh frozen plasma/prothrombin complex  
  transfusion of, 438
- "Fried egg" cells, 508, 544
- Friedreich ataxia, 62, **549**  
  chromosome association, 64  
  hypertrophic cardiomyopathy, 318
- Frontal bossing, 347
- Frontal eye fields  
  effects of lesions, 528
- Frontal lobe  
  effects of lesions, 528  
  lesions in, 527  
  stroke effects, 532
- Frontotemporal dementia, 538  
  symptoms and histologic findings, 538
- Fructokinase, 80
- Fructose-1,6-bisphosphatase  
  rate-determining enzyme, 73
- Fructose-2,6-bisphosphate, 73  
  glycolysis regulation, **76**
- Fructose intolerance, 80
- Fructose metabolism  
  disorders, **80**
- Fructosuria, 80
- FTA-ABS, 125, 147
- Full-thickness burn, 497
- Fumarate, 84
- Functional hypothalamic amenorrhea, 669
- Functional neurologic symptom disorder, 589
- Functional organization of a eukaryotic gene, **41**
- Functional residual capacity (FRC), 688
- Fungal infections  
  dermatophytes, 152  
  infections with  
    immunodeficiencies, 118
- Fungi, 179  
  culture requirements, 126  
  immunocompromised patients, 179  
  opportunistic infections, 153  
  topical infections, 199
- "Funny" current, 301
- "Funny" sodium channels, 332
- Furosemide, 253  
  gout with, 253  
  mechanism, use and adverse effects, 631  
  pancreatitis, 252
- Fusion protein EWS-FLI1, 477
- Fusobacterium* spp  
  alcoholism, 179  
  anaerobic metabolism of, 127
- G**
- G20210A gene mutation, 437
- G6PD  
  deficiency, 61, 79  
  HMP shunt and, 73
- G6PD deficiency  
  causes and findings, **432**
- GABA  
  basal ganglia and, 516  
  benzodiazepine effects, 566
- changes with disease, 510  
  epilepsy drugs, 564  
  vitamin B<sub>6</sub> and, 67
- Gabapentin  
  epilepsy therapy, 564  
  neuropathic pain treatment, 483
- GABA<sub>B</sub> receptor agonists, 541
- gag gene, 175
- Gag reflex, 523
- Gait disturbance  
  Friedreich ataxia, 549  
  gait apraxia, 540  
  Parkinson disease, 537  
  steppage, 462
- Trendelenburg sign/gait, 463
- vitamin B<sub>12</sub> deficiency, 548  
  waddling, 61
- Galactocerebrosidase, 88
- Galactocerebroside, 88
- Galactokinase deficiency, 80  
  cataracts and, 554
- Galactorrhea  
  antipsychotic drugs and, 336  
  tuberoinfundibular pathway, 514
- Galactose-1-phosphate uridylyltransferase, 80
- Galactose metabolism  
  disorders of, 80
- Galactosemia, 80
- Galantamine, 243, 569
- Galant reflex, 527
- Gallbladder  
  biliary structures, 378  
  blood supply and innervation of, 374  
  Salmonella typhi colonization, 144
- Gallbladder cancer  
  porcelain gallbladder and, 407  
  sclerosing cholangitis and, 405
- Gallstone ileus, 406
- Gambling disorder, **591**
- γ-glutamyltransferase (GGT)  
  alcohol use, 594
- γ-glutamyl transpeptidase  
  liver damage, 400
- Ganciclovir  
  agranulocytosis, 253  
  mechanism and clinical use, **202**
- Ganglion cyst, 472
- Ganglioneuromatosis  
  oral/intestinal, 360
- Gangrene, 133  
  Buerger disease, 484  
  diabetes mellitus, 354
- Gangrenous necrosis, 209
- Gap junctions, 488
- Gardener's pupil, 244
- Gardner syndrome, 397
- Gardnerella vaginalis*, 148  
  metronidazole, 195
- Gas gangrene  
  alpha toxin, 133  
  *Clostridium perfringens*, 138, 179
- Gastrectomy, 430
- Gastric acid  
  histamine receptors and, 241  
  secretion of, 382
- Gastric arteries  
  celiac trunk, 370
- Gastric bypass surgery  
  ghrelin and, 381  
  vitamin B<sub>12</sub> deficiency, 69
- Gastric cancer  
  carcinogens causing, 226  
  *Helicobacter pylori*, 146
- oncogenes and, 225  
  oncogenic microbes and, 227  
  sign of Leser-Trélat and, 229  
  types of, 389
- Gastric inhibitory peptide (GIP), 361
- Gastric outlet obstruction, 369
- Gastric ulcers, 390  
  hemorrhage, 390  
  NSAID toxicity, 500
- Gastric vessels, 371
- Gastrin, 381  
  effects on acid secretion, 383  
  signaling pathways for, 345  
  somatostatinomas and, 361  
  source, action, and regulation of, 381
- Gastrinomas  
  gastrin secretion by, 364  
  treatment of, 381
- Gastrin-releasing peptide (GRP), 381
- Gastritis, 146  
  gastrin in, 381  
  H<sub>2</sub> blockers for, 409  
  proton pump inhibitors for, 409  
  stomach cancer and, 389  
  types of, **389**
- Gastrocolic ligament, 371
- Gastroenteritis  
  caliciviruses, 167  
  *Listeria monocytogenes*, 139  
  *Salmonella* spp, 144  
  rotavirus, 168
- Gastroepiploic arteries, 371
- Gastroesophageal reflux disease (GERD), 387  
  Barrett esophagus, 388  
  esophageal cancer and, 388  
  presentation, 387
- Gastrohepatic ligament, 371
- Gastrointestinal bleeding  
  acute, 390  
  hereditary hemorrhagic telangiectasia, 324
- Gastrointestinal blood supply/  
  innervation, **374**
- Gastrointestinal drug reactions, 252
- Gastrointestinal infections  
  protozoa, 155
- Gastrointestinal ligaments  
  connections and structures contained, 371
- Gastrointestinal regulatory substances, **381**
- Gastrointestinal secretory cell locations, **383**
- Gastrointestinal secretory products  
  source and action, **382**
- Gastrointestinal stromal tumors (GISTs), 225
- Gastrointestinal system  
  embryology, 368  
  innervation of, 376  
  ligaments, **371**  
  pathology, 386  
  pharmacology, 408  
  physiology, 381
- Gastroschisis, 368  
  characteristics of, 368
- Gastrosplenic ligament, 371
- Gastrulation, 636
- Gaucher disease, 88  
  avascular necrosis, 475
- Gaussian distribution, 267
- G cells, 381
- Gefitinib, 453
- Gemfibrozil, 328
- Gender- and sexuality-inclusive history taking, **274**
- Gender dysphoria, **590**
- Gene expression  
  modifications, **56**  
  regulation, **41**
- Generalized anxiety disorder, **586**
- Generalized anxiety disorder (GAD), 585
- buspirone, 598
- drug therapy for, 596
- Selective serotonin reuptake inhibitors (SSRIs) for, 598
- serotonin-norepinephrine reuptake inhibitors (SNRIs) for, 598
- Generalized seizures, 535  
  types of, 535
- Generalized transduction, 130
- "General paresis", 147
- Genetic/antigen drift, 169
- Genetics  
  anticipation, 62  
  autosomal trisomies, 63  
  chromosome disorders, **64**  
  code features, 37  
  inheritance modes, 59  
  introns vs exons, 43  
  muscular dystrophies, 61  
  mutations in cancer, 222  
  terms, **56-57**  
  trinucleotide repeat expansion diseases, 61  
  viral, **162**
- Genital herpes, 184
- Genitalia, 663  
  ambiguous, 646  
  embryology of, 645  
  male/female homologs, **647**
- Genital ulcers, 184
- Genital warts, 184
- Genitofemoral nerve, 462
- Genitourinary/renal drug reactions, **254**
- Genitourinary trauma, **651**
- Genotyping microarrays, 54
- Gentamicin, 191
- Geriatric patients  
  Beers criteria in, 250  
  causes of seizures, 535  
  colorectal cancer, 398  
  common causes of death, 279  
  drug-related delirium in, 581  
  normal pressure hydrocephalus, 540  
  nosocomial infections, 185  
  osteoporosis, 474  
  PPI adverse effects, 409  
  recurrent lobar hemorrhagic stroke, 531  
  respiratory system changes in, 689  
  vascular skin tumors, 492
- Germ cell tumors  
  cryptorchidism risk for, 675  
  extragonadal, 676  
  hormone levels in, 676, 677  
  testicular, 677
- Germinal center (spleen), 96
- Gerstmann syndrome, 528
- Gestational age, **657**
- Gestational diabetes, 658
- Gestational hypertension, 667
- GFAP (glial fibrillary acid proteins)  
  cytoskeletal elements, 48  
  tumor identification, 228

- Ghrelin, 513  
 appetite regulation, 344  
 source and action of, 381
- Giant cell pneumonia, 170
- Giant cell (temporal) arteritis, 484  
 polymyalgia rheumatica, 483
- Giant cell tumor, 476
- Giardia* spp  
 stain for, 125  
 watery diarrhea, 179
- Giardia lamblia*, 155
- Giardiasis, 155  
 in immunodeficiency, 118
- Giemsa stain  
*Borrelia*, 146
- Gilbert syndrome, 404  
 hyperbilirubinemia in, 403
- Gingival hyperplasia  
 cyclosporine, 120  
 drug reaction and, 253
- Gingivostomatitis, 164
- Gitelman syndrome  
 renal disorder features, 615  
 renal tubular defects, 610
- Glans penis  
 lymphatic drainage of, 648
- Glanzmann thrombasthenia, 436
- Glaucoma, 245, 555  
 atropine, 244
- Glaucoma therapy, 573
- Glioblastoma  
 description and histology, 544
- Glioblastoma multiforme  
 nitrosoureas for, 451
- Glipizide, 363
- Global aphasia, 534
- Globoid cells  
 Krabbe disease, 88
- Globose nucleus, 515
- Globus pallidus externus, 516
- Glomerular disorders/disease  
 nomenclature, 618  
 types of, 619
- Glomerular dynamics  
 factors affecting, 607
- Glomerular filtration barrier, 605
- Glomerular filtration rate (GFR), 606
- Glomerulonephritis  
 azathioprine for, 120  
 granulomatosis with polyangiitis, 485  
*Streptococcus pyogenes*, 136  
 RBC casts in, 618
- Glomus tumor, 492
- Glossitis  
 B-complex deficiency, 65  
 iron deficiency, 428  
 vitamin B<sub>3</sub> deficiency, 67  
 vitamin B<sub>9</sub> deficiency, 68
- Glossopharyngeal (CNIX), 523
- Glossopharyngeal nerve (CN IX)  
 pharyngeal arch derivative, 644
- GLP-1 analog, 363
- Glucagon  
 fructose bisphosphatase-2, 76  
 somatostatinoma, 361  
 source, function, and regulation, 341
- Glucagonoma, 358, 361
- Glucocerebrosidase  
 Gaucher disease, 88
- Glucocerebroside  
 in sphingolipidoses, 88
- Glucocorticoids  
 calcium pyrophosphate deposition disease, 479  
 gout, 501
- immunosuppression, 120  
 myopathy, 253  
 rheumatoid arthritis, 478
- Glucokinase  
 hexokinase vs, 76  
 vs hexokinase, 75
- Gluconeogenesis  
 cortisol and, 344  
 ethanol metabolism and, 72  
 irreversible enzymes, 78  
 metabolic site, 74  
 organic acidemias, 85  
 pyruvate metabolism and, 77  
 rate-determining enzyme for, 73  
 thyroid hormone and, 339
- Glucose  
 blood-brain barrier and, 511  
 glycogen metabolism, 87  
 metabolism of, 40
- Glucose-6-phosphatase  
 gluconeogenesis, 78  
 HMP shunt, 79  
 Von Gierke disease, 87
- Glucose-6-phosphatase  
 dehydrogenase  
 deficiency, 79
- Glucose clearance, 608
- Glucose-dependent insulinotropic peptide (GIP)  
 insulin regulation, 342  
 source and action of, 381
- Glucosuria  
 threshold for, 608
- Glutamic acid  
 classification of, 81
- Glutathione peroxidase, 210
- Glutathione reductase, 354  
 NADPH and, 75
- Gluten-sensitive enteropathy, 391
- Gluteus maximus, 461
- Gluteus maximus muscle, 463
- Gluteus medius, 461
- Gluteus minimus, 461
- GLUT transporters, 342
- Glyburide, 363
- Glycerol  
 starvation, 91
- Glycogen  
 metabolism and storage, 73  
 metabolism of, 86  
 regulation, 86  
 stain for, 125  
 storage, 87
- Glycogenesis, 73
- Glycogenolysis  
 rate-determining enzyme for, 73  
 thyroid hormone and, 339
- Glycogen storage diseases, 87
- Glycogen synthase, 73
- Glycolysis  
 hexokinase/glucokinase in, 76  
 metabolic site, 74  
 pyruvate metabolism and, 75  
 rate-determining enzyme for, 73  
 regulation of, 76
- Glycolysis regulation  
 key enzymes in, 76  
 pyruvate dehydrogenase, 76
- Glycoproteins  
 HIV, 175
- Glycopyrrolate, 244
- Glycosylation  
 collagen synthesis, 50  
 protein synthesis, 42, 45
- GNAQ gene mutation, 543
- GNAS gene mutation, 352
- GnRH analogs  
 mechanism, use and adverse effects, 680
- Goblet cells, 372, 686
- Goiter  
 causes of, 346  
 iodine deficiency with, 345  
 toxic multinodular, 346
- Golfer's elbow, 469
- Golgi tendon organ, 468
- Golinumab, 502
- Gonadal mosaicism, 57
- Gonadal venous/lymphatic drainage, 648
- Gonadotropin-releasing hormone (GnRH)  
 function of, 336  
 neurons producing, 513  
 ovulation, 655  
 prolactin and, 336  
 signaling pathways for, 345  
 spermatogenesis, 652
- Gonads  
 dysgenesis of, 629  
 venous and lymphatic drainage, 648
- Gonococci vs meningococci, 142
- Gonorrhea  
 ceftriaxone, 189  
*Neisseria*, 142  
 STI, 184
- Goodpasture syndrome, 50  
 autoantibody, 115  
 hematuria/hemoptysis, 620
- Good syndrome  
 paraneoplastic syndrome, 229  
 thymoma and, 98
- Goserelin, 680
- Gottron papules, 229
- Gout  
 acute treatment drugs, 501  
 drug reaction and, 253  
 findings, symptoms and treatment, 479  
 kidney stones and, 622  
*Lesch-Nyhan* syndrome, 37  
 loop diuretics and, 631  
 preventive therapy, 501  
 Von Gierke disease, 87
- Gower maneuver/sign, 61
- gp41, 203
- G-protein-coupled receptors, 241
- G-protein-linked 2nd messengers, 241
- Gracilis muscle, 462
- Graft-versus-host disease, 119  
 Type IV hypersensitivity, 113
- Graft-versus-tumor effect  
 organ transplant rejection, 119
- Gram-negative organisms  
 cephalosporins, 189  
 lab algorithm, 141
- Gram-positive organisms  
 antibiotic tests, 134  
 cephalosporins, 189  
 lab algorithm, 134  
 vancomycin, 190
- Gram stain, 125
- Grand mal (tonic-clonic) seizures, 535
- Granisetron, 453
- Granular casts  
 acute tubular necrosis, 625  
 "muddy brown" in urine, 618
- Granulocyte-colony stimulating factor (G-CSF), 345
- Granulocytes  
 morulae, 150
- Granulocytopenia  
 trimethoprim, 194
- Granuloma inguinale, 184
- Granulomas  
 in systemic mycoses, 151  
 in tuberculosis, 140  
 macrophages and, 417  
 syphilis, 147
- Granulomatosis infantiseptica  
*Listeria monocytogenes*, 139
- Granulomatosis with polyangiitis  
 autoantibody, 115  
 glomerulonephritis with, 620
- Granulomatous disease  
 excess vitamin D in, 70  
 hypervitaminosis D with, 476  
 infectious vs noninfectious etiology, 218
- Granulomatous inflammation, 218
- Granulosa cells  
 tumors of, 671
- Grapefruit juice and cytochrome P-450, 255
- Graves disease  
 autoantibody, 115  
 causes and findings, 350  
 HLA subtype, 100  
 ophthalmopathy, 348  
 thyroid cellular action in, 339  
 type II hypersensitivity, 112
- Gray baby syndrome, 203, 253
- Gray hepatization, 707
- Grazoprevir, 204
- Greater omental sac, 371
- Greenstick fracture, 474
- Grief, 578
- Griseofulvin  
 cytochrome P-450 interaction, 255  
 mechanism and clinical use, 200  
 microtubules and, 48
- "Ground-glass" appearance (X-ray)  
*Pneumocystis jirovecii*, 154, 177
- "ground-glass" appearance (X-ray), 685
- Group B Streptococcus  
 encapsulated bacteria, 127
- Growth factors  
 tumor suppressor gene mutations and, 46
- Growth hormone (GH)  
 diabetes mellitus, 354  
 for hypopituitarism, 347  
 function and secretion of, 337  
 insulin resistance and, 336  
 replacement therapy, 364
- Growth hormone releasing hormone (GHRH)  
 function of, 336
- Growth retardation  
 with renal failure, 626
- Growth signal self-sufficiency, 222
- GTPase, 225
- GTP (guanosine triphosphate), 77
- Guanfacine, 246
- Guanosine analogs  
 mechanism and use, 202
- Gubernaculum, 648, 649
- Guessing during USMLE Step 1 exam, 23
- Guillain-Barré syndrome  
 acute inflammatory demyelinating polyradiculopathy, 542  
 peripheral nerves in, 510
- Schwann cell injury, 508

Gummas  
syphilis, 147, 184  
Guselkumab  
target and clinical use, 122  
Gustatory hallucinations, 581  
Gustatory pathway  
thalamic relay for, 513  
Guyon canal syndrome, **470**  
Gynecologic tumor epidemiology, **667**  
Gynecomastia, 673  
azoles, 199  
cimetidine, 409  
SHBG and, 345  
spironolactone, 682  
tuberoinfundibular pathway, 514

**H**

*Haemophilus ducreyi*  
sexual transmission of, 184  
*Haemophilus influenzae*, 142  
cephalosporins, 189  
chloramphenicol, 192  
encapsulation, 127  
meningitis, 180  
pneumonia, 179  
rifamycins, 196  
vaccine, 179  
Hair  
“kinky”, 51  
Menkes disease, 51  
vitamin C deficiency, 69  
Hairy cell leukemia, 442  
cladribine for, 450  
Hairy leukoplakia  
HIV-positive adults, 177  
skin infection, 493  
Half-life (t<sub>1/2</sub>), 233  
Halitosis  
Zenker diverticulum, 394

Hallmarks of cancer, **222**  
Hallucinations  
cocaine, 595  
delirium, 581  
mesolimbic pathway, 514  
postpartum psychosis, 585  
tricyclic antidepressants, 599  
types of, **582**  
Hallucinogen intoxication and withdrawal, 594  
Haloperidol, 597  
Halothane, 570  
hepatic necrosis, 252  
mechanism and adverse effects, 570

Hamartin protein, 225, 543  
Hamartomas, 221  
Hamartomatous colonic polyps, 397  
Hamate bone, 459  
Hamman sign crepitus, 696  
Hammer toes, 549  
Hand  
distortions of, **460**  
muscles of, **460**  
squamous cell carcinoma, 498  
Hand-foot-mouth disease, 183  
Hansen disease, 141  
animal transmission, 149  
dapsone, 194  
erythema nodosum, 496  
Hantavirus  
hemorrhagic fever, 167  
Haptens  
acute interstitial nephritis, 625  
amiodarone as, 331  
Haptoglobin, 214, 431

Hardy-Weinberg population genetics, **57**  
Hartnup disease, 67  
vitamin B<sub>3</sub> deficiency, 67  
Hashimoto thyroiditis, 349  
autoantibody, 115  
HLA subtype, 100  
Hasimoto thyroiditis, 349  
Hassall corpuscles, 98  
HbA<sub>1c</sub> test, 354  
HBcAg (hepatitis B core antigen), 174  
HbC disease, 432  
target cells in, 425  
HBsAg (hepatitis B surface antigen), 174  
HBV  
immunity, 110  
oncogenicity, 227  
hCG  
embryonal carcinoma, 677  
serum tumor markers, 227  
HCV  
oncogenicity, 227  
HDL (high-density lipoprotein), 94  
Headache  
“thunderclap headache”, 534  
“worst headache of my life”, 534  
Headaches, 536  
adverse effects with drugs, 199, 200  
classification and treatment, **536**  
pituitary apoplexy, 347  
Head and neck cancer, 695  
Healthcare delivery, 278  
Healthcare payment models, **278**  
Health maintenance organization, 278  
Health maintenance organization plan, 278  
Hearing loss  
cytomegalovirus, 182  
diagnosis of, 552  
osteitis deformans, 475  
osteogenesis imperfecta, 51  
sensorineural deafness, 620  
types of, 551  
Heart  
anatomy, **292**  
autoregulation of, 304  
blood supply, 292  
electrocardiograms, 302  
embryology, 288, **290**  
ischemia in, 210  
morphogenesis of, **288–289**  
myocardial action potential, 301  
normal pressures in, 303  
pacemaker action potential, 301  
sclerosis of, 487  
Heartburn, 387  
Heart disease  
congenital, 63  
death causes by age, 279  
Fabry disease, 88  
ischemic, 312  
Heart failure, 319  
ACE inhibitors for, 633  
left heart failure, 319  
right heart, 319  
Heart failure cells, 685  
Heart morphogenesis  
aortic arch derivatives, 289  
atria, 288  
cardiac looping, 288  
fetal-postnatal derivatives, 291  
Outflow tract formation, 289

septation of heart chambers, 288  
valve development, 289  
ventricles, 289  
Heart murmurs, 300  
cardiomyopathies, 318  
continuous, 300  
diastolic, 300  
patent ductus arteriosus, 307  
systolic, 300  
Heart rate, 246  
Heart sounds, 296  
cardiac cycle, 296  
cardiac tamponade, 320  
in heart failure, 319  
splitting in, 298  
Heart transplant  
dilated cardiomyopathy, 318  
Heart valve development, 289  
Heat-labile toxin  
*Clostridium botulinum*, 138  
Heat shock proteins, 45  
Heat-stable toxin (ST)  
resorption of NaCl and H<sub>2</sub>O in gut, 132  
Heat stroke, 534  
pathophysiology, **534**  
Heavy menstrual bleeding (AUB/HMB), 657  
Heel pain, 472  
Heel-to-shin test, 515  
Heinz bodies, 79  
associated pathology, 426  
Helicase, 38  
*Helicobacter pylori*, **146**  
as oncogenic microbe, 227  
disease association, 389  
metronidazole, 195  
oncogenicity, 227  
penicillins for, 188  
silver stain, 125  
stains for, 125  
urease-positive, 128  
Heliotrope rash, 229  
HELLP syndrome, 667  
“Helmet cells”, 433  
“Helmet” cells, 424  
Helminthic infections  
eosinophils and, 418  
Helper T cells  
cell surface proteins, 110  
cytokine secretion, 108  
Hemagglutinin, 169  
influenza viruses, 169  
parainfluenza viruses, 170  
Hemangioblastoma, 544  
Hemangioblastomas, 543  
Hemangioma, 492  
Hemangiomas, 221  
pyogenic granuloma, 492  
strawberry, 492  
Hemarthroses  
hemophilias, 435  
Hematemesis  
esophageal varices, 387  
GI bleeding, 390  
Hematin, 126, 142  
Hematochezia  
diverticulosis, 393  
intestinal disorders, 396  
Meckel diverticulum, 394  
Hematocrit  
polycythemia vera, 443  
Hematologic abnormalities  
laboratory techniques for, 54  
Hematologic disorders  
paraneoplastic syndromes, 229

Hematologic drug reactions, 253  
Hematology/oncology  
anatomy, 416  
pathology, 424  
pharmacology, 445  
physiology, 420  
Hematopoiesis, **416**  
extramedullary, 475  
myelodysplastic syndromes, **441**  
Hematopoietic stem cells, 110  
Hematuria, 627  
bladder cancer, 629  
granulomatosis with polyangiitis, 485  
hereditary hemorrhagic telangiectasia, 324  
*Schistosoma haematobium*, 161  
kidney stones, 622  
painless, 629  
renal papillary necrosis, 626  
transitional cell carcinoma, 629  
UTIs, 181  
Heme  
bilirubin and, 385  
chloroquine, 200  
porphyria and, 434  
synthesis of, 434  
vitamin B<sub>6</sub> and, 67  
Heme synthesis  
iron deficiency, 428  
lead poisoning, 429  
porphyrias and, 434  
Hemianopia, 532, 562  
Hemiballismus, 537  
brain lesions and, 528  
Hemidesmosome, 488, 494  
Hemineglect, 532  
Hemiparesis  
saccular aneurysms, 534  
Hemochromatosis, **405**  
calcium pyrophosphate deposition disease, 479  
cardiomyopathy with, 318  
chromosome association, 64  
chronic, 435  
free radical injury, 210  
Hemoglobin  
carbon dioxide transport, 694  
development, 414  
electrophoresis, **420**  
kinetics of, 232  
structure and oxygen affinity, **689**  
Hemoglobinuria  
acute tubular necrosis and, 626  
G6PD deficiency, 432  
intravascular hemolysis, 432  
paroxysmal nocturnal, 122  
Hemolysis  
alpha toxin, 133  
G6PD deficiency, 253  
HELLP syndrome, 667  
*Clostridium perfringens*, 138  
sulfonamides, 194  
Hemolytic anemia  
autoimmune, 189  
babesiosis, 157  
cephalosporins, 187  
direct Coombs-positive, 253  
due to infections, 433  
extrinsic, 433  
folate deficiency and, 430  
G6PD deficiency, 79  
intrinsic, 432  
penicillin G V, 187  
pyruvate kinase deficiency and, 432

- spherocytes in, 425  
sulfa drug allergies, 255  
Wilson disease, 405
- Hemolytic disease of fetus and newborn**, **415**  
Type II hypersensitivity, 112
- Hemolytic-uremic syndrome (HUS)**  
exotoxins, 132  
*Escherichia coli*, 145  
platelet disorders, 436
- Hemophagocytic lymphohistiocytosis**, **445**, 564
- Hemophilia**, 435  
therapeutic antibodies for, 122  
X-linked recessive disorder, 61
- Hemophilis influenzae**  
culture requirements for, 126  
vaccine for, 127
- Hemoptysis**, 177  
bronchiectasis, 699  
choriocarcinomas, 666  
granulomatosis with polyangiitis, 485  
lung cancer, 709  
tuberculosis, 140
- Hemorrhage**  
acute pancreatitis, 407  
AIDS retinitis, 165  
baroreceptors and, 303  
delirium caused by, 581  
Ebola virus, 171  
intracranial, 531  
intraventricular, 530  
pulmonary, 137  
shock from, 320  
subarachnoid, 530  
subarachnoid hemorrhage, 534  
ulcer disease, 390  
ulcers, 390  
Weil disease, 147
- Hemorrhagic cystitis**  
adenovirus, 164  
drug reaction, 254
- Hemorrhagic fever**, 167  
filovirus, 167
- Hemorrhoids**, 376  
GI bleeding association, 390
- Hemosideruria**, 431
- Hemostasis**  
platelet plug formation, 421  
thrombocytes (platelets), 417
- Hepadnaviruses**  
characteristics of, 163  
envelope and medical significance, 164
- Heparin**  
acute coronary syndromes, 317  
deep venous thrombosis, 445  
in coagulation cascade, 423  
mechanism and clinical use, **445**  
osteoporosis, 253  
reversal of, **447**  
thrombocytopenia, 231  
toxicity treatment, 251  
warfarin vs, 446
- Hepatic adenoma**, 402
- Hepatic angiosarcoma**, 402
- Hepatic arteries**, 371
- Hepatic ascites**, 632
- Hepatic encephalopathy**  
ammonia production/removal in, **401**  
lactulose for, 411  
Reye syndrome, 400
- Hepatic fibrosis**, 377
- Hepatic hemangioma, 402  
Hepatic lipase  
IDL modification by, 94  
in lipid transport, 93
- Hepatic necrosis, 252, 499
- Hepatic steatosis, 401
- Hepatic stellate (Ito) cells, 377
- Hepatitis  
alcoholic, 401  
hyperbilirubinemia, 403  
hyperbilirubinemia in, 403
- Hepatitis A (HAV)  
characteristics of, 173  
picornavirus, 167, 168  
serologic markers, 174
- Hepatitis antigens, 174
- Hepatitis B (HBV)  
characteristics of, 173  
medical importance, 164  
nosocomial infection, 185  
passive antibodies for, 110  
polyarteritis nodosa and, 484  
serologic markers, 174  
sexually transmitted infection, 184
- Hepatitis C (HCV)  
characteristics of, 173  
extrahepatic manifestations, 174  
flaviviruses, 167  
lichen planus, 496  
therapy for, 204
- Hepatitis D (HDV), 173  
characteristics, 173
- Hepatitis E (HEV), 173  
characteristics, 173  
hepevirus, 167
- Hepatitis viruses, 173  
presentation and characteristics, **173**  
serologic markers for, **174**
- Hepatocellular carcinoma (HCC)**, 402  
carcinogens causing, 226  
cirrhosis and, 399  
*Aspergillus fumigatus*, 153  
non-alcoholic fatty liver disease, 401  
oncogenic microbes, 217, 227
- Hepatocytes**  
glycogen in, 86
- Hepatoduodenal ligament**, 371
- Hepatomegaly**, 87  
Budd-Chiari syndrome, 402  
galactosemia, 80  
Zellweger syndrome, 48
- Hepatosplenomegaly**  
Hurler syndrome, 88  
organ transplant rejection, 119
- Hepatosteatosis**  
ethanol metabolism and, 72
- Hepatotoxicity**  
amiodarone, 331  
bosentan, 711  
danazol, 682  
inhaled anesthetics, 570  
leflunomide, 500  
methotrexate, 450  
terbinafine, 199  
thionamides, 364  
zileuton, 682
- Hepcidin, 214, 431  
in anemia of chronic disease, 431
- Hepeviruses**  
genomes, 163
- HER2/neu (erbB2)*, 674
- HER2/neu (ERBB2)* gene, 225
- "Herald patch" ( pityriasis rosea), 496
- Hereditary amyloidosis**, 213
- Hereditary angioedema**, 682  
complement disorder and, 107
- Hereditary channelopathies**, **315**
- Hereditary elliptocytosis**, 424
- Hereditary hemorrhagic telangiectasia**, 324  
autosomal dominance of, 60
- Hereditary hyperbilirubinemias**, **404**
- Hereditary motor and sensory neuropathy**, 542
- Hereditary spherocytosis**  
causes and findings, 432  
spherocytes in, 425
- Hereditary thrombophilias**, **437**
- Hernia**, **380**  
diaphragmatic, 684
- Herniation syndromes**, 547
- Heroin**, 572  
detoxification medications, 600  
intoxication and withdrawal, 600  
opioids for withdrawal, 573
- Herpes genitalis**, 164, 493
- Herpes labialis**, 164, 493
- Herpes simplex virus (HSV)**  
cidofovir, 202  
clinical significance, 165  
envelope, 164  
foscarnet for, 202  
guanosine analogs, 202  
HSV-1/HSV-2, 182  
identification, 166  
meningitis caused by, 180  
TORCH infection, 182
- Herpesviruses**  
envelope and medical importance, 164  
transmission and clinical significance, **164**
- Herpes virus infections (HSV1 and HSV2)**  
skin infection, 493  
transmission and clinical significance, 164
- Herpes zoster**  
dorsal root latency, 165  
famciclovir, 202
- Herpetic whitlow**, 164, 493
- Heterochromatin**, 34
- Heterodimer**, 48
- Heterodisomy**, 57
- Heterogeneous nuclear RNA (hnRNA)**, 41
- Heteroplasmy**, 57
- Heterozygosity loss**, 56
- Hexokinase**  
vs glucokinase, 75
- HFE gene**  
hemochromatosis and, 405
- HGPRT (hypoxanthine guanine phosphoribosyltransferase)**, 37
- Hiatal hernia**, 380
- Hiccups**, 537
- High altitude respiratory response**, 693, **694**
- High-frequency recombination (Hfr) cells**, 130
- Highly resistant bacteria**  
treatment of, 198
- Hilar lymph node calcification**, 701
- Hilar mass (lung)**, 709
- Hindgut**  
blood supply/innervation of, 374
- Hip**  
dysplasia of, 473  
muscles and actions of, **461**  
nerve injury with dislocation, 462
- Hip injuries/conditions**  
developmental dysplasia, 473
- Hippocampus**  
lesion effects, 528  
limbic system, 514  
pyramidal cells, 210
- Hippurate test for *Streptococcus agalactiae***, 137
- Hirschsprung disease**, **394**
- Hirsutism**  
cyclosporine, 120  
danazol, 682  
menopause, 659  
SHBG and, 345
- his**  
failing, 24–25
- Histaminase**, 418
- Histamine blockers**, 409
- Histamine receptors**, 243
- Histamines**  
cortisol effect on, 344  
signaling pathways for, 345  
vitamin B<sub>6</sub> and, 67
- Histamine (scombrotoxin poisoning)**, 250
- Histamine-<sub>2</sub> blockers**  
cimetidine, 409  
mechanism and clinical use, **409**
- Histidine**, 81
- Histiocytosis (Langerhans cell)**, 444
- Histocompatibility complex I and II**, 100
- Histology**  
adult primary brain tumors, 544–573  
basal cell carcinoma, 498  
childhood primary brain tumors, 546–573  
digestive tract, 372
- Female reproductive epithelial**, **650**  
granulomatous inflammation, 218  
Graves disease, 350  
hydatidiform mole, 666  
ischemic brain disease/stroke, 529  
lung cancer, 709  
myocardial infarction, 313  
myositis ossificans, 483  
myxomas, 324  
necrosis, 209  
papillary carcinoma, 351  
rhabdomyosarcoma, 324  
tumor grade, 221
- Histones**  
acetylation, 34  
amino acids in, 81  
deacetylation, 34  
methylation, 34
- Histoplasma capsulatum**  
HIV-positive adults, 177  
necrosis and, 209
- Histoplasma spp**  
treatment, 199
- Histoplasmosis**, 151  
erythema nodosum, 496
- Histrelin**, 680
- Histrionic**, 588
- HIT type 1**, 445
- HIT type 2**, 445
- HIV**  
heroin addiction and, 598  
pulmonary arterial hypertension, 703

- HIV-associated dementia  
  symptoms and histologic findings, 539
- HIV (human immunodeficiency virus)  
  aplastic anemia in, 431  
  characteristics, 175  
  dementia, 177  
  diagnosis, 175  
  flow cytometry diagnosis, 54  
  Kaposi sarcoma, 165, 492  
  lymphopenia, 433  
  T cells and, 419  
  therapy, 203  
  TORCH infections, 182  
  untreated infection timecourse, 176
- HIV (human immunodeficiency virus) therapy  
  NNRTIs, 203  
  NRTIs, 203  
  NS3/4A inhibitors, 204  
  NS5B inhibitors, 204  
  ribavirin, 204
- HLA-B8  
  Graves disease and, 350
- HLA-DR4, 478
- HLA genes  
  disease associations, 350, 481  
  DM type 1 association, 355  
  seronegative spondyloarthritis, 481
- HLA subtypes associated with diseases, 100
- HMG-CoA reductase  
  cholesterol synthesis, 73
- HMG-CoA reductase inhibitors, 328
- HMG-CoA synthase, 73
- HMP shunt  
  metabolic site, 73  
  NADPH production, 75, 78  
  rate-determining enzyme, 73  
  vitamin B<sub>1</sub> deficiency, 66
- Hoarseness  
  gastroesophageal reflux disease, 387  
  lung cancer, 709  
  Ortner syndrome, 292  
  Pancoast tumor, 709  
  thyroid cancer, 351
- Hodgkin lymphoma  
  bleomycin for, 449  
  non-Hodgkin vs, 438  
  paraneoplastic cerebellar degeneration and, 229  
  vinca alkaloids for, 451
- Holistic medical therapy, 277
- Holoprosencephaly, 505  
  Patau syndrome, 63
- Homatropine, 244
- Homeobox (*Hox*) genes, 636
- homeostasis, 341
- Homer-Wright rosettes, 358, 546
- Homicide, 279
- Homocysteine  
  vitamin B<sub>9</sub> deficiency, 68
- Homocysteine methyltransferase deficiency in, 85
- Homocystinuria  
  causes of, 85  
  presentation and characteristics, 52
- Homologous recombination repair, 39
- Homunculus, 518
- Hookworms, 159
- Hormone effects on kidney, 614
- Hormone replacement therapy  
  combined contraception, 681  
  estrogens for, 680
- for hypopituitarism, 347  
  thrombotic complications, 253
- Hormone-sensitive lipase, 93
- Horn cysts, 491
- Horner syndrome  
  Brown-Séquard syndrome, 549  
  cavernous sinus, 562  
  headache and, 536  
  ipsilateral, 532  
  lung cancer, 709  
  Pancoast tumor, 709  
  sympathetic nervous system and, 559
- Horseshoe kidney, 603
- Hospice care, 279
- Hot flashes  
  drug reaction and, 252  
  “Hourglass stomach”, 380
- Howell-Jolly bodies, 426
- H<sub>1</sub> antihistamines, 710
- H<sub>2</sub>-antagonist  
  naming conventions for, 257
- H<sub>2</sub>blockers  
  cimetidine, 409
- HTLV-1  
  oncogenicity, 227
- Hu antigens, 229
- Human chorionic gonadotropin  
  choriocarcinomas, 666  
  hydatidiform moles, 666  
  secretion of, 658  
  signaling pathways, 345  
  source and functions of, 658
- Human factors design, 280
- Human herpesvirus 6 and 7 (HHV-6, HHV-7)  
  transmission and clinical significance, 165
- Human herpesvirus 6 (HHV-6), 165, 183
- Human herpesvirus 8 (HHV-8)  
  in HIV positive adults, 177  
  Kaposi sarcoma, 492  
  oncogenicity, 227  
  transmission and clinical significance, 165
- Humanized monoclonal antibodies  
  active vs passive immunity, 110
- Human papillomavirus 6 (HPV-6), 184
- Human papillomavirus 11 (HPV-11), 184
- Human papillomavirus 16 (HPV-16), 669, 695
- Human papillomavirus 18 (HPV-18), 669
- Human papillomavirus (HPV)  
  cervical pathology, 669  
  HIV-positive adults, 177  
  oncogenicity, 227  
  penile cancer, 675  
  tumor epidemiology, 667  
  verrucae, 491  
  warts, 164
- Human placental lactogen, 658
- Humerus fracture  
  radial nerve with, 457
- Humerus fractures  
  axillary nerve, 456, 457  
  radial nerve, 456
- Humor, 577
- Humoral immune response, 101, 419
- Hunger/satiety regulation, 513
- Hunter syndrome, 88
- Huntington disease  
  drug therapy for, 569  
  movement disorders, 537
- neurotransmitter changes with, 510  
  symptoms and histologic findings, 538
- trinucleotide repeat expansion diseases, 62
- Hürthle cells, 349
- Hyaline arteriolosclerosis, 309
- Hyaline casts in urine, 618
- Hydatid cysts, 160
- Hydatidiform mole  
  complete vs partial, 666  
  hCG in, 658  
  theca-lutein cysts and, 670
- Hydralazine  
  hypertension in pregnancy, 324  
  in heart failure, 319  
  mechanism and clinical use, 326
- Hydrocele (scrotal)  
  acquired, 676  
  congenital, 676
- Hydrocephalus  
  childhood tumors, 546  
  *Toxoplasma gondii*, 182  
  lissencephaly association, 505  
  noncommunicating, 506  
  risk for developing, 531  
  Toxoplasma gondii, 156  
  types of, 540
- Hydrochlorothiazide (HCTZ), 632  
  hyperglycemia, 252  
  pancreatitis, 252
- Hydrogen peroxide, 204
- Hydronephrosis, 622, 623  
  kidney stones, 622  
  posterior urethral valves, 602  
  prenatal, 602
- Hydrophobia, 171
- Hydrops fetalis  
  parvovirus B19, 182  
  syphilis, 182
- Hydroxychloroquine  
  myopathy, 253
- Hydroxylases, 73
- Hydroxylation  
  in protein synthesis, 45  
  Vitamin C and, 50
- Hydroxyurea  
  mechanism and clinical use, 450  
  polycythemia vera, 443  
  purine synthesis, 36  
  sickle cell anemia, 432
- Hyoid artery, 289
- Hyoscymamine, 244
- Hyperacute transplant rejection, 119  
  Type II hypersensitivity, 112
- Hyperaldosteronism  
  clinical features, 358  
  hypertension with, 308  
  potassium-sparing diuretics for, 632
- Hyperammonemia, 82, 85  
  fatty acid metabolism and, 89
- Hyperbilirubinemia  
  conjugated (direct), 404  
  jaundice with, 404  
  unconjugated (indirect), 403
- Hypercalcemia  
  acute pancreatitis and, 407  
  adult T-cell lymphoma, 439  
  bisphosphonates for, 500  
  calcium carbonate antacid effects, 409  
  familial hypocalciuric hypercalcemia, 353  
  hyperparathyroidism, 353
- loop diuretics for, 631
- lung cancer, 709
- paraneoplastic syndrome, 229
- succinylcholine, 571
- teriparatide, 501
- thiazides, 632
- Williams syndrome, 64
- Hypercalcuria  
  hyperparathyroidism, 353  
  thiazides for, 632
- Hypercapnia  
  oxygen diffusion limitation and, 692
- Hypercholesterolemia, 309  
  familial, 60  
  familial dyslipidemias, 94
- Hyperchylomicronemia  
  familial dyslipidemias, 94
- Hypercoagulability  
  deep venous thrombosis, 695  
  dural venous sinus thrombosis, 519  
  marantic endocarditis in, 321
- Hyperemesis gravidarum, 666
- Hyperemia  
  pseudoephedrine/phenylephrine, 711
- Hypereosinophilic syndrome, 318
- Hyperestrogenism, 670
- Hyperglycemia, 356  
  diabetic retinopathy, 556  
  drug reaction and, 252  
  immunosuppressants, 120  
  pancreatic cell tumors, 361  
  protease inhibitors, 203  
  thiazides, 632  
  vitamin B<sub>3</sub> toxicity, 67
- Hyperglycemic emergencies, 355
- Hypergonadotropic hypogonadism, 662
- Hypergranulosis, 496  
  characteristics, 489
- Hyper-IgM syndrome, 117
- Hyperinsulinemia, 669
- Hyperkalemia  
  aldosterone in, 612  
  alsikiren, 633  
  angiotensin II receptor blockers, 633  
  cardiac glycosides, 329  
  potassium shifts and, 614  
  potassium-sparing diuretics, 632
- Hyperkalemic tubular acidosis (RTA)  
  type 4, 617
- Hyperkeratosis  
  characteristics, 489  
  verrucae, 491
- Hyperlipidemia  
  atherosclerosis and, 310  
  immunosuppressants, 120  
  signs of, 309  
  thiazides, 632
- Hyperopia, 553
- Hyperosmolar hyperglycemic state  
  DM type, 354  
  signs, symptoms, and treatment, 355
- Hyperparathyroidism  
  calcium pyrophosphate deposition disease, 479  
  cinacalcet for, 365  
  lab values in, 476  
  types and presentation, 353
- Hyperphagia  
  depression with, 584  
  hypothalamus and, 513

- Hyperphosphatemia  
  hyperparathyroidism (secondary), 353  
  hypoparathyroidism, 352  
  renal osteodystrophy and, 627
- Hyperpigmentation  
  bleomycin, 449  
  busulfan, 451  
  fludrocortisone, 364  
  hemochromatosis, 405  
  Peutz-Jeghers syndrome, 397  
  primary adrenal insufficiency, 357
- Hyperplasia, 206  
  adrenal, 356  
  parathyroid, 353, 360  
  uterine bleeding with, 657
- Hyperplastic arteriolosclerosis, 309
- Hyperplastic polyps, 397
- Hyperprolactinemia, 252, 336, 545  
  anovulation, 669  
  calcium channel blockers and, 326  
  risperidone and, 252
- Hyperpyrexia  
  with TCAs, 599
- Hyperresonance (chest percussion), 706
- Hypersensitivity pneumonitis, 699
- Hypersensitivity reactions  
  Arthus reaction, 113  
  cephalosporins, 189  
  Graves disease, 350  
  immune complex-mediated, 113  
  mast cells and, 418  
  organ transplants, 119  
  penicillins, 187  
  rheumatic fever, 322  
  sulfonamides, 194  
  types of, 112
- Hypersensitivity reaction (type III)  
  acute poststreptococcal  
    glomerulonephritis, 620
- Hypersensitivity reaction type IV  
  contact dermatitis, 491
- Hypersomnia, 584
- Hypertension, 308  
  ACE inhibitors for, 633  
  acromegaly and, 347  
  intracranial hemorrhage with, 531  
  renovascular disease, 628
- Hypertension in pregnancy, 667  
  eclampsia, 667  
  gestational hypertension, 667  
  HELLP syndrome, 667  
  preeclampsia, 667
- Hypertension treatment, 324  
  in asthma, 324  
  in pregnancy, 324  
  primary (essential) hypertension, 324  
  with diabetes mellitus, 324  
  with heart failure, 324
- Hypertensive crisis  
  as psychiatric emergency, 593  
  MAO inhibitors, 599  
  phenoxybenzamine for, 247  
  pheochromocytoma, 359
- Hypertensive emergency, 308  
  RBC casts in, 618  
  treatment, 326
- Hypertensive nephropathy, 308
- Hypertensive retinopathy, 556
- Hyperthermia  
  atropine causing, 244  
  MDMA, 595
- Hyperthyroidism  
  amiodarone and, 331  
  causes and findings, 350
- findings, 348  
  vs hypothyroidism, 348
- Hypertriglyceridemia  
  acute pancreatitis and, 407
- Hypertrophic cardiomyopathy, 318
- Hypertrophic osteoarthropathy, 709  
  paraneoplasticsyndromes, 229
- Hypertrophic pyloric stenosis, 369
- Hypertrophic scars, 219
- Hypertrophy, 206  
  skeletal muscle, 467
- Hyperuricemia  
  drug reaction and, 253  
  gout and, 479  
  kidney stones and, 622
- Lesch-Nyhan syndrome, 37
- thiazides, 632  
  vitamin B<sub>3</sub> toxicity, 67
- Hyperventilation  
  metabolic acidosis compensatory response, 616  
  therapeutic, 517
- Hypervitaminosis D, 476
- Hypetriglyceridemia  
  familial dyslipidemias, 94
- Hynagogic hallucinations  
  narcolepsy, 582, 591
- Hynopompic hallucinations  
  narcolepsy, 582, 591
- Hypoaldosteronism, 617
- Hypocalcemia, 351  
  acute pancreatitis and, 407  
  cinacalcet causing, 365  
  hypermagnesemia and, 615  
  hypoparathyroidism, 352  
  laboratory values by disorder, 352  
  renal osteodystrophy, 627  
  thyroidectomy, 351  
  tumor lysis syndrome, 445
- Hypocholesterolemia hypergastrinemia, 389
- Hypocretin, 591
- Hypodermis, 487
- Hypofibrinogenemia, 215
- Hypogammaglobulinemia, 229
- Hypoglossal nerve (CN XII), 523  
  lesion in, 550  
  with stroke, 533
- Hypoglycemia, 361  
  fructose intolerance, 80  
  gluconeogenesis and, 78  
  in diabetes mellitus, 356  
  in ethanol metabolism, 72  
  neonatal, 638  
  Von Gierke disease, 87
- Hypogonadism, 405  
  diagnosis of, 662  
  estrogens for, 680  
  gynecomastia, 673  
  Kallmann syndrome, 663  
  pituitary prolactinomas, 336  
  testosterone/methyltestosterone, 682  
  zinc deficiency, 71
- Hypokalemia  
  antacid use, 409  
  cystic fibrosis, 60  
  loop diuretics, 631  
  on ECG, 302  
  potassium shifts with, 614  
  VIPomas and, 381
- Hypomanic episode, 584
- Hypomanic episodes, 584
- Hyponatremia  
  as paraneoplastic syndrome, 229  
  euvolumic, 346
- MDMA, 595  
  thiazides, 632
- Hypoparathyroidism  
  lab values in, 352  
  types and findings, 352
- Hypophosphatemia  
  hyperparathyroidism, 353
- Hypopituitarism, 347
- Hypoplasia, 637
- Hypopyon, 555
- Hyporeflexia  
  magnesium hydroxide and, 409
- Hypospadias, 647
- Hypotension, 199  
  adrenal insufficiency, 357  
  aliskiren, 633  
  angiotensin II receptor blockers, 633  
  baroreceptors in, 303  
  cardiac tamponade, 320  
  endotoxins, 131  
  ephedrine for, 245  
  hypermagnesemia, 615  
  in pregnancy, 667  
  local anesthetics, 571  
  magnesium hydroxide and, 409  
  midodrine for, 245  
  norepinephrine for, 245  
  orthostatic, 357  
  phenylephrine for, 245  
  scombrotoxic poisoning, 250  
  sympatholytic drugs and, 246
- Hypothalamic/pituitary drugs  
  clinical use and adverse effects of, 364
- Hypothalamic-pituitary hormones  
  adrenal insufficiency, 357  
  functions of, 336
- Hypothalamus  
  ADH secretion, 335  
  functions and nuclei of, 513  
  homeostasis and, 513  
  nuclei of, 513  
  reproductive hormone control, 680  
  sleep cycle role of, 512  
  TRH sensitivity, 335
- Hypothenar muscles, 460  
  Klumpke palsy, 458
- Hypotheses (statistical), 268
- Hypothyroidism  
  amiodarone and, 331  
  carpal tunnel syndrome with, 470  
  causes and findings, 349  
  drug reaction and, 252  
  findings, 348  
  hormone replacement, 364  
  iodine deficiency or excess, 349  
  lithium, 598  
  vs hyperthyroidism, 348
- Hypotonia  
  poliomyelitis, 549  
  Zellweger syndrome, 48
- Hypoventilation, 693  
  metabolic alkalosis compensatory response, 616
- Hypovolemic shock, 320
- Hypoxanthine guanine phosphoribosyltransferase (HGPRT), 37
- Hypoxemia  
  oxygen deprivation, 693  
  vasoconstriction, 703
- Hypoxia  
  erythropoietin production, 613  
  lung diseases, 703  
  nocturnal, 703  
  oxygen deprivation, 693
- regions susceptible to, 210  
  renal, 690  
  vasoconstriction/vasodilation and, 304  
  with limited oxygen diffusion, 692
- Hypoxia inducible factor 1a, 225
- Hypoxic stroke, 528, 529
- Hypoxic vasoconstriction  
  (pulmonary), 692  
  high altitude, 694  
  pulmonary hypertension, 692
- Hysteresis, 689
- I**
- Iatrogenic abnormal uterine bleeding, 657
- Ibandronate, 500
- IBD-associated arthritis  
  HLA subtype, 100
- Ibuprofen, 500  
  hemolysis in G6PD deficiency, 253
- ICAM-1 protein  
  in leukocyte extravasation, 216  
  viral receptor, 166
- I cells  
  cholecystokinin secretion, 381  
  disease, 47
- Icosahedral viruses, 163
- Icterohemorrhagic leptospirosis, 147
- Idealization, 577
- Identification, 577
- Idiopathic intracranial hypertension, 540  
  empty sella syndrome, 347
- Idiopathic pulmonary fibrosis, 699, 700
- IDL (intermediate-density lipoprotein), 94
- IFN- $\beta$  (Interferon- $\beta$ )  
  clinical uses, 109
- IFN- $\beta$  (Interferon- $\beta$ )  
  clinical uses, 121
- IFN- $\gamma$  (Interferon- $\gamma$ )  
  clinical uses, 109, 121
- IFN- $\alpha$  (Interferon- $\alpha$ )  
  clinical uses, 109, 121  
  myopathy, 253
- Ifosfamide  
  adverse effects, 451  
  hemorrhagic cystitis, 254
- IgA and IgG deamidated gliadin peptide autoantibody, 115
- IgA antibodies  
  anti-endomysial autoantibody, 115  
  anti-tissue transglutaminase autoantibody, 115  
  functions of, 105  
  hyper-IgM syndrome, 117  
  passive immunity, 105  
  Peyer patches and, 384
- IgA deficiency  
  ataxia-telangiectasia, 117
- IgA nephropathy (Berger disease)  
  nephritic syndrome, 620
- IgA protease  
  bacterial virulence, 129
- IgD antibodies  
  B cells and, 105
- IgE antibodies  
  allergen-specific, 112  
  ataxia-telangiectasia, 117  
  atopic dermatitis, 491  
  functions of, 105  
  hyper-IgM syndrome, 117  
  immunotherapy, 122  
  type I hypersensitivity, 112

- IgG antibodies  
as passive immunity, 110  
ataxia-telangiectasia, 117  
bullous pemphigoid, 494  
hepatitis A (HAV), 174  
pemphigus vulgaris, 494  
response to antigen, 105  
type III hypersensitivity reactions, 113
- IgM antibodies  
antigen response, 105  
hepatitis A (HAV), 174  
hyper-IgM syndrome, 117  
in biliary cirrhosis, 405  
overproduction, 440
- IL-12/IL-23  
immunotherapy target, 122
- IL-12 receptor deficiency, 116
- IL-17A  
immunotherapy target, 122
- IL-23  
immunotherapy target, 122
- Ileum  
basal electric rhythm, 372  
histology of, 372
- ileus, 396  
bacterial peritonitis (spontaneous), 400
- Iliacus, 462
- Iliohypogastric nerve, 462
- Iliotibial band syndrome, 472
- Illness anxiety disorder, 589
- Iloperidone, 597
- Imatinib  
CML, 442  
mechanism, use and adverse effects, 453
- IMG registration timeframe, 6
- Imipenem  
seizures with, 254
- Imipramine, 256
- Imiquimod  
clinical use, 121
- Immature teratoma, 671
- Immune checkpoint interactions, 223
- Immune complex  
Type III hypersensitivity, 113
- Immune evasion  
in cancer, 222
- Immune responses  
acute-phase reactants, 99  
antigen type and memory, 104  
cell surface proteins, 110  
complement, 104  
cytokines, 108  
hypersensitivity types, 113  
*Bordetella pertussis*, 143  
immunoglobulin, 105  
transfusion reactions, 114
- Immune system organs, **96**
- Immune thrombocytopenia, 436  
Type II hypersensitivity, 112
- Immunoassays  
HIV diagnosis, 175
- Immunocompromised patients  
common organisms affecting, 179  
esophagitis in, 387  
*Candida albicans* in, 153  
*Cryptococcus neoformans*, 153  
*Cryptosporidium*, 153  
*Listeria monocytogenes*, 139  
invasive aspergillosis, 153  
*Pneumocystis jirovecii*, 153
- Immunodeficiencies, **116**  
Th1 response, 116  
Th17 cell deficiency, 116
- Immunodeficiency syndromes  
flow cytometry diagnosis, 54  
infections in, 118
- Immunofluorescence  
*pemphigus vulgaris* vs bullous pemphigoid, 494
- Immunoglobulin A vasculitis, 484  
epidemiology/presentation, 484
- Immunoglobulins  
adaptive immunity and, 99  
breast milk and, 659  
for Kawasaki disease, 484  
isotypes of, 105  
monoclonal gammopathy, 440
- Immunohistochemical stains  
for tumor identification, **228**
- Immunology  
cellular components, 99  
immune responses, 104  
immunosuppressants, 120  
lymphoid structures, 96
- Immunophenotype assessment, 54
- Immunosuppressants  
for aplastic anemia, 431  
targets, 120  
transplant rejection, 120
- Immunosuppression  
squamous cell carcinoma and, 498  
targets, **121**  
vitamin A deficiency, 66
- Immunotherapy  
recombinant cytokines, 121
- Impaired colleague, 277
- Imperforate hymen, 668
- Impetigo, 492  
crusts with, 489  
*Streptococcus pyogenes*, 136
- implantation, 656
- Imprinting disorders, **58**
- Inactivated (killed) vaccine, 111
- Incidence vs prevalence, 265
- Inclusions  
associated pathology, **426**  
Cowdry A, 166  
Negri bodies, 171  
“owl eye”, 165  
RBCs, **426**  
reticulate bodies, 148
- Incomplete penetrance, 56
- Incontinence (fecal/urinary), 463
- Incus (ossicles), 551  
pharyngeal arch derivative, 644
- India ink stain, 125
- Indicator media, 126
- Indirect bilirubin, 385
- Indirect cholinomimetic agonists, 243
- Indirect Coombs test, 420
- Indirect inguinal hernia, 380
- Indirect sympathomimetics, 245
- Indomethacin, 500
- Infant  
deprivation effects, **579**
- Infant development, 578
- Infarction  
bone and marrow, 475  
hypoxia/ischemia and, 210
- Infarcts  
atherosclerosis, 310  
cortical watershed areas, 518  
pituitary, 347  
types of, 210
- Infections, 153  
brain abscess with, 180  
dilated cardiomyopathy and, 318
- ESR in, 215
- IL-12 receptor deficiency, 116  
in immunocompromised patients, 139  
in immunodeficiency, 118
- Inferior coliculi, 520
- Inferior gluteal nerve, 463
- Inferior oblique muscle, 560
- Inferior rectal artery, 375
- Inferior rectus muscle, 560
- Infertility  
clomiphene, 680  
Kallmann syndrome, 663  
Kartagener syndrome, 49  
leuprolide for, 680  
mumps, 678  
salpingitis, 185  
varicoceles, 675  
with uterine anomalies, 646
- Infiltrative cardiomyopathy, 318
- Inflammosome, 215
- inflammation  
cryptogenic organizing pneumonia, 707
- Inflammation  
acute, **215**  
cardinal signs, 214  
chronic, 217  
ESR in, 215  
granulomatous, 218  
in atherosclerosis, 310  
Intrinsic (mitochondrial) pathway, 208
- neutrophils in, 416
- systemic manifestations (acute-phase reaction), 214
- types of, **214**
- wound healing, 217
- Inflammatory bowel disease, **481**
- Inflammatory bowel diseases, **392**  
colorectal cancer and, 397  
erythema nodosum, 496  
methotrexate for, 450  
microscopic colitis, 392  
sclerosing cholangitis and, 405  
spondyloarthritis, 481  
therapeutic antibodies for, 122
- Inflammatory breast disease, 673, 674
- Infliximab  
for Crohn disease, 392  
target and clinical use, 122, 502
- Influenza  
orthomyxovirus, 167  
pneumonia, 707  
treatment/prevention, 201
- Influenza viruses  
characteristics, **169**
- Informed consent, 270, **271**
- Infraspinatus muscle  
Erb palsy, 458
- Infundibulopelvic ligament, 649
- Infundibulopelvic (suspensory) ligament, 649
- Inguinal canal, 379
- Inguinal hernia, 380
- Inguinal ligament, 378
- Inguinal triangle, 380
- Inhalational injury/sequelae, **700**
- Inhaled anesthetics, 570
- Inhaled psychoactive drugs, 594
- Inheritance modes, 59
- Inhibin  
Sertoli cell secretion of, 652
- Injury (unintentional), 279
- Innate immune system  
in acute inflammation, 215
- Innate immunity  
components and mechanism, 99, 419
- Inner ear, 551
- Inotropes, 320
- Inotropy, 295
- INR (international normalized ratio), 435
- Insomnia  
barbiturates for, 566  
stimulants causing, 591
- Inspiratory capacity (IC), 688
- Inspiratory reserve volume (IRV), 688
- Insulin  
fructose bisphosphatase-2 and, 76  
glycogen regulation, 70, 86  
potassium shifts with, 614  
synthesis, function, and regulation, **342**
- Insulin deficiency, 614
- Insulin-like growth factor 1 (IGF-1)  
acromegaly, 347  
signaling pathways for, 345
- Insulinoma, 361  
insulin and C-peptide in, 342  
MEN 1 syndrome, 358  
pancreatic cell tumor, 358
- Insulin preparations, **362**
- Insulin resistance, 658  
acanthosis nigricans and, 496  
acromegaly, 347  
cortisol, 344  
Cushing syndrome, 356  
GH, 337  
non-alcoholic fatty liver disease, 401  
polycystic ovarian syndrome, 669
- Insurance  
disregarding in treatment, 277  
types of plans, 278
- Integrase inhibitors, 203
- Integrins  
epithelial cell junctions, 488  
viral receptor, 166
- Intellectual disability, 580  
autism and, 580  
childhood and early-onset disorders, **580**  
cri-du-chat syndrome, 64  
Patau syndrome, 63  
phenylketonuria, 84  
Williams syndrome, 64
- Intellectualization, 577
- Intention tremor, 537  
cerebellar lesions, 528
- Interdigital tinea pedis, 152
- Interferons  
clinical use, 121  
mechanism and clinical use, **109**
- Interferon- $\gamma$   
secretion and function, 108
- Interleukin 1 (IL-1), 108
- Interleukin 2 (IL-2), 108  
clinical use, 121  
sirolimus and, 120  
tacrolimus and, 120
- Interleukin 3 (IL-3), 108
- Interleukin-4  
functions of, 108
- Interleukin 5 (IL-5)  
functions of, 108
- Interleukin 6 (IL-6), 108
- Interleukin 8 (IL-8), 108
- Interleukin 10 (IL-10)  
functions of, 108
- Interleukin 12 (IL-12), 108

- Interleukin receptor modulators naming conventions for, 258
- Intermediate acting insulin, 362
- Intermediate filaments cytoskeletal element, 48
- Intermenstrual bleeding (IMB), 657
- Intermittent explosive disorder, 580
- Internal carotid artery cavernous sinus, 562
- Internal hemorrhoids, 376
- Internal jugular vein, 519
- Internal oblique muscle, 462
- Internal rotation arm (rotator cuff), 456 hip, 461
- International Foundations of Medicine (IFOM), 12
- Internuclear ophthalmoplegia, 528, 563
- Interossei muscles Klumpke palsy, 458
- Interpersonal therapy, 596
- Interpreting study results, 266
- Interstitial (atypical) pneumonia, 707
- Interstitial fluid, 303
- Interstitial lung disease, 699
- Interstitial nephritis acute, 625 as drug reaction, 254 NSAID toxicity, 500 penicillins, 188
- Interstitial pneumonia, 707
- Interstitial leukocyte extravasation and, 215
- Interventricular foramen, 289
- Interventricular septal rupture, 313, 317
- “Intestinal angina”, 396
- Intestinal atresia, 369
- Intestinal obstruction intermittent, 373 superior mesenteric artery syndrome, 373
- Intimate partner violence, 277
- Intoxication (psychoactive drugs), 594
- Intracellular bacteria, 127
- Intracellular receptors endocrine hormone signaling pathways, 345
- Intracranial calcifications Toxoplasma gondii, 156
- Intracranial hemorrhage eclampsia, 667 epidural hematoma, 531 intraparenchymal, 531 subarachnoid, 530 subdural hematoma, 531
- Intracranial hypertension idiopathic, 540 vitamin A toxicity, 66
- Intracranial pressure (ICP) cerebral ischemia, 303 hydrocephalus, 540 in perfusion regulation, 517 papilledema, 557 superior vena cava syndrome, 710
- Intraductal papilloma, 673
- Intraepithelial adenocarcinoma, 668
- Intraocular pressure (IOP), 555
- Intraparenchymal hemorrhage, 531
- Intrauterine device (IUD) copper, 681
- Intrauterine growth restriction (IUGR) low birth weight, 658 substance abuse, 638
- Intravascular hemolysis causes and findings with, 431 G6PD deficiency, 432 microangiopathic hemolytic anemia, 433 paroxysmal nocturnal hemoglobinuria, 107
- Intravenous anesthetics, 570
- Intraventricular hemorrhage, 530
- Intrinsic factor source and action, 382
- Intrinsic hemolytic anemias, 432
- Intrinsic (mitochondrial) pathway regulating factors for, 208
- Intrinsic pathway, 435 coagulation defects of, 435 heparin and, 446
- Intrinsic renal failure, 625
- Introms splicing out, 41 vs exons, 43
- intussusception, 394
- Intussusception, 395
- Inulin glomerular filtration rate and, 605 in proximal convoluted tubules, 611
- Inulin clearance, 606
- Invariant chain, 100
- Invasive carcinoma cervix, 669
- Invasive lobular carcinoma (breast), 674
- Inversion, 463
- In vivo biofilm-producing bacteria, 128
- Involuntary treatment, 273
- Iodine infection control, 204 teratogenic effects, 638
- Iodine-induced hyperthyroidism, 350
- Iodophors, 204
- Ionizing radiation carcinogenicity, 226
- Ionizing radiation toxicity, 211
- IP3 endocrine hormone signaling pathways, 345
- Ipilimumab, 452
- Ipratropium, 244, 712
- Irinotecan, 452
- Iritis, 555
- Iron absorption and vitamin C, 69 absorption of, 69 excess, 67 in hemochromatosis, 405 toxicity of, 69 toxicity treatment, 251
- Iron deficiency lab findings with anemia, 428
- Iron deficiency anemia, 428 with colorectal cancer, 398
- Iron granules (in RBCs), 426
- Iron poisoning acute vs chronic, 435
- Iron studies, interpretation, 429
- Irritable bowel disease (IBD) GI bleeding with, 390
- Irritable bowel syndrome criteria and symptoms, 393
- Irritable bowel syndrome (IBS) antispasmodic drugs, 244
- Isavuconazole mucormycosis treatment, 153
- Ischemia, 207 acute tubular necrosis from, 625 atherosclerosis, 310
- colon, 396 digital, 486 mesenteric, 396 oxygen deprivation, 693 vulnerable organs and mechanisms, 210 watershed areas, 210
- Ischemic brain disease/stroke consequences of, 529
- Ischemic heart disease contraindicated antiarrhythmics, 330 heart murmurs in, 300
- Ischemic heart disease manifestations, 312
- Ischemic priapism, 675
- Ischemic stroke types of, 529
- Islet cell cytoplasmic antibodies, 94
- Islets of Langerhans, 335
- Isocarboxazid, 599
- Isocitrate dehydrogenase rate-determining enzyme, 73
- Isodisomy, 57
- Isoflurane, 570
- Isolated atrial amyloidosis, 213
- Isolation of affect, 577
- Isoleucine classification of, 81 maple syrup urine disease and, 81
- Isoniazid cytochrome P-450, 255 hemolysis in G6PD deficiency, 253 hepatitis, 252 mechanism and clinical use, 197 seizures with, 253
- Isoproterenol sympathomimetic action, 246
- Isosorbide dinitrate, 326
- Isosorbide mononitrate, 326
- Isotretinoin cystic acne, 66 teratogenicity of, 638
- Isovolumetric contraction, 296
- Isovolumetric relaxation, 296
- Itraconazole, 151 azoles, 199 *Sporothrix schenckii*, 154
- Ivabradine mechanism and clinical use, 332
- IVC, 370
- Ivermectin, 200 “Ivory white” plaques, 701
- IV phlebitis, 199
- Ixazomib, 453
- Ixekizumab target and clinical use, 122
- Ixodes ticks, 146
- J**
- JAK2 gene, 225
- JAK2 gene myeloproliferative disorders, 442
- Janeway lesions, 321
- Jarisch-Herxheimer reaction, 148
- Jaundice, 80, 403 biliary tract disease, 403 cholangitis, 407 drug reaction and, 252 galactosemia, 80 graft-versus-host disease, 119 hepatitis B, 182 hereditary hyperbilirubinemias, 404
- neonatal, 403 painless, 378 pancreatic cancer, 408
- TORCH infections, 182 yellow fever, 171
- Jaw jerk reflex, 523
- JC virus PML in HIV, 164
- JC virus (John Cunningham virus) HIV-positive adults, 177 immunocompromised patients, 118 polyomaviruses, 164
- Jejunum histology, 372
- Jervell and Lange-Nielsen syndrome, 315
- JAK2 gene in myeloproliferative disorders, 443
- Jimson weed, 244
- Jod-Basedow phenomenon causes and findings, 350
- Joint hypermobility, 51
- jugular venous distention (JVD) heart failure, 319
- Jugular venous distention (JVD), 710 right heart failure, 319
- Jugular venous pulse, 296
- Justice (ethics), 270
- Juvenile polyposis, 397
- Juvenile polyposis syndrome, 397
- Juxtaglomerular apparatus (JGA), 613 renin secretion, 613
- Juxtaglomerular cells tumors in, 358
- K**
- Kala-azar, 158
- kallikrein, 107
- Kallmann syndrome, 513, 663
- Kaposi sarcoma, 492 bacillary angiomatosis vs, 492 HHV-8, 165 HIV-positive adults, 177 oncogenic microbes and, 227
- Kartagener syndrome, 49 dextrocardia, 288 obstructive lung disease, 699
- Karyotyping, 55
- KatG, 197
- Kawasaki disease, 484
- Kayser-Fleischer rings, 405
- K cells GIP production, 381
- K complexes/sleep spindles, 512
- Kegel exercises, 623
- Keloid scars, 219
- Keratinocytes, 217
- Keratin pearls, 709
- Keratoacanthoma characteristics of, 498
- Keratoconjunctivitis, 164
- Keratoconjunctivitis sicca, 480
- Keratomalacia, 66
- Keratosis actinic, 496 hyperkeratosis, 489 parakeratosis, 489 seborrheic, 491
- Kemiciterus, 204, 404
- Kernohan notch, 547
- Ketamine, 570
- Ketoacidosis in ethanol metabolism, 72
- Ketoconazole, 682 cytochrome P-450, 255 mechanism and clinical use, 199
- Ketogenesis metabolic site, 72 rate-determining enzyme for, 73

Ketone bodies  
in alcoholism, 90  
in starvation, 91  
Ketorolac, 500  
Kidney  
anatomy and glomerular structure, 604  
changes in glomerular dynamics, 607  
glucose clearance, 608  
reabsorption and secretion rate calculation, 608  
Kidney disease  
acute injury, 625  
hypertension, 307  
Kidneys  
blood flow regulation to, 304  
chronic graft nephropathy, 119  
electrolyte disturbances, 615  
embryology, 602  
hormones acting on, 614  
ischemia in, 210  
transplant prophylaxis, 120  
Kidney stones  
content and characteristics of, 622  
hyperparathyroidism, 353  
presentation and findings with, 622  
risk factors for, 617  
UTIs, 181  
Kiesselbach plexus, 695  
Killian triangle, 394  
Kinases, 73  
Kinesin  
movement of, 48  
Kinin cascade/pathways, 422  
*Klebsiella* spp, 145  
alcoholism, 179  
kidney stones and, 622  
nosocomial infections, 185  
pneumonia, 707  
urease-positive, 127  
*Klebsiella pneumoniae*  
cephalosporins, 189  
encapsulation, 127  
UTIs, 181  
Klinefelter syndrome  
characteristics of, 661  
chromosome association, 64  
gynecomastia, 673  
Klumpke palsy  
injury and deficits, 458  
Klüber-Bucy syndrome, 528  
Knee injuries/conditions  
Baker cyst, 471  
common, 471  
ilitibial band syndrome, 472  
ligament and meniscus, 471  
Osgood-Schlatter disease, 473  
prepatellar bursitis, 471  
test procedure, 464  
KOH preparation, 152  
Koilocytes  
condyloma acuminata, 184  
Koilocytosis, 491  
Koilonychia, 428  
Koplik spots, 183  
Korsakoff syndrome, 66, 581  
Krabbe disease, 88  
KRAS gene, 225  
adenomatous colonic polyps and, 397  
lung cancer and, 709  
Krukenberg tumor, 389  
 $K_m$ , 232  
Kübler-Ross grief model, 578  
Kulchitsky cells, 709

Kupffer cells, 377  
Kuru, 178  
Kussmaul sign, 324  
Kwashiorkor, 71  
Kyphoscoliosis, 549  
Kyphosis  
in homocystinuria, 85  
osteoporosis, 474

**L**

labetalol, 326  
Labetalol  
hypertension in pregnancy, 324  
Labia, 649  
Labile cells, 46  
*Lac* operons, 40  
Lachman test, 464  
Lacrimation reflex, 523  
Lactase deficiency, 81  
Lactation, 654, 659  
Lactational mastitis, 673  
Lactic acid dehydrogenase, 77  
Lactic acidosis  
ethanol metabolism and, 72  
exercise and, 694  
pyruvate dehydrogenase complex deficiency, 77  
Lactose-fermenting enteric bacteria, 126, 144  
Lactose hydrogen breath test, 391  
Lactose intolerance, 391  
Lactose metabolism  
genetic response to environmental change, 40  
Lactulose  
for hepatic encephalopathy, 401  
Lacunar infarcts, 532  
Ladd bands, 395  
Lambert-Eaton myasthenic syndrome  
as paraneoplastic syndrome, 229  
autoantibody, 115  
pathophysiology, symptoms of, 486  
small cell lung cancer, 709  
Lamina propria  
in Whipple disease, 391  
Peyer patches in, 384  
Lamins, 48  
Lamivudine, 203  
Lamotrigine  
epilepsy therapy, 564  
rash caused by, 253  
Lancet-shaped diplococci, 136  
Landmarks (anatomical)  
for dermatomes, 527  
vertebral, 374  
Langerhans cell histiocytosis  
presentation, 444  
pulmonary, 699  
Lansoprazole, 409  
Laplace law, 293, 685  
Large cell carcinoma of lung, 709  
Large-vessel vasculitis  
presentation and pathology, 484  
Larva migrans, 159  
Laryngopharyngeal reflux, 387  
Laryngospasm, 369  
drug-induced, 593  
Larynx, 686  
Larynx muscles, 644  
Lassa fever encephalitis, 167  
Latanoprost, 573  
Latent errors, 281  
Lateral collateral ligament (LCL) injury, 464  
Lateral corticospinal tract, 526  
Lateral epicondylitis, 469

Lateral femoral cutaneous nerve, 462  
Lateral geniculate nucleus (LGN), 513  
Lateral medullary syndrome, 533  
Lateral medullary (Wallenberg) syndrome, 533  
Lateral pterygoid muscle, 524  
Lateral rectus muscle, 560  
Lateral spinothalamic tract, 526  
Lateral thoracic artery, 465  
Lateral ventricles  
optic radiation, 562  
ventricular system, 520  
Laxatives  
types and adverse effects, 411  
LD50 (lethal median dose), 237  
LDH  
serum tumor marker, 227  
LDL (low-density lipoprotein), 94  
PCSK9 enzyme, 93  
receptor binding, 93  
Leaden paralysis, 584  
Lead poisoning  
anemia with, 429  
mechanism and presentation, 434  
signs/symptoms and treatment, 429  
Lead-time bias, 266  
Leber hereditary optic neuropathy (LHON), 59  
Lecithinase, 133, 138  
Lecithin-cholesterol acyltransferase (LCAT)  
activation of, 93  
Lecithin-cholesterol acyltransferase, 93  
Leflunomide  
dihydroorotate dehydrogenase inhibition, 36  
mechanism, use and adverse effects, 500  
Left bundle branch, 302  
Left circumflex coronary artery, 313  
Left heart disease  
pulmonary hypertension, 703  
Left heart failure, 319  
Left shift, 416  
Left ventricular (LV) failure  
pulmonary edema, 317  
Legg-Calvé-Perthes disease, 473  
*Legionella* spp  
atypical organism, 179  
culture requirements, 126  
facultative intracellular organisms, 127  
intracellular organism, 127  
macrolides, 193  
nosocomial infection, 182  
pneumonia, 707  
stain for, 125  
*Legionella pneumophila*, 143  
*Legionella*  
Gram stain for, 125  
*Legionella* spp  
culture requirements, 126  
Legionnaires' disease, 143  
Leiomyoma (fibroid), 672  
nomenclature for, 221  
uterine bleeding with, 657  
Leiomyosarcoma, 221, 672  
Leishmania, 200  
*Leishmania* spp  
visceral infections, 158  
Length-time bias, 266  
Lens  
collagen in, 50  
infantile cataracts, 80

Lens dislocation  
Marfan syndrome and homocystinuria, 52  
Lens subluxation  
in homocystinuria, 85  
Lenticulostriate artery  
stroke effects in, 532  
Lentiform nucleus, 516  
Leonine facies, 141  
Lepromatous leprosy, 141  
Leprosy, 141  
Leptin  
appetite regulation, 344  
hypothalamus, 513  
*Leptospira interrogans*, 147  
*Leptospira* spp  
Gram stain of, 125  
zoonotic infections, 149  
Leptospirosis, 147  
Lesch-Nyhan syndrome  
purine salvage deficiency, 37  
Leser-Trélat sign, 229  
GI adenocarcinoma, 491  
stomach cancer, 389  
Lesser omental sac, 371  
Letrozole, 680  
Leucine  
classification of, 81  
maple syrup urine disease and, 81  
Leucovorin, 450, 453  
Leukemia, 223  
vs lymphoma, 438  
Leukemias  
cause and presentation of, 442  
cell type, 221  
cyclophosphamide for, 449  
cytarabine for, 450  
lymphoma comparison, 438  
mucormycosis, 153  
nomenclature for, 221  
suppressor genes, 225  
vinca alkaloids for, 451  
Leukemoid reaction vs chronic myelogenous leukemia, 443  
Leukocoria, 557  
Leukocyte adhesion deficiency immunodeficiencies, 117  
Leukocyte alkaline phosphatase (LAP), 416  
Leukocyte esterase, 181, 624  
Leukocyte extravasation  
acute inflammation, 215  
CD34 protein, 215  
process and steps of, 216  
Leukocytes  
in urine (pyuria), 181, 618  
leukemias, 442  
Leukocytoclastic vasculitis, 174  
Leukocytosis, 214  
nosocomial infections, 182  
Leukodystrophies, 508  
Leukoerythroblastic reaction, 416  
Leukopenias, 194  
cell counts and causes, 433  
ganciclovir, 202  
Leukoplakia  
hairy, 493  
vulvar carcinoma and, 668  
Leukotrienes  
cortisol effects, 344  
Leuprolide, 680  
Leutinizing hormone(LH)  
clomiphene effects on, 680  
Levator veli palatini muscle, 644  
Levetiracetam, 564

- Levodopa, 568  
 Levodopa (l-DOPA)/carbidopa, 568  
 Levofloxacin, 195  
 Levomilnacipran, 599  
 Levonorgestrel, 681  
 Levothyroxine/liothyronine mechanism, use and adverse effects, 364  
 Lewy bodies, 538, 539 dementia, 538  
 Lewy body dementia symptoms and histologic findings, 539  
 Leydig cells cryptorchidism, 675 endocrine function, **652**, 660 genital embryology, 645 tumors of, 676  
 Leydig cell tumor, 676  
 LFA-1 antigens, 216  
 LFA-1 integrin protein defect in phagocytes, 117  
 Libido testosterone and, 659  
 Libman-Sacks endocarditis, 482  
 Lice head/scalp, 161 treatment, 200  
 Lichen planus, 174, 489, 496  
 Lichen sclerosus, 668  
 Lichen simplex chronicus, 668  
 Liddle syndrome renal disorder features, 615 renal tubular defects, 610  
 Lid lag/retraction, 348  
 LildocaIne, 571  
 Life support withdrawal, 277  
 Li-Fraumeni syndrome osteosarcomas, 477 tumor suppressor genes in, 46  
 Ligaments female reproductive anatomy, 649 gastrointestinal anatomy, **371**  
 Ligamentum arteriosum, 291  
 Ligamentum teres hepatis, 371  
 Ligamentum teres hepatis (round ligament), 291  
 Ligamentum venosum, 291  
 Lightheadedness, 552  
 Likelihood ratio (LR), 263  
 Limb compartment syndrome, 472  
 Limbic system, 514  
 Limited scleroderma autoantibody, 115, 487  
 Limitless replicative potential, 222  
 Linagliptin, 363  
 Linear ulcers, 387  
 Linear viruses, 163  
 Lines of Zahn, 696  
 Lineeweaver-Burk plot, 232  
 Linezolid highly resistant organisms, 198 mechanism and clinical use, **193** protein synthesis inhibition, 191  
 Lingula (lung), 687  
 Linkage disequilibrium, 57  
 Liothyronine (T<sub>3</sub>), 364  
 Lipase in pancreatitis, 407  
 Lipases pancreatic secretion, 383  
 Lipid-lowering agents mechanism and adverse effects, 328  
 Lipids transport of, 89  
 Lipid transport key enzymes in, **93**  
 Lipodystrophy tesamorelin for, 336  
 Lipofuscin, **212**  
 Lipoic acid, 76  
 Lipolysis cortisol and, 344 sympathetic receptors and, 241 thyroid hormone and, 339  
 Lipomas, 221  
 lipooligosaccharides (LOS) endotoxin activity, 142  
 Lipoprotein lipase, 93  
 Lipoproteins functions of, **94**  
 Liposarcomas, 221  
 Lipoteichoic acid cytoplasmic membrane, 124  
 Liquefactive necrosis, 209  
 Liraglutide, 363  
 Lisch nodules, 543  
 Lisdexamfetamine, 596  
 Lisinopril, 633  
 Lissencephaly, 505  
*Listeria* spp facultative intracellular organisms, 127 intracellular organism, 127  
*Listeria monocytogenes*, **139** food poisoning, 178  
 Lithium diabetes insipidus and, 252 mechanism and use, **598** prenatal exposure, 308 teratogenicity of, 638 thyroid functions with, 252 toxicity of, 593  
 Live attenuated vaccines, 111  
 Liver in gastrointestinal anatomy, 371 ischemia in, 210 lipid transport and, 94 sources of metastases, 224, 402 tissue architecture, 377 tumors of, **402**  
 Liver/biliary disease alcoholic, 401 Budd-Chiari syndrome and, 402 cirrhosis, 71, 80 cystic fibrosis, 60 drug dosages with, 233 hepatosteatosis, 72 hereditary, 404 serum markers, 400 sources of metastases, 224 Wilson disease and, 405  
 Liver failure movement disorder in, 537  
 Liver fluke hyperbilirubinemia with, 403  
 Liver function tests cholestatic pattern of, 405 serum markers for, **400** thyroid storm, 350  
 Liver markers in alcohol use, 594  
 Liver transplants graft-versus-host disease, 119  
 Living wills, 272  
*Loa loa*, 158 tissue infections, 159  
 Loading dose calculations, 233  
 Lobar pneumonia natural history of, 707 organisms and characteristics, 707 physical findings with, 704  
 Lobular carcinoma in situ, 674  
 Localized amyloidosis, 213  
 Locked-in syndrome osmotic demyelination syndrome, 542  
 Locus ceruleus, 510  
 Locus heterogeneity, 57  
 Löffler endocarditis restrictive/infiltrative cardiomyopathy, 318  
 Löffler medium, 126 *Corynebacterium diphtheriae*, 139  
 Long acting insulin, 362  
 Long-chain fatty acid (LCFA) metabolism of, 89  
 Long QT syndrome sudden cardiac death, 312  
 Long thoracic nerve neurovascular pairing, 465  
 Loop diuretics, **631** for heart failure, 319 toxicity of, 254  
 Loop of Henle, 631 Bartter syndrome and, 610 ethacrynic acid effect on, 631  
 "Loose associations", 582  
 Loperamide mechanism and clinical use, 410  
 Lopinavir, 203  
 Loratadine, 710  
 Lorazepam alcohol withdrawal, 596  
 Losartan, 633  
 loss, 483  
 Lou Gehrig disease, 548  
 Low birth weight, 658  
 Löwenstein-Jensen agar/medium, 126  
 Lower esophageal sphincter (LES) achalasia and, 381 nitric oxide and, 381  
 Lower extremity nerves innervation, injury and presentation, **462**  
 Lower extremity ulcers, **495**  
 Lower GI bleeding, 390  
 Lower left quadrant (LLQ) pain, 393  
 Lower motor neuron (LMN), 526, 550 Brown-Séquard syndrome, 549 deficits in amyotrophic lateral sclerosis, 548  
 facial nerve lesion, 550 facial paralysis, 532 lesion signs in, 547 poliomyelitis, 549  
 LPS endotoxin, 131  
 LTB<sub>4</sub> (Leukotriene B4), 416, 499  
 Lumbar puncture, 524  
 Lumbosacral radiculopathy, 465  
 Lumbrical muscles, 460 Klumpke palsy and, 458  
 Lumefantrine, 200  
 Lunate bone, 459  
 Lung abscess, **708**  
 Lung and chest wall, **689** compliance, 689 elastic recoil, 689 hysteresis, 689  
 Lung cancer cisplatin/carboplatin for, 452 hypercalcemia and, 229  
 incidence/mortality in, 223 metastases to, 223 non-small cell, 709 presentation and complications, 709 small cell, 709 types, location and characteristics, **709**  
 Lung diseases obstructive, 698 physical findings in, **704** restrictive, 699  
 Lungs anatomical relationships, 687 anatomy, **687** blood flow regulation, 304 physical findings, 704 sclerosis of, 487 stages of, **684** structural development, 684 volumes and capacities, **688**  
 Lung zones, 693  
 Lupus marantic endocarditis in, 321 microangiopathic hemolytic anemia, 433 nephritis, 482 neutropenia, 433  
 Lupus anticoagulant, 115  
 Lurasidone, 597  
 Luteinizing hormone (LH) contraception, 681 estrogen/progesterone, 654 ovulation, 654 PCOS, 670 premature ovarian failure, 659 signaling pathways of, 345 spermatogenesis, 652  
 Lyme disease, **146** animal transmission, 149 ceftriaxone, 189  
 Lymphadenopathy hilar, 699 *Corynebacterium diphtheriae*, 132 in viral infections, 96 *Toxoplasma gondii*, 182 *Trypanosoma brucei*, 156  
 Lymphogranuloma venereum, 184 mediastinal, 700 mononucleosis, 165 rubella, 169, 182 serum sickness, 113 syphilis, 184 tinea capitis, 152  
 Lymphatic exudate, 705  
 Lymphatic filariasis (elephantiasis) *Wuchereria bancrofti*, 159  
 Lymphatic gonadal drainage, 648  
 Lymph drainage superficial inguinal nodes, 648  
 Lymph nodes anatomy and function, **96** drainage sites, 97 gonadal drainage, 648 tumor metastases, 224  
 Lymphocyte-depleted lymphoma, 438  
 Lymphocytes, **419** breast milk and, 659 CLL/small cell lymphocytic lymphoma, 442 corticosteroid effect on, 433 lichen planus, 496 non-Hodgkin lymphoma, 439 spleen, 96 thymus, 96

- Lymphocytic choriomeningitis virus (LCMV)  
arenaviruses, 167
- Lymphogranuloma venereum, 184  
*Chlamydia trachomatis*, 149
- Lymphoid hyperplasia, 393
- Lymphoid neoplasms, 439  
types of, 442
- Lymphoid structures  
Peyer patches, 384
- Lymphomas, 451  
Burkitt, 439  
cytarabine for, 450  
diffuse large B-cell lymphoma, 439  
doxorubicin for, 449  
EBV and, 165  
follicular, 439  
Hodgkin, 438  
hypercalcemia and, 229  
leukemia comparison, 438  
mantle cell, 439  
nomenclature for, 221  
non-Hodgkin, 439  
of stomach, 389  
oncogene for, 225  
oncogenic microbes, 227  
paraneoplastic syndromes with, 229  
testicular, 677
- Lymphopenias  
ataxia-telangiectasia, 117  
cell counts and causes, 433  
corticosteroid effect on, 433
- Lynch syndrome, 398  
colorectal and associated cancers, 398  
mismatch repair and, 39
- Lyonization (x-inactivation)  
Barr body formation, 61
- Lysergic acid diethylamide (LSD), 595
- Lysine  
classification of, 81  
for pyruvate dehydrogenase complex deficiency, 77  
in cystinuria, 85  
kidney stones, 622
- Lysogenic phage infection, 130
- Lysosomal storage diseases, 47  
causes and effects of, 87
- Lysosomal trafficking regulator gene (LYST), 117
- Lysosomal  $\alpha$ -1 4-glucosidase, 86, 87
- LYST gene, 117
- Lytic bone lesions  
adult T-cell lymphoma and, 439  
Langerhans cell histiocytosis, 444
- M**
- MacConkey agar, 126, 144  
“Machine-like” murmur, 300
- Macroangiopathic hemolytic anemia  
causes and findings, 433
- Macrocytic anemias, 429
- Macroglobulinemia, 440
- Macrolides  
*Bordetella pertussis*, 143  
*Mycoplasma pneumoniae*, 150  
mechanism and clinical use, 193  
mechanism and use, 192  
protein synthesis inhibition, 191  
torsades de pointes, 251
- Macro-ovalocytes  
associated pathology, 425
- Macrophage-lymphocyte interaction, 102  
Macrophages, 417  
apoptosis and, 209  
breast milk and, 659  
cell surface proteins, 110  
cytokines secreted by, 108  
endotoxin activation, 133  
in MI, 313  
in wound healing, 217  
lymphocyte interaction, 96, 102  
pneumoconioses, 701
- Macrosomia, 638
- Macula densa  
juxtaglomerular apparatus, 613
- Macular cherry-red spot, 88
- Macular degeneration, 556
- Macules  
characteristics, 489  
junctional nevi, 491
- Maculopapular rash  
graft-versus-host disease, 119  
measles, 169  
syphilis, 147
- Magnesium  
antiarrhythmic treatment, 332  
cardiac glycoside overdose, 329  
cardiac glycoside toxicity, 332  
laxative effects of, 411  
torsades de pointes and, 315
- Magnesium hydroxide, 409
- Magnesium sulfate  
preeclampsia/eclampsia, 667
- Magnetic gait, 540
- Maintenance drug dose, 233
- Major apolipoproteins, 93
- Major depressive disorder  
peripartum onset, 585  
with psychotic features, 584  
with seasonal pattern, 584
- Major depressive disorder (MDD)  
diagnostic symptoms for, 584  
persistent depressive disorder (dysthymia), 584
- Major functions of B and T cells, 101
- Malabsorption/malnutrition  
inflammatory bowel diseases, 392
- Malabsorption syndromes, 391  
fat-soluble vitamin deficiencies, 65
- Malaria  
artesunate for, 200  
*Plasmodium*, 157  
quinidine/quinine for, 198
- Malassezia spp  
cutaneous mycoses, 152  
seborheic dermatitis, 490
- Malathion, 161
- Male/female genital homologs, 647
- Male genital embryology, 645
- Male reproductive anatomy, 650
- Male sexual response, 651
- Malformation (morphogenesis), 637
- Malignancy  
marantic endocarditis in, 321  
uterine bleeding with, 657
- Malignancy/hyperplasia  
uterine bleeding with, 657
- Malignant hyperthermia, 570
- Malignant mesothelioma, 226
- Malignant tumors, 221  
bones, 477
- Malingering, 589  
vs factitious disorder and somatic symptom disorders, 589
- Malleus (ossicles), 551, 644
- Mallory bodies  
in alcoholic hepatitis, 401
- Mallory-Weiss syndrome, 387
- Malnutrition, 71  
superior mesenteric artery syndrome with, 373
- Malrotation, 395  
“Maltese cross” appearance, 157
- MALT lymphoma  
*H. pylori* and, 389
- MALT lymphomas  
*Helicobacter pylori*, 146  
oncogenic microbes and, 227  
Sjögren syndrome, 480
- Mammary glands, 637
- Mammillary bodies  
limbic system, 514
- Mammillary bodies (bilateral)  
lesion effects, 528
- Mandibular process, 644
- Manic episode, 583
- Mannitol, 630  
extracellular volume measurement, 605  
mechanism and clinical use, 630  
mechanism, use and adverse effects, 630
- Mantle cell lymphomas, 444  
occurrence and genetics, 439
- Maple syrup urine disease, 84
- Marantic endocarditis, 229, 321
- Marasmus, 71
- Maraviroc, 203
- Marburg hemorrhagic fever  
filoviruses, 167
- Marcus Gunn pupil, 559
- Marcus Gunn pupils  
multiple sclerosis, 541
- Marfanoid habitus  
homocystinuria, 85  
MEN 2B syndrome and, 360
- Marfan syndrome  
aortic dissection and, 310  
cardiac defect association, 308  
cataracts, 554  
chromosome association, 64  
elastin and, 52  
heart murmur with, 300  
thoracic aortic aneurysm and, 310
- Marginal zone lymphoma  
occurrence and causes, 439
- Marginal zone (spleen), 98
- Marine omega-3 fatty acids, 328
- Masseter muscle, 523, 524
- Mast cells, 418  
cromolyn sodium for, 418
- Mast cell stabilizers, 712
- Mastectomy  
winged scapula with, 458
- Mastication muscles, 523, 524
- Mastoid air cells, 644
- Mastoiditis  
brain abscesses, 180  
granulomatosis with polyangiitis, 485
- Maternal PKU, 84
- Mature cystic teratoma, 671
- Mature ego defenses, 577
- Maxillary artery, 289
- Maxillary process, 644
- Mayer-Rokitansky-Küster-Hauser syndrome, 645
- McArdle disease, 87
- McBurney point, 393
- McCune-Albright syndrome, 57, 660
- M cells  
antigen presentation, 384
- McMurray test, 464
- Mean arterial pressure  
equation for, 294  
gradient with intracranial pressure, 517
- Mean (statistics), 267
- Measles, 183  
paramyxovirus, 167, 168  
vitamin A for, 66
- Measles (rubeola) virus  
presentation, 170  
unvaccinated children, 186
- Measurement bias, 266
- Measures of central tendency, 267
- Measures of dispersion, 267
- Mebendazole, 200  
microtubules and, 48
- mecA gene  
penicillin resistance and, 135
- Meckel diverticulum, 394, 642
- Meconium ileus, 396  
cystic fibrosis, 60
- Medial calcific sclerosis, 309
- Medial collateral ligament (MCL)  
injury  
in “unhappy triad”, 471
- Medial epicondylitis, 469
- Medial femoral circumflex artery, 475
- Medial geniculate nucleus (MGN), 513
- Medial lemniscus, 533
- Medial longitudinal fasciculus (MLF)  
effects of lesions, 528  
eye movements and, 563
- Medial medullary syndrome, 533
- Medial meniscal tear, 464
- Medial pterygoid muscle, 524
- Medial tibial stress syndrome, 472
- Medial umbilical ligament, 291
- “Median claw”, 460
- Median nerve  
carpal tunnel syndrome, 470  
injury and presentation, 457  
neurovascular pairing, 465  
recurrent branch, 457
- Median umbilical ligament, 291
- Mediastinal lymphadenopathy, 699
- Mediastinal masses, 696
- Mediastinal pathology, 696  
lymphadenopathy, 699  
masses, 696  
mediastinitis, 137, 696  
pneumomediastinum, 696
- Medical abortion  
ethical situations, 276  
methotrexate for, 450
- Medical error analysis, 281
- Medical errors  
types of, 281
- Medical insurance plans, 278
- Medical power of attorney, 272
- Medicare/Medicaid, 279
- Medium-chain acyl-CoA dehydrogenase deficiency, 89
- Medium-vessel vasculitis  
presentation and pathology, 484
- Medroxyprogesterone, 681
- Medulla (brain)  
cranial nerves and nuclei, 520
- Medulla (lymph nodes)  
thymus, 96
- Medullary breast carcinomas, 674
- Medullary carcinoma (thyroid), 351
- Medullary cystic kidney disease, 627
- Medullary thyroid cancer  
amyloid deposits in, 213

- Medullary thyroid carcinomas, 360  
 Medulloblastoma, 358, 546  
 "Medusa head" appearance, 137  
 Mefloquine, 157  
 Megaeosophagus  
     *Trypanosoma cruzi*, 158  
 Megakaryocytes, 417  
 Megakaryocytes in essential thrombocythemia, 443  
 Megaloblastic anemia  
     causes and findings, 430  
     drug reaction and, 253  
*Diphyllobothrium latum*, 160  
 trimethoprim, 194  
 tropical sprue, 391  
 vitamin B<sub>9</sub> deficiency, 68  
 Megestrol, 681  
 Meglitinides, 363  
 Meissner corpuscles, 509  
 Meissner plexus, 394  
 Melanocytes  
     tumor nomenclature in, 221  
 Melanocyte-stimulating hormone (MSH)  
     function of, 336  
     signaling pathways of, 345  
 Melanocytic nevus, 491  
 Melanoma  
     metastasis of, 205  
     nomenclature for, 221  
     recombinant cytokines for  
         metastatic, 121  
     tumor suppressor gene, 225  
     types of, 498  
 Melarsoprol, 200  
 Melasma (cholasma), 490  
 MELAS syndrome, 59  
 Melena  
     GI bleeding, 390  
     Meckel diverticulum, 394, 642  
     polyarteritis nodosa, 484  
 Meloxicam, 500  
 Memantine, 569  
 Membrane attack complex (MAC), 106  
 Membranoproliferative glomerulonephritis  
     nephritic syndrome, 620  
 Membranoproliferative glomerulonephritis (MPGN)  
     hepatitis B and C, 174  
 Membranous glomerular disorders, 618  
     hepatitis B and C, 174  
 Membranous interventricular septum, 289  
 Membranous nephropathy, 621  
     primary autoantibody, 115  
 Membranous ossification, 468  
 Memory  
     neural structures and, 514  
 Memory loss  
     anti-NMDA receptor encephalitis, 229  
     lead poisoning, 434  
     Wernicke-Korsakoff syndrome, 528  
 MEN 1, 360  
 MEN1 gene, 205, 360  
 MEN 2A, 360  
 MEN 2B, 360  
 Ménétrier disease, 389  
 Ménière disease, 552  
 Menin, 225  
 Meninges, 511  
 Meningitis  
     chloramphenicol, 192  
     coccidioidomycosis, 151  
     common causes by age, 180  
     CSF findings in, 180  
     fluconazole, 199  
     flucytosine, 199  
     HIV-positive adults, 177  
*Cryptococcus neoformans*, 153  
*Listeria monocytogenes*, 139  
*Streptococcus agalactiae*, 137  
 mumps, 170  
 picornavirus, 168  
 unvaccinated children, 186  
 viral causes of, 180  
 Meningocele, 505  
 Meningococcal prophylaxis, 198  
 Meningococcal vaccine, 127  
 Meningococemia  
     endotoxins, 131  
 Meningococci  
     vs gonococci, 142  
 Meningoencephalitis  
     HSV-2, 182  
*Naegleria fowleri*, 156  
 West Nile virus, 167  
 Menkes disease  
     collagen crosslinking in, 50  
     mechanism and symptoms, 51  
 Menopause, 659  
     hormone replacement therapy, 681  
     Turner syndrome, 661  
 Menorrhagia, 657  
     anemia with, 428  
 Menstrual cycle  
     phases of, 656  
 Meperidine, 572  
 Mepivacaine, 571  
 Mercury poisoning, 251  
 Merkel discs, 509  
 Merlin protein, 225  
 MERS (Middle East respiratory syndrome), 164  
 Mesalamine, 392  
 Mesangial cells  
     juxtaglomerular apparatus, 613  
 Mesencephalon, 504  
 Mesenchymal tumors  
     nomenclature of, 221  
 Mesenchyme  
     tumor nomenclature, 221  
 Mesenteric arteries, 369  
 Mesenteric ischemia, 396  
 Mesna, 453  
 Mesocortical pathway, 514  
 Mesoderm, 504  
     derivatives, 637  
     pharyngeal (branchial) arches  
         derivation, 643  
 Mesolimbic pathway, 514  
 Mesometrium, 649  
 Mesosalpinx, 649  
 Mesothelioma, 702  
 Mesovarium, 649  
 Mestranol, 680  
 Meta-analysis, 269  
 Metabolic acidosis  
     laboratory findings with, 616  
     renal failure, 626  
 Metabolic alkalosis  
     in hypertrophic pyloric stenosis, 369  
     laboratory findings with, 616  
     nephron transport, 610  
     thiazides, 632  
 Metabolic disorders  
     fructose, 82  
     galactose, 80, 82  
     glycogen storage, 87  
 Metabolic drugs  
     name conventions for, 257  
 Metabolic fuel use, 91  
 Metabolic syndrome  
     non-alcoholic fatty liver disease  
         and, 401  
 Metabolism, 73  
     amino acid derivatives, 84  
     amino acids, 80  
     disorders of, 80  
     dyslipidemias, 94  
     ethanol, 70  
     fuel use, 89  
     gluconeogenesis, 78  
     lipoprotein functions, 94  
     pyruvate, 77  
     rate-determining enzymes, 73  
     sites, 74  
     summary of pathways, 74  
     TCA cycle, 77  
     tyrosine catabolism, 82  
 Metacarpal neck fracture, 470  
 Metacarpophalangeal (MCP) joints, 478  
 Metachromatic granules, 139  
 Metachromatic leukodystrophy, 88  
 Metalloproteinases, 217  
 Metal storage diseases, 210  
 Metanephric diverticulum, 602  
 Metanephries  
     in neuroblastomas, 359  
 Metanephros, 602  
 Metaphase, 46  
 Metaplasia, 206  
     esophagus, 388  
     intestinal, 389  
     specialized intestinal, 388  
 Metastases  
     common, 224  
 Metastasis, 221  
     gastric cancer, 389  
     heart tumors from, 324  
     lung cancer, 709  
     mechanisms, 222  
     melanoma, 498  
     neoplastic progression, 220  
 Metastatic calcification  
     characteristics of, 212  
 Metatarsophalangeal (MTP) joints  
     gout, 479  
 Metencephalon, 504  
 Metformin, 363  
     diarrhea with, 252  
 Methacholine, 243  
 Methadone, 572  
     heroin addiction, 572  
     opioid detoxification, 600  
     opioid withdrawal treatment, 594  
 Methamphetamine, 594  
 Methanol toxicity, 251  
 Methemoglobin, 690  
     toxicity treatment, 251  
 Methemoglobinemia  
     blood oxygen in, 690  
     local anesthetics and, 571  
     presentation, 690  
     treatment, 690  
 Methimazole, 364  
     agranulocytosis, 253  
     aplastic anemia, 253  
     teratogenicity of, 638  
 Methionine  
     classification of, 81  
     start codons, 44  
 Methotrexate  
     choriocarcinoma, 666  
     hydatidiform moles, 666  
     mechanism, use and adverse effects, 450  
     megaloblastic anemia, 253  
     pulmonary fibrosis, 254  
     pyrimidine synthesis and, 36  
     rheumatoid arthritis, 478  
     vitamin B<sub>9</sub> deficiency, 68  
 Methoxyflurane, 570  
 Methyldopa  
     Coombs-positive hemolytic anemia, 253  
     hypertension in pregnancy, 324  
 Methylene blue, 251, 690  
 Methylenetetrahydrofolate reductase (MTHFR) deficiency, 85  
 Methylmalonic acid  
     vitamin B<sub>9</sub> deficiency, 68  
     vitamin B<sub>12</sub> deficiency, 69  
 Methylmalonic acidemia, 85  
 Methylmalonyl-CoA mutase, 69  
 Methylmercury, 638  
 Methylnaltrexone, 572  
 Methylphenidate  
     ADHD, 596  
     CNS stimulant, 596  
 Methyltestosterone, 682  
 Methylxanthines, 712  
 Metoclopramide, 410  
     Parkinson-like syndrome, 254  
     tardive dyskinesia, 254  
     with chemotherapy, 453  
 Metolazone, 632  
 Metoprolol, 248, 331  
 Metronidazole  
     bacterial vaginosis, 148  
     clindamycin vs, 192  
     disulfiram-like reaction, 254  
     for Crohn disease, 392  
*Giardia lamblia*, 155  
     mechanism and clinical use, 195  
     vaginal infections, 181  
     vaginitis, 158  
 Meyer loop, 562  
 MHC (major histocompatibility complex) I and II, 100  
 Micafungin, 200  
 Michaelis-Menten kinetics, 232  
 Miconazole, 199  
 Microalbuminuria  
     diabetes mellitus, 354  
 Microangiopathic hemolytic anemia  
     causes and findings, 433  
     hypertensive emergency and, 308  
     intravascular hemolysis in, 431  
 Microarrays, 54  
 Microbiology, 123  
     antimicrobial therapy, 187  
     clinical bacteriology, 134  
     mycology, 151  
     oncogenic organisms, 227  
     parasitology, 155  
     systems, 178  
     virology, 162  
 Microcephaly, 63  
     cri-du-chat syndrome, 64  
     maternal phenylketonuria, 84  
     with lissencephaly, 505  
 Microcytic anemia  
     *Ancylostoma*, 159  
     lead poisoning, 434

- Microcytic, hypochromic anemias, 428
- Microcytosis, 215
- Microdeletion 22q11, 116  
congenital, 64  
fluorescence in situ hybridization, 55
- Microfilaments, 48
- Microglia, 504, 507
- Micrognathia, 63  
Edwards syndrome, 63  
Pierre Robin sequence, 644
- Micromelia, 638
- Microphthalmia, 63
- MicroRNA (miRNA), 42, 56
- Microscopic colitis, **392**
- Microscopic polyangiitis  
autoantibody, 115  
corticosteroids, 485  
epidemiology/presentation, 485  
glomerulonephritis with, 620
- Microsomal transfer protein (MTP)  
abetalipoproteinemia, 94
- Microsporum*, 152
- Microtubule, **48**
- Microtubule inhibitors  
mechanism, use and adverse effects, 451
- Microtubules  
drugs acting on, 48  
dysfunction of, 117  
structure and function of, **48**
- Micturition center, 240
- Micturition control, **240**
- Midazolam, 566, 570
- Midbrain  
lesions in, 528
- Middlebrook medium, 126
- Middle cerebral artery (MCA)  
saccular aneurysms, 534  
stroke effects, 532
- Middle ear, 551
- Middle meningeal artery  
epidural hematoma and, 531
- Middle rectal vein, 375
- Midgut  
blood supply/innervation of, 374
- Midgut volvulus, 396
- Midodrine, 245
- Mifepristone, 681
- Miglitol, 363
- Migraine headaches  
characteristics and treatment, 536  
hormonal contraception  
contra-indication, 681  
triptans for, 567
- Migrating motor complexes (MMC), 381
- Migratory polyarthritis, 322
- Milnacipran, 599
- Milrinone, 249
- mineralocorticoids, 357
- Mineralocorticoids  
adrenal steroids and, 344
- Mineral oil, 65
- Minimal alveolar concentration, 570
- Minimal change disease, 621
- Minocycline, 192
- Minors consent for, **272**
- Minoxidil, **682**
- Minute ventilation, 688
- Miosis  
cholinomimetic agents, 243
- Horner syndrome, 559
- pupillary control, 558
- Mirabegron, 245
- Mirtazapine, 247  
major depressive disorder, 584  
use and adverse effects, 600
- Mismatch repair, 39
- Misoprostol  
mechanism and clinical use, 409  
off-label use, 409
- Missense mutations, 40, 420
- Mites/louse treatment, 200
- Mitochondria  
high altitude and, 694  
metabolism in, 74
- Mitochondrial encephalopathy, 59
- Mitochondrial inheritance, 59
- Mitochondrial myopathies, 59
- mitosis, 200
- Mitosis, 46
- Mitral regurgitation, 297  
in MI, 313  
murmurs with, 300
- Mitral stenosis, 297  
murmurs caused by, 299
- Mitral/tricuspid regurgitation, **300**
- Mitral valve  
in cardiac cycle, 296  
regurgitation in, 322
- Mitral valve prolapse, 300  
Marfan syndrome, 52  
renal cyst disorders and, 627
- Mittelschmerz, 655
- Mixed cellularity lymphoma, 438
- Mixed connective tissue disease, **482**  
anti-U1 RNP antibodies, **482**  
autoantibody, 115
- Mixed cryoglobulinemia  
epidemiology/presentation, 485
- Mixed (direct and indirect)  
hyperbilirubinemia, 403
- Mixed platelet and coagulation disorders, **437**
- MMR vaccine, 170
- Mobitz type II block, 316
- Mobitz type I (Wenckebach), 316
- Modafinil, 591
- Modes of inheritance, **59**
- Mode (statistics), 267
- Molecular cloning, **55**
- Molecular mimicry  
autoimmune response in rheumatic fever, 129
- Molecular motor proteins, 48
- Molluscum contagiosum, 164  
skin infection, 493
- Mönckeberg sclerosis, 309
- "Monday disease", 326
- Monoamine oxidase (MAO)  
inhibitors  
atypical depression, 584  
mechanism and clinical use, 599
- Parkinson disease, 569
- selegiline/rasagiline, 569
- Monobactams  
*Pseudomonas aeruginosa*, 143
- Monoclonal antibodies  
naming conventions for, 258
- Monoclonal gammopathy of undetermined significance, 440
- Monoclonal immunoglobulin (Ig) overproduction, 440
- Monocytes, **417**  
morulae in, 150
- Monozygotic ("identical") twins, 641
- Montelukast, 712
- Mood disorder, **582**, 583  
bipolar disorder, 584  
hypomanic episode, 584  
manic episode, 583
- Mood stabilizing drugs, 584
- Moro reflex, 527
- Morphine, 237  
for acute coronary syndromes, 317
- Morphogenesis  
errors in, **637**
- Mortality rate, 263
- Morulae, 150
- Mosaic bone architecture, 476
- Mosaicism, 57
- mosquito, 159
- Mosquitoes (disease vectors)  
malaria, 157  
Zika virus, 172
- Motilin  
source, action, and regulation of, 381
- Motion sickness, 244
- Motivational interviewing, **275**, 596
- Motoneuron action potential, 466
- Motor cortex, 528  
topographic representation, 518
- Motor innervation  
derivation of, 644  
lower extremity, 462
- Motor neuron signs, **547**
- Movement disorders  
dopaminergic pathways and, 514  
presentation and lesions, **537**
- Moxifloxacin, 195
- M phase, 46
- M protein  
bacterial virulence, 129  
rheumatic fever and, 136
- mRNA  
aminoglycosides, 191  
hepatitis viruses, 173  
pre-mRNA splicing, 41  
processing, 41  
protease inhibitors, 203  
stop codons, 44
- MRSA (methicillin-resistant *Staphylococcus aureus*), 135
- cephalosporins, 189
- daptomycin, 195
- nosocomial infections, 135
- treatment of highly resistant, 198
- Mucicarmine stain  
polysaccharide capsule staining, 125
- Mucinous carcinoma, 670
- Mucinous cystadenoma, 670
- Mucociliary escalator, 686
- Mucocutaneous lymph node syndrome, 484
- Mucoepidermoid carcinoma, 386
- Mucopolysaccharidoses, 88
- Mucor  
in immunodeficiency, 118
- Mucor* spp  
amphotericin B, 199  
opportunistic infection, 153
- Mucosa, 372
- Mucosal cells, 382
- Mucosal neuromas, 360
- Mucosal polyps, 397
- Mucositis  
methotrexate, 450
- Mucus  
broncial production of, 241
- "Muddy brown" casts (urine), 618
- Mulberry molars, 147
- Müllerian duct  
agenesis, 645  
anomalies of, 645  
derivatives of, 645
- Müllerian inhibitory factor (MIF), 645  
Sertoli cell production, 646
- Multicystic dysplastic kidney, 603
- Multidrug resistance protein 1 (MDR1), 228
- Multifactorial pulmonary hypertension, 703
- Multiple endocrine neoplasias (MEN syndromes)  
subtypes, **360**  
Zollinger-Ellison syndrome, 360
- Multiple gestations, 658
- Multiple myeloma  
metastasis to, 224  
metastatic calcification, 212  
monoclonal gammopathy transition to, 440  
plasma cell dyscrasia, 419
- Multiple sclerosis  
drug therapy for, 572  
findings and treatment, **541**  
interuclear ophthalmoplegia, 563  
recombinant cytokines for, 121  
therapeutic antibodies for, 122
- Mumps  
acute pancreatitis with, 407  
paramyxoviruses, 167
- Mumps virus  
characteristics, **170**
- Munchausen syndrome, 589
- Munchausen syndrome by proxy, 589
- Munro microabscesses, 491
- Murphy sign, 406
- Muscarinic agonists, 240
- Muscarinic antagonist, 244
- Muscarinic antagonists, **244**  
for asthma, 712  
multiple sclerosis, 541
- Muscarinic receptor  
detrusor muscle in, 243
- Muscle contraction  
motoneuron action potential and, 466
- Muscle proprioceptors, **468**
- Muscles  
in starvation, 90  
metabolism in, 87  
ragged red fibers in, 59
- Muscle spindle, 466
- Muscle stretch receptors, 468
- Muscle tone, motor neuron lesions, 547
- Muscular dystrophies, **61**  
frameshift mutation, 61  
X-linked recessive disorder, 61
- Muscularis externa, 372
- Musculocutaneous nerve  
injury and presentation, 456
- Musculoskeletal paraneoplastic syndromes, 229
- Musculoskeletal/skin/connective tissue  
dermatology, **487–502**  
pharmacology, 499
- Musculoskeletal system  
childhood conditions, **473**  
common conditions, **472**  
drug reactions, 253
- Mutase, 73
- Mutations  
BRAF, 442  
BRCA1 gene, 54

- de novo, 61  
*COL3A1*, 51  
*COL5A1*, 51  
*COL5A2*, 51  
 in cancer, 222  
 in HbS and HbC, 420  
 in PBPs, 187  
*WT1* deletion, 629  
*JAK2*, 443  
 locus heterogeneity in, 57  
 muscular dystrophies, 61  
 myelodysplastic syndromes, 441  
 non-Hodgkin lymphoma, 439  
 same locus, 57  
*STAT3*, 116  
 tumor suppressor genes, 46
- M**
- Myalgias, 171  
 fluoroquinolones, 195  
 genital herpes, 184  
*Trichinella spiralis*, 159  
 Jarisch-Herxheimer reaction, 148  
*Leptospira interrogans*, 147  
 Lyme disease, 146  
 meningitis, 186  
*polymyalgia rheumatica*, 483  
 trichinosis, 159  
 vasculitides, 484
- Myasthenia gravis  
 as paraneoplastic syndrome, 229  
 autoantibody, 115  
 neostigmine for, 243  
 pathophysiology, symptoms, 486  
 pyridostigmine for, 243  
 restrictive lung diseases, 699  
 Type II hypersensitivity, 112
- MYCL1** gene, 225
- Mycobacteria, 140**
- Mycobacterial infections  
 IL-12 receptor deficiency, 116
- Mycobacterium avium* complex  
 in HIV positive adults, 177
- Mycobacterium avium-intracellulare*  
 in HIV positive adults, 177
- Mycobacterium avium-intracellulare*,  
 139  
 HIV-positive adults, 177  
 prophylaxis with HIV, 197
- Mycobacterium spp*, 140  
 facultative intracellular organisms,  
 127  
 Gram stain, 125  
 intracellular organism, 127  
 Ziehl-Neelsen stain, 125
- Mycobacterium leprae*  
 animal transmission, 149  
 diagnosis, 141
- Mycobacterium marinum*, 140
- Mycobacterium pneumoniae*, 126  
 culture requirements, 126
- Mycobacterium scrofulaceum*, 140
- Mycobacterium tuberculosis*  
 vertebral osteomyelitis, 180
- Mycobacterium tuberculosis*  
 culture requirements for, 126  
 osteomyelitis, 180  
 reactivation site, 140  
 symptoms of, 140  
 therapeutic agents, 196, 197
- Mycolic acid  
 isoniazid, 125
- Mycology, 151
- Mycophenolate  
 inosine monophosphate  
 dehydrogenase inhibition, 36
- Mycophenolate mofetil, 120
- Mycoplasma spp*  
 atypical organisms, 179  
 Gram stain, 125  
 macrolides, 193  
 pneumonia caused by, 707
- Mycoses  
 cutaneous, 152  
 systemic, 151
- Mycosis fungoïdes, 439
- Mycosis fungoïdes/Sézary syndrome  
 occurrence and causes, 439
- Mydriasis  
 glaucoma treatment and, 573  
 G-protein-linked second receptor,  
 241  
 muscarinic antagonists for, 244  
 pupillary control, 558  
 saccular aneurysm, 534
- Myelencephalon, 504
- Myelin, 508**
- Myeloblasts (peripheral smear), 442
- Myelodysplastic syndromes, 441**  
 acute myelogenous leukemia  
 (AML), 442  
 Leukemias, 442  
 lymphoid neoplasms, 442  
 myeloid neoplasms, 442  
 sideroblastic anemia, 429
- Myelofibrosis, 443
- Myeloid neoplasms, 442
- Myelomeningocele, 63, 505
- Myeloperoxidase, 109  
 $H_2O_2$  degradation, 128  
 in neutrophils, 416
- Myeloperoxidase-antineutrophil  
 cytoplasmic antibody  
 (MPO-ANCA)  
 autoantibody, 115
- Myeloproliferative disorders  
 chronic, 442  
 in AML, 442
- Myeloschisis, 505
- Myelosuppression  
 alkylating agents, 451  
 antimetabolites, 450
- Myocardial action potential, 301
- Myocardial depression, 570
- Myocardial hibernation, 312
- Myocardial infarction  
 CK-MB in diagnosis, 314
- Myocardial infarction (MI), 312  
 complications of, 317  
 diabetes mellitus, 354  
 diagnosis of, 314  
 evolution of, 313
- Myocardial O<sub>2</sub> consumption/  
 demand, 293  
 angina treatment, 327
- Myocarditis  
 adenovirus, 164  
 causes of, 323  
 coxsackievirus, 167  
 diphtheria, 139  
 drug-related, 323  
*Toxocara canis*, 159
- Myoclonic seizures, 535
- Myoclonus, 537
- Myofibroblasts, 217
- Myoglobin, 689  
 oxygen-hemoglobin dissociation  
 curve, 690
- Myoglobinuria  
 acute tubular necrosis, 625
- McArdle disease, 87
- Myonecrosis, 138
- Myopathy**  
 daptomycin, 195  
 drug reaction and, 253
- Myopia, 553
- Myositis ossificans, 483**
- Myotonic dystrophy, 61, 62  
 cataracts and, 554
- Myxedema  
 thyroid hormones for, 364
- Myxomas, 324**  
 atrial tumors, 324
- Myxomatous degeneration, 300
- N**
- N-acetylcysteine  
 for acetaminophen toxicity, 251
- N-acetylglucosaminyl-1-  
 phosphotransferase, 47
- N-formylmethionine (fMet), 44
- NADH (reduced nicotinamide  
 adenine dinucleotide)  
 electron transport chain, 78  
 TCA cycle, 77
- Nadolol, 248
- NADPH (reduced nicotinamide  
 adenine dinucleotide  
 phosphate)  
 HMP shunt and, 79  
 universal electron acceptors, 75
- Nafarelin, 680
- Nafillin  
 characteristics of, 188
- Nagleria fowleri*  
 CNS infections, 156
- Nails  
 clubbing, 60  
 glomus body tumors, 492  
 hemorrhages in bed of, 321  
 pitting, 491  
 splinter hemorrhages, 321  
 with psoriatic arthritis, 481
- Naked viral genome infectivity, 163
- Nalbuphine, 572
- Naloxone  
 dextromethorphan overdose, 711  
 for opioid toxicity, 251, 571, 594, 600  
 opioid detoxification, 600
- Nalfexone  
 alcoholism, 595  
 opioid toxicity, 572  
 relapse prevention, 600
- Naproxen, 500
- Narcissistic personality disorder, 588
- Narcolepsy  
 amphetamines for, 245  
 diagnosis and treatment, 591  
 hypnagogic/hypnopompic  
 hallucinations, 591  
 treatment, 591
- Narrow-angle glaucoma, 555
- Nasal congestion, 711
- Nasal decongestion  
 ephedrine for, 245
- Nasal polyps  
 cystic fibrosis, 60
- Nasal septum perforation, 485
- Nasopharyngeal carcinoma  
 EBV and, 165  
 oncogenic microbes and, 227
- Natalizumab, 122  
 multiple sclerosis, 541
- Nateglinide, 363
- National Board of Medical Examiners  
 (NBME), 2, 11
- Natriuretic peptide, 303
- Natural killer (NK) cell, 99
- Natural killer (NK) cells, 419  
 function of, 419  
 functions of, 101
- Nausea  
 adverse drug effects, 410  
 antiemetics for, 410  
 biliary colic, 406  
 migraine headaches, 536  
 ranolazine, 327  
 vitamin A toxicity, 66  
 vitamin C toxicity, 69  
 with appendicitis, 393  
 with MI, 313
- Near miss (medical errors), 281
- Nebivolol, 248
- Necator americanus*  
 intestinal infections, 159
- Necator spp*  
 disease associations, 161  
 infection routes, 158
- Neck and head cancer, 695
- necrosis, 544
- Necrosis  
 acute pancreatitis, 407  
 Arthus reaction, 113  
 benign tumors, 221  
 causes and histology of, 209  
 enterocolitis, 396  
 femoral head, 120  
 fibrinoid, 478  
 granulomatous inflammation, 218  
 hepatic, 499  
 jaw, 500  
 saponification, 209  
 transplant reaction, 120
- Necrotizing enterocolitis, 396
- Necrotizing fascitis, 493
- Necrotizing glomerulonephritis, 485
- Negative predictive value (NPV), 264
- Negative reinforcement, 576
- Negative skew distribution, 267
- Negative-stranded viruses, 168
- Negri bodies, 171
- Neisseria gonorrhoeae*  
 culture requirements, 126  
 cystitis, 624  
 epididymitis and orchitis, 678  
 osteomyelitis, 180  
 prostatitis, 678  
 septic arthritis, 480  
 STI, 184
- Neisseria spp*, 142  
 cephalosporins, 189  
 gram-negative algorithm, 142  
 intracellular organism, 127  
 transformation in, 130
- Neisseria meningitidis*  
 chloramphenicol, 192  
 culture requirements, 126  
 encapsulation, 127  
 meningitis, 180  
 penicillin G/V for, 184
- Nelson syndrome, 357
- Nematodes  
 infection routes, 158  
 intestinal roundworms, 159  
 tissue infections, 159
- Neomycin  
 aminoglycosides, 191
- Neonatal conjunctivitis  
*Chlamydia trachomatis*, 149
- Neonatal lupus, 482

- Neonatal respiratory distress syndrome, **685**
- Neonates**  
abstinence syndrome, **639**  
Apgar score, 658  
coagulation cascade in, 423  
conjunctivitis, 142  
galactosemia in, 80  
hernias in, 380  
herpes in, 164  
hyperthermia in, 244  
hypertrophic pyloric stenosis in, 369  
*Candida albicans* in, 153  
*Listeria monocytogenes* in, 139  
intraventricular hemorrhage, 530  
*Streptococcus agalactiae* in, 137  
jaundice in, 403  
kernicterus, 194  
low birth weight, 658  
meningitis in, 180  
necrotizing enterocolitis and, 396  
normal flora, 178  
obesity risk factors, 659  
pneumonia causes in, 179
- Neoplasia**  
pathology of, 220
- Neoplasms of mature B cells**, **439**
- Neoplasms of mature T cells**, **439**
- Neoplastic progression**, **220**
- Neoplastic transformation**, 217
- Neostigmine**, 243
- Nephritic-nephrotic syndrome**, 619
- Nephritic syndrome**, 619, 620  
etiology and presentation, **619**
- Nephroblastoma**, **629**
- Nephrocalcinosis**, 212
- Nephrogenic diabetes insipidus**, 346  
lithium toxicity, 593  
treatment, 632
- Nephrolithiasis**, 629  
calcium oxalate, 69
- Nephron transport physiology**, **609**
- Nephropathy**  
diabetes mellitus, 354  
hypertension and, 308  
transplant rejection, 120
- Nephrotic syndrome**, 619, **621**  
early-onset, 629  
ESR in, 215  
fatty casts in, 618
- Nephrotoxicity**  
aminoglycosides, 190  
amphotericin B, 199  
cidofovir, 202  
immunosuppressants, 120  
inhaled anesthetics, 570  
streptomycin, 197  
sulfonamides, 194
- Nephrilysin inhibitor**, 327
- Nerve fibers**, 510
- Nerves**  
lower extremity, 463  
upper extremity, **456**
- Nesiritide**, 303
- Neural crest**  
derivatives, 637
- Neural crest cells**, 504
- Neural development**, 504
- Neural plate**, 504
- Neural tube**, 504  
derivatives, 637
- Neural tube defects**, **505**  
diabetes in pregnancy, 638  
prevention, 68
- Neuroblastomas**, 358  
incidence and mortality, 223  
oncogenes and, 225  
paraneoplastic syndromes with, 229
- Neurocutaneous disorders**  
genetics and presentation, **543**  
neurofibromatosis type I and II, 543  
Sturge-Weber syndrome, 543  
tuberous sclerosis, 543  
Von Hippel-Lindau disease, 543
- Neurocyticosclerosis**, 160
- Neurodegeneration**  
Tay-Sachs disease, 88
- Neurodegenerative diseases**  
therapy for, 569
- Neurodegenerative disorders**  
description and findings, **538–539**  
drug therapy for, **569**
- Neuroectoderm**, 504  
derivatives, 636
- Neuroendocrine tumors**, **358**
- Neurofibromatosis**, 543  
chromosome association, 64  
types I and II, 543  
variable expressivity, 56
- Neurofilament**  
tumor identification, 228
- Neurofilaments**  
cytoskeletal element, 48
- Neurogenic ileus**, 243
- Neuroglycopenic symptoms**, 356
- Neurohypophysis**  
hypothalamus and, 513
- Neuroleptic malignant syndrome**, 593
- Neuroleptic malignant syndrome (NMS)**, 572
- Neurologic**  
drug reactions, 254
- Neurologic defects**  
pyruvate dehydrogenase complex deficiency, 77
- Neurologic drug reactions**, 254
- Neurologic signs/symptoms**  
unvaccinated children, 186
- Neurologic symptoms**  
vitamin B<sub>12</sub> (cobalamin) deficiency, 430
- Neurology and special senses**  
anatomy and physiology, 507  
embryology, 503  
ophthalmology, 503, 553  
otology, 503, 551  
pathology, 528  
pharmacology, 564
- Neuromuscular blocking drugs**, **571**  
depolarizing, 571  
nondepolarizing, 571
- Neuromuscular disorders**  
paraneoplastic syndromes, 229
- Neuromuscular junction**  
diseases of, **486**  
skeletal muscle, 239
- Neuron action potential**, **509**
- Neurons**, 507  
primary motor cortex, 513, 526
- Neuron-specific enolase**, 227, 358
- Neuropathic pain**, 533  
treatment agents, 483
- Neuropathic ulcer**, 495
- Neuropsychiatric disturbances**  
primary hyperparathyroidism, 353
- Neurospherosis**, 147
- Neurotoxicity**  
immunosuppressants, 120  
methylmercury exposure, 638  
methylxanthines, 712  
neurotransmitter, 132
- Neurotransmitter release**  
exotoxin inhibition of, 132
- Neurotransmitters**  
bacterial toxin effects, 132  
synthesis and changes with disease, **510**
- Neurovascular pairing**, **465**
- Neutropenia**  
cell counts and causes, 433  
disseminated candidiasis, 153  
ganciclovir, 202  
rheumatoid arthritis, 478  
ticlopidine, 447
- Neutrophils**, **416**  
chemotactic agents, 416, 499  
chemotaxis in, 44  
in leukocyte adhesion deficiency, 117  
in MI, 313  
megaloblastic anemia, 430  
nonmegaloblastic anemia, 430  
pseudo-Pelger-Huet anomaly, 441  
stimulation of, 44  
wound healing, 217
- Never event (medical error)**, 281
- Nevi**  
dysplastic, 498  
junctional, 491
- Nevirapine**, 255  
HIV therapy, 203
- Nevus flammeus**, 543
- Nevus/mole**, 221
- NF-κB**  
activation, 99
- Niacin**  
cutaneous flushing, 251  
gout, 253  
hyperglycemia, 252  
lipid lowering agents, 328  
myopathy caused by, 253
- Nicardipine**, 326
- Nickel carcinogenicity**, 226
- Nicotinamides**, 75
- Nicotine**  
intoxication and withdrawal, 595
- Nicotinic**, 239
- Nicotinic acetylcholine receptors**, 166
- Niemann-Pick disease**, 87, 88
- Nifedipine**, 667
- Nifurtimox**, 200
- Nigrostriatal pathway**, 514
- Nikolsky sign**  
blistering skin disorders, 493, 495  
scalded skin syndrome, 493
- Nilotinib**, 453
- Nimodipine**, 326, 531
- N-myc oncogene**, 358
- Nipple**  
intraductal papilloma, 673  
lactational mastitis, 673
- Nissl bodies**, 47
- Nitazoxanide**, 155
- Nitrates**  
and hydralazine in heart failure, 319  
antianginal therapy, 327  
mechanism and clinical use, 326
- Nitric oxide**  
source and action of, 381
- Nitroblue tetrazolium dye reduction test**, 117
- Nitrofurantoin**  
hemolysis in G6PD deficiency, 253  
pulmonary fibrosis, 253
- Nitrogen mustards**  
mechanism and clinical use, 451
- Nitroglycerin**, 326  
acute coronary syndromes, 317  
angina, 312
- Nitroprusside**, 326
- Nitrosamines**  
carcinogenicity, 226  
stomach cancer and, 389
- Nitrosoureas**  
mechanism, use and adverse effects, 451
- Nitrous oxide**, 570
- Nivolumab**, 452
- Nizatidine**, 409
- NK cells**  
cell surface proteins, 110
- NMDA receptor antagonist**  
ketamine as, 570  
memantine as, 570
- NNRTIs**, 203  
in HIV therapy, 203
- Nocardia spp.**, 139  
aerobic culture requirements, 126  
comparison with *Actinomyces* spp., 139  
sulfonamides, 194
- Nocturia**, 678
- Nocturnal enuresis**, 337
- Nodes of Ranyier**, 508
- Nodular phlebitis**, 484
- Noise-induced hearing loss**, 551
- Nonadherent patients**, 276
- Nonalcoholic fatty liver disease**, **401**
- Nonbacterial endocarditis**, 321
- Nonbacterial thrombotic endocarditis**, 229
- Nonbenzodiazepine hypnotics**  
mechanism and adverse effects of, **567**
- Noncaseating granulomas**, 218  
sarcoidosis, 700
- Noncommunicating hydrocephalus**, 540
- Noncompetitive agonists**, 232
- Noncompetitive antagonist**, 237
- Noncompetitive inhibitors**, 232
- Nondepolarizing neuromuscular blocking drugs**, 571
- Non-frameshift mutations**  
deletions, 61
- Nonhemolytic normocytic anemia**, 431
- Non-Hodgkin lymphoma**, 439  
corticosteroids, 120  
HIV-positive adults, 177  
Hodgkin lymphoma vs, 439  
oncogenes and, 225  
rituximab for, 451  
vinca alkaloids for, 451
- Nonhomologous end joining**, 39
- Nonmaleficence (ethics)**, 270
- Nonmegaloblastic anemia**, 430
- Non-neoplastic malformations**, 221
- Nonnormal distributions**, 267
- Nonoverlapping genetic code**, 37
- Nonreceptor tyrosine kinase**  
endocrine hormone signaling pathways, 345
- Nonsecreting pituitary adenoma**, 347

- Nonselective antagonists, 248  
 Nonsense mutations, 40  
 Non-small cell lung cancer  
   Adenocarcinoma, 709  
   squamous cell carcinoma, 709  
 Nonspecific PDE inhibitor, 249  
 Nonspecific screening antibody  
   autoantibody in, 115  
 Nonsteroidal anti-inflammatory drugs (NSAIDs)  
   acute gout treatment, 501  
   acute pericarditis, 323  
   aplastic anemia, 253  
   Beers criteria, 250  
   calcium pyrophosphate deposition disease, 479  
   chemopreventive for CRC, 399  
   esophagitis from, 387  
   GFR effects of, 613  
   gout, 479, 501  
   headaches, 536  
   interstitial nephritis, 254  
   loop diuretics and, 631  
   mechanism, use and adverse effects, 500  
   misoprostol use with, 409  
   osteoarthritis, 478  
   peptic ulcer disease and, 390  
   renal papillary necrosis, 626  
   rheumatoid arthritis, 478  
 Non-ST-segment elevation MI (NSTEMI)  
   diagnosis of, 312  
   STEMI comparison, 312  
   treatment, 312  
 Nonthyroidal illness syndrome, 349  
 non- $\alpha$ , non- $\beta$  islet cell pancreatic tumor, 381  
 Norepinephrine  
   changes with disease, 510  
 Norepinephrine (NE)  
   bupropion effect on, 600  
   direct sympathomimetic, 245  
   isoproterenol vs, 245  
   MAO inhibitor effects, 599  
   pheochromocytoma secretion, 359  
   vitamin B<sub>6</sub> and, 67  
 Norethindrone, 681  
 Norfloxacin, 195  
 Normal distribution, 267  
 Normal flora  
   colonic, 137  
   female genital tract, 136  
   neonates, 178  
   oropharynx, 136  
   skin, 135  
 Normal pressure hydrocephalus, 540  
 Normal splitting, 298  
 Normocytic, normochromic anemias  
   causes and findings, 431  
 Norovirus, 179  
 Northern blot, 53  
 Nortriptyline, 599  
 Nosocomial infections, 182  
   Ebola, 171  
   enterococci, 137  
   *Klebsiella*, 145  
   *Pseudomonas aeruginosa*, 143  
   MRSA, 135  
   pneumonias, 179  
   risk factors and unique signs/symptoms, 185  
 Notched (Hutchinson) teeth, 147  
 Notochord, 504, 636  
 Novobiocin  
   gram-positive antibiotic test, 134  
   *Staphylococcus epidermidis*, 136  
 NRTIs, 203  
 NS3/4A inhibitors, 204  
 NS5A inhibitors, 204  
 NS5B inhibitors, 204  
 NSAIDs, 409  
 Nuchal translucency, 63  
 Nucleosome, 34  
 Nucleotide excision repair, 39  
 Nucleotides, 35  
   deamination reactions, 35  
   synthesis, 74  
 Nucleus accumbens, 510  
 Nucleus ambiguus  
   function and cranial nerves, 521  
 Nucleus cuneatus, 526  
 Nucleus gracilis, 526  
 Nucleus pulposus  
   collagen in, 50  
 Nucleus tractus solitarius  
   function and cranial nerves, 521  
 Nucleus tractus solitarius (NTS), 511  
 Null hypothesis, 268  
 Number needed to harm (NNH), 262  
 Number needed to treat (NNT), 262  
 Nursemaid's elbow, 473  
 Nutcracker syndrome, 373  
 Nutmeg liver, 402  
 Nyctalopia, 66  
 Nystagmus  
   cerebellum, 515  
   Friedreich ataxia, 549  
   internuclear ophthalmoplegia, 563  
   medbrain lesions, 528  
   PCP, 154  
   phenytoin, 564  
 Nystatin  
   mechanisms and clinical use, 199
- O**
- Obesity, 308, 406  
   amphetamine for, 245  
   anovulation with, 669  
   DM type 2 and, 355  
   esophageal cancer and, 388  
   hypoventilation syndrome, 703  
   lateral femoral cutaneous nerve injury, 462  
   osteoarthritis/rheumatoid arthritis, 478  
   renal cell carcinoma association, 628  
   sleep apnea, 703  
   stress incontinence and, 623  
 Obesity hypoventilation syndrome, 703  
 Obligate intracellular bacteria, 127  
 Observational studies, 260  
 Observational study  
   design and measures for, 260  
 Observer-expectancy bias, 266  
 Obsessive-compulsive disorder, 586  
 Obsessive-compulsive disorder (OCD)  
   drug therapy for, 596  
   SSRIs for, 596  
   venlafaxine for, 596  
 Obstructive jaundice, 408  
 Obstructive lung diseases, 698  
   asthma, 698  
   bronchiectasis, 699  
 chronic bronchitis, 698  
 emphysema, 698  
 flow-volume loops, 697  
 flow volume loops in, 697  
 Obstructive shock, 320  
 Obstructive sleep apnea, 703  
   pulsus paradoxus in, 294  
 Obturator nerve, 462  
 Obturator sign, 393  
 Occipital lobe, 532  
 Occult bleeding  
   FOBT for, 398  
 Octreotide  
   acromegaly, 347  
   GH excess, 337  
   hypothalamic/pituitary drugs, 364  
   mechanism and clinical use, 410  
 Ocular motility, 560  
 Oculomotor nerve (CN III)  
   damage to, 561  
   functions of, 523  
   ocular motility, 560  
   palsy, 347  
   palsy of, 531, 550  
   pupillary contraction, 558  
 Odds ratio, 262  
 Odds ratio (OR), 260  
 Ofloxacin, 195  
 "OK gesture", 460  
 Olanzapine, 597  
 Olaparib, 453  
 Olfaction  
   hallucinations, 582  
   limbic system in, 513  
 Olfactory nerve (CN I), 523  
 Oligoclonal bands, 541  
 Oligodendrocytes  
   derivation and functions, 508  
 Oligodendroglia  
   in multiple sclerosis, 508  
 Oligodendrogliomas, 544  
 Oligohydramnios, 640  
 Oligomenorrhea, 657  
 Oligomycin, 78  
 Oligospermia, 410  
 Olive-shaped mass, 369  
 Omalizumab  
   target and clinical use, 122  
 Ombitasvir, 204  
 Omega-3 fatty acids  
   lipid lowering agents, 328  
 Omental foramen, 371  
 Omeprazole, 409  
 Omphalocele  
   characteristics of, 368  
 Onchocerca volvulus  
   tissue infections, 159  
 Oncogenes  
   gene product and associated neoplasm, 225  
 Oncogenic microbes, 227  
 Ondansetron  
   mechanism and clinical use, 410  
   with chemotherapy, 453  
 1,25-(OH)<sub>2</sub>D<sub>3</sub>  
   kidney endocrine function, 613  
 "100-day cough", 132  
 "Onion skin" periosteal reaction, 477  
 Onychomycosis  
   terbinafine, 199  
   tinea unguium, 152  
 Oocysts  
   acid-fast stain, 155  
   Toxoplasmosis, 156  
 Oogenesis, 655  
 Open-angle glaucoma, 555  
   carbachol for, 243  
   pilocarpine for, 243  
 Operant conditioning, 576  
 Ophthalmoplegia  
   cavernous sinus syndrome, 562  
   internuclear, 563  
   Wernicke-Korsakoff syndrome, 595  
 Opiod  
   overdose, 594  
 Opioid analgesics  
   agonists, 572  
   Beers criteria, 250  
   intoxication and withdrawal, 594  
   mechanism and use, 572  
   mixed agonist/antagonist analgesics, 573  
   sleep apnea, 703  
   toxicity treatment, 251  
 Opioids  
   detoxification and relapse prevention, 600  
 Opponens digiti minimi muscle, 460  
 Opponens pollicis muscle, 460  
 Opportunistic fungal infections, 153  
 Oppositional defiant disorder, 580  
 Opposition (thumb), 457  
 Opsoclonus-myoclonus syndrome, 358  
 Opsonins  
   functions of, 106  
 Opsonization  
   complement activation and, 106  
 Optic disc  
   papilledema in, 557  
 Optic nerve (CN II), 523  
 Optic neuritis, 541  
 Optic neuropathy, 59  
 Optochin  
   gram-positive antibiotic test, 134  
 Oral advance directives, 272  
 Oral contraceptives (OCPs)  
   reproductive hormones, 679  
   SHBG effects on, 345  
 Oral glucose tolerance test  
   diabetes mellitus diagnosis, 354  
 Oral hairy leukoplakia, 177  
 Oral/intestinal ganglioneuromatosis, 360  
 Oral thrush, 177  
 Orange body fluids, 196  
 Orchiectomy, 676  
 Orchiopexy, 675  
 Orchitis, 170, 678  
 Orexigenic effect, 344  
 Orexin, 591  
 Organ failure in acute pancreatitis, 407  
 Organic acidemias, 85  
 Organ of Corti, 551  
 Organogenesis  
   errors in, 636  
   teratogens, 636  
 Organophosphates  
   toxicity treatment, 251  
 Organ transplants  
   azathioprine for, 450  
   Kaposi sarcoma with, 492  
   WBC casts, 618  
 Organum vasculosum of the lamina terminalis (OVLT), 511  
 Orientation, 581  
 Origin of replication, 38  
 Orlistat  
   diarrhea, 252  
   mechanism and clinical use, 411

- Ornithine  
cystinuria, 85  
kidney stones and, 622  
Ornithine transcarbamylase deficiency, 61, **83**  
Orofacial clefts  
lip and palate, **645**  
Orotic acid, 83  
Orotic aciduria, 430  
Orthomyxoviruses, 168  
characteristics and medical importance, 167  
influenza viruses, 168  
Orthopedic conditions  
childhood, 473  
hip and knee, 471  
Orthopnea  
heart failure, 319  
left heart failure, 319  
Ortolani maneuver, 473  
Oseltamivir, **201**  
Osgood-Schlatter disease, 473  
Osler nodes, 321  
Osmoreceptors, 511  
Osmotic demyelination syndrome, 542  
SIADH and, 346  
Osmotic diarrhea, 391  
Osmotic laxatives, 411  
Ossicles, 551  
conductive hearing loss and, 51  
Ossification, 468  
Osteitis deformans, 475  
lab values in, 476  
Osteitis fibrosa cystica, 353  
lab values in, 476  
Osteoarthritis  
celecoxib for, 500  
pathogenesis, findings and treatment, 478  
vs rheumatoid arthritis, 478  
Osteoarthropathy  
cancer association of hypertrophic, 229  
Osteoblast  
bone formation, 469  
Osteoblastoma, 476  
Osteoblasts  
bone formation, 468  
cortisol effect on, 344  
Osteochondroma, 476  
Osteoclast  
bone formation, 469  
Osteoclasts  
bisphosphonate effects, 500  
bone formation, 468  
osteopetrosis, 475  
Osteodystrophy  
renal, 352, 627  
Osteogenesis imperfecta, **51**  
bisphosphonates, **500**  
collagen synthesis in, 51  
Osteoid osteoma, 476  
Osteoma, 476  
nomenclature for, 221  
Osteomalacia  
hypophosphatemia, 615  
Osteomalacia/rickets  
lab values in, 476  
presentation and lab values, **475**  
Osteomyelitis  
associated infection and risk, 180  
*Pseudomonas aeruginosa*, 143  
*Staphylococcus aureus*, 135  
sickle cell anemia, 432  
Osteonecrosis, 500
- Osteopenia, 475  
Osteopetrosis, **475**  
lab values in, 476  
Osteophytes, 478  
Osteoporosis  
bisphosphonates, 500  
corticosteroids, 120  
denosumab, 122  
diagnosis and complications of, **474**  
drug reaction and, 253  
Gaucher disease, 88  
homocystinuria, 85  
hormone replacement therapy, 681  
lab values in, 476  
teriparatide for, 501  
Osteosarcoma, 221, **477**  
epidemiology and characteristics, 477  
risk with osteitis deformans, 475  
Ostium primum, 288  
Ostium secundum, 288  
Otitis media  
granulomatosis with polyangiitis and, 485  
*Haemophilus influenzae*, 142  
*Streptococcus pneumoniae*, 136  
Langerhans cell histiocytosis, 444  
Otology, 551  
Ototoxicity  
aminoglycosides, 204  
cisplatin/carboplatin, 451  
drug reaction and, 254  
ethacrynic acid, 631  
loop diuretics, 631  
Outcome quality measurement, 280  
Outer ear, 551  
Outer membrane (bacteria), 124  
“Oval fat bodies”, 618  
Ovarian artery, 649  
Ovarian cancer  
cisplatin/carboplatin for, 451  
epidemiology of, 667  
hypercalcemia and, 229  
paclitaxel for, 451  
tumor suppressor genes and, 227  
Ovarian cycle, 655  
Ovarian cysts  
follicular, **670**  
theca lutein, 670  
Ovarian ligament, 649  
male/female homologs, 648  
Ovarian teratomas  
paraneoplastic syndrome, 229  
Ovarian tumors  
epithelial tumors, 670  
germ cell tumors, 671  
sex cord stromal tumors, 670, 671  
Ovaries  
descent of, 648  
epithelial histology, 650  
estrogen production, 654  
lymphatic drainage, 648  
Overflow incontinence, 623  
Overuse injury  
elbow, **469**  
knee, 473  
radial nerve, 456  
wrist and hand, **470**  
Ovotesticular disorder of sex development, 661  
Ovulation  
anovulation causes, 669  
progesterone and, 654  
prolactin effect on, 336  
regulation of, 654
- Ovulatory uterine bleeding, 657  
“Owl eyes” inclusions, 438  
Oxacillin  
characteristics of, 188  
Oxaliplatin, 451  
Oxazepam, 566  
oxidation, 73  
Oxidative burst, 109  
Oxidative phosphorylation, 78  
electron transport chain, **78**  
metabolic site, 74  
poisons, 78  
Oxybutynin, 244  
Oxygen  
exercise and, 693  
for carbon monoxide poisoning, 251  
in blood, 690  
Oxygen deprivation, **693**  
Oxygen-hemoglobin dissociation curve, **690**  
Oxygen toxicity, 210  
Oxytocin  
function of, 336  
hypothalamus production, 513  
lactation and, 659  
signaling pathways for, 345
- P**
- P-450, 75  
Pacemaker action potential, 301  
Pacinian corpuscles, 509  
Packed RBCs, transfusion of, 438  
Paget disease  
in breast, 674  
Paget disease (extramammary), 668  
Paget disease of bone  
bisphosphonates, 500  
lab values in, 476  
osteosarcomas and, 477  
woven bone in, 468  
Pain  
cape-like loss of, 506  
periorbital, 536  
post-stroke syndrome, 533  
sensory receptors for, 509  
thalamic nuclei and, 513  
treatment in multiple sclerosis, 541  
unilateral visual loss and, 540  
Palbociclib, 453  
Pale infarct, 210  
Paliperidone, 597  
“Palisading” nuclei, 498  
Palivizumab  
pneumonia prophylaxis, 169  
target and clinical use, 122  
Pallor in aplastic anemia, 431  
PALM, 657  
Palmar interossei, 460  
Palmar reflex, 527  
PALM-COEIN uterine bleeding classification, **657**  
PALP, 677  
Panacinar emphysema, 403, 698  
Pancoast tumor  
findings with, 710  
lung cancer, 709  
superior vena cava syndrome, 710  
thoracic outlet syndrome, 458  
Pancreas  
annular, 370  
biliary structures and, 378  
buds, 370  
divisum, 370  
embryology, 370  
endocrine cell types, 335
- Pancreas and spleen embryology, **370**  
Pancreatic adenocarcinoma, 408  
Pancreatic cancer  
adenocarcinomas, 378, 407  
biliary cirrhosis and, 405  
5-Fluorouracil, 450  
hyperbilirubinemia with, 403  
paraneoplastic syndromes with, 229
- Pancreatic ducts, 368, 378  
Pancreatic insufficiency, **391**, 407  
Pancreatic islet cell tumors, 361  
Pancreatic lipase, 93  
Pancreatic secretions  
enzymes and function of, **383**  
Pancreatitis, 353  
acute, 405  
ARDS and, 702  
chronic, 407  
corticosteroids and, 252  
drug reactions and, 252  
hyperchylomicronemia, 94  
hyperparathyroidism, 353  
hypertriglyceridemia, 94  
mumps, 170  
Pancytopenia, 431  
Chédiak-Higashi syndrome, 117  
Diamond-Blackfan anemia, 430  
Gaucher disease, 88  
leishmaniasis, 158  
osteopetrosis and, 475  
with hairy cell leukemia, 442  
with immunosuppressants, 120  
Panic disorder, **586**  
drug therapy for, 596  
SSRIs for, 586, 599  
symptoms and treatment, 586  
venlafaxine for, 596  
Panitumumab, 452  
Panniculitis, 496  
Pantoprazole, 409  
Pantothenic acid, 67  
Papillary carcinoma  
causes and findings, 351  
nomenclature, 221  
Papillary cystadenoma  
lymphomatous, 386  
Papillary muscle  
blood supply to, 317  
rupture, 313, 317  
Papillary thyroid carcinomas  
carcinogens for, 226  
Papilledema  
hydrocephalus, 540  
hypertensive emergency and, 308  
hypertensive retinopathy, 556  
idiopathic intracranial hypertension, 540  
optic disc with, **557**  
Papillomas, 221  
Papillomavirus  
nonenveloped, 163  
Papillomaviruses  
envelope and medical importance, 164  
Pappenheimer bodies  
associated pathology, 426  
Papules  
actinic keratosis, 496  
capillary, 492  
characteristics, 489  
dermatitis herpetiformis, 495  
molluscum contagiosum, 493  
rosacea, 491  
Para-aminohippuric acid (PAH), 606  
Para-aortic lymph nodes, 648

- Paracoccidioidomycosis, 151  
 Paracortex (lymph node), 96  
 Paracrine, 613  
 Paradoxical splitting, 298  
 Paraesophageal hiatal hernia, 380  
 Parainfluenza  
   croup, 170  
   paramyxovirus, 169  
 Parakeratosis  
   characteristics, 489  
   psoriasis, 491  
 paralysis, 532  
 Paralysis  
   conversion disorder and, 589  
   Guillain-Barré syndrome, 542  
   limb compartment syndrome, 472  
   of face, 532  
   rabies, 171  
   unvaccinated children, 186  
 Paramedian pontine reticular formation  
   effects of lesions, 528  
   extraocular movements, 512  
 Paramesonephric (Müllerian) duct, 645  
 Paramyxo viruses  
   characteristics and medical importance, 167  
   characteristics of, 169  
   croup, 169  
   mumps, 169  
 Paraneoplastic syndromes, 628  
   manifestation and mechanism of, 229  
 Paranoia  
   LSD, 595  
 Parasite infestations  
   sign/symptom association hints, 161  
 Parasites  
   infections with immunodeficiency, 118  
 Parasitic infections  
   myocarditis with, 323  
 Parasitology, 155  
 Parasympathetic nervous system  
   cranial nerves supply of, 239  
   gastric innervation of, 374  
   male erection, 651  
   receptor targets, 239  
   VIP and, 381  
 Parathyroid adenoma of bone, 476  
 Parathyroid adenomas  
   hyperparathyroidism caused by, 353  
   MEN 1/MEN 2A syndromes, 360  
 Parathyroid disease  
   diagnosis and causes, 352  
 Parathyroid glands  
   pharyngeal pouch derivation, 644  
 Parathyroid hormone  
   calcium homeostasis, 341  
   source, function, and regulation, 340  
 Parathyroid hormone (PTH)  
   bone formation and disorders, 469  
   Paget disease of bone, 476  
   signaling pathways of, 345  
 Paraumbilical vein, 371  
 Paraventricular nucleus, 513  
 Paresthesia  
   limb compartment syndrome, 455  
   lumbosacral radiculopathy, 465  
 Paresthesias  
   acetazolamide use, 631  
   vitamin B<sub>12</sub> deficiency, 69  
 Parietal cells (stomach)  
   secretions of, 382  
 Parietal peritoneum, 380  
 Parinaud syndrome, 528, 546  
 Parkinson disease, 537  
   benztropine for, 244  
   dopaminergic pathways, 514  
   Lewy bodies, 539  
   metoclopramide contraindication, 410  
   neurotransmitter changes with, 510  
   nigrostriatal pathway and, 514  
   resting tremor in, 537  
   seborrheic dermatitis association, 490  
   symptoms and histologic findings, 538  
   therapy for, 569  
   therapy strategies, 568  
   trihexyphenidyl, 244  
   ubiquitin-proteasome system in, 48  
 Parkinson disease therapy, 568  
 Parkinson-like syndrome, 254  
 Parotid gland  
   embryologic derivation, 637  
   enlargement of, 480  
   stones in, 386  
   tumors in, 386  
 Parotitis  
   mumps, 170  
 Paroxetine, 599  
 Paroxysmal nocturnal dyspnea, 319  
 Paroxysmal nocturnal hemoglobinuria  
   causes and findings, 432  
   CD55 deficiency, 107  
   eculizumab for, 122  
   flow cytometry diagnosis, 54  
   intravascular hemolysis in, 431  
 Paroxysmal supraventricular tachycardia, 315  
 Partial agonist, 237  
 Partial (focal) seizures, 535  
 Partial thromboplastin time (PTT), 435  
 partial β-agonists  
   with angina, 327  
 Parvovirus  
   characteristics of, 164  
   DNA viruses, 164  
   naked viruses, 164  
 Parvovirus B19  
   hereditary spherocytosis, 432  
   hydrops fetalis, 183  
   rash, 182  
 Passive abduction (knee), 464  
 Passive adduction (knee), 464  
 Passive aggression, 577  
 Passive immunity  
   acquisition of, 110  
 Passive vs active immunity, 110  
*Pasteurella* spp  
   culture requirements, 126  
*Pasteurella multocida*  
   osteomyelitis, 180  
   transmission, 149  
 Patau syndrome  
   holoprosencephaly, 505  
 Patau syndrome (trisomy 13)  
   chromosome association, 63  
 Patches (skin)  
   characteristics, 489  
 Patellar reflex, 527  
 Patellofemoral syndrome, 473  
 Patent ductus arteriosus (PDA)  
   congenital rubella, 307  
   fetal alcohol syndrome, 307  
   heart murmur with, 300  
   indomethacin for, 500  
   mechanism and treatment, 307  
   neonatal respiratory distress syndrome and, 685  
 Patent foramen ovale  
   atrial septal defect vs, 306  
 Patent urachus, 642  
 Patent vitelline duct, 642  
 Pathogen-associated molecular patterns (PAMPs), 99, 164  
 Pathology  
   cellular injury, 206–213  
   endocrine, 346  
   gastrointestinal, 386  
   hematology/oncology, 424  
   inflammation, 214–219  
   musculoskeletal/skin/connective tissue, 469  
   neoplasia, 220–229  
   renal, 618  
   reproductive, 661  
   respiratory, 695  
 Patient-centered interviewing techniques, 273  
 Pattern recognition receptors, 99  
 Pautrier microabscess, 439  
 Payment models for healthcare, 278  
 P-bodies, 41  
 PCP (phencyclidine)  
   intoxication and withdrawal, 595  
 PCSK9, 93  
 PCSK9 inhibitors, 328  
 PCV13 (pneumococcal conjugate vaccine), 127  
 PDE-3 inhibitor, 249  
 PDE-4 inhibitor, 249  
 PDE-5 inhibitors, 249  
 PDSA cycle, 280  
 Peau d'orange, 674  
 Pectinate line, 376  
 Pectenous, 461  
 Pectoriloquy (whispered), 704  
 Pediatric patients  
   abuse, 579  
   arthritis in, 480  
   brachial plexus injury, 458  
   causes of seizures in, 535  
   common causes of death, 279  
   common fractures, 474  
   cystic fibrosis, 60  
   growth retardation in, 626  
   hyperbilirubinemia (newborns), 403  
   intraventricular hemorrhage, 530  
   juvenile polyposis syndrome, 397  
   juvenile polyposis syndrome in, 397  
   leukocoria in, 557  
   Munchausen syndrome by proxy, 589  
   neglect in, 579  
   neuroblastomas in, 358  
   pathogens affecting, 186  
   precocious puberty, 57  
   primary brain tumors, 546  
   rashes, 185  
   rhabdomyomas in, 324  
   scalded skin syndrome in, 493  
   sleep terror disorder in, 591  
   strawberry hemangiomas in, 492  
   tetracycline side effects, 192  
   Wilms tumors in, 629  
 Pediculus humanus  
   disease and treatment, 161  
 Pegloticase, 501  
 Pegvisomant, 347  
 Pellagra, 67  
 Pelvic inflammatory disease (PID), 185  
   chlamydia, 185  
   clinical features, 185  
   copper IUD, 681  
   gonorrhea, 185  
   Neisseria spp, 142  
 Pelvic organ prolapse, 649  
 Pelvic splanchnic nerves, 239  
 Pelvis  
   fracture and nerve injury, 462  
   nerve injury with surgery, 462  
 Pembrolizumab, 452  
 Pemphigus vulgaris  
   acantholysis and, 489  
   pathophysiology and morphology, 494  
   type II hypersensitivity, 112  
 Penicillamine  
   for lead poisoning, 251  
   for Wilson disease, 405  
   myopathy, 253  
 Penicillin  
   Actinomycetes treatment, 139  
   antipseudomonal, 188  
   Coombs-positive hemolytic anemia, 253  
   penicillinase-resistant, 188  
   penicillinase-sensitive, 188  
   prophylaxis, 198  
   rash, 253  
 Penicillinase-resistant penicillins  
   mechanism and clinical use, 188  
 Penicillinase-sensitive penicillins  
   mechanism and clinical use, 188  
 Penicillin G, V  
   mechanism and clinical use, 187  
   meningococci treatment, 142  
   prophylaxis, 198  
 Penile cancer, 227  
 Penile pathology, 675  
 Penis  
   congenital abnormalities, 647  
   lymphatic drainage, 648  
   pathology of, 675  
 Pentamidine, 154  
 Pentazocine, 572, 573  
 Pentobarbital, 566  
 Pentose phosphate pathway  
   functions of, 79  
 Pentostatin, 442  
   mechanism and clinical use, 450  
 PEP carboxykinase, 78  
 Pepsin  
   secretion and action, 382  
 Pepsinogen  
   location of, 382  
 Peptic ulcer disease  
   complications of, 390  
   glycopyrrrolate for, 244  
   H. pylori risk for, 389  
   H<sub>2</sub> blockers for, 409  
   mechanism and presentation, 390  
   misoprostol for, 409  
   proton pump inhibitors for, 409  
   Zollinger-Ellison syndrome, 361  
 Peptidoglycan  
   in gram negative bacteria, 125  
*Peptostreptococcus* spp  
   alcoholism, 179  
 Percussion, 704  
 Perforation (GI), 390  
   necrotizing enterocolitis, 396  
 Perforin  
   cytotoxic T cells and, 101

- Performance anxiety, 586  
 Perfusion-limited gas exchange, 692  
 Periarteriolar lymphatic sheath, 98  
 Pericardial effusion, 709  
 Pericarditis  
     fibrinous, 313  
     jugular venous pulse in, 296  
     picornaviruses, 167  
     postinfarction, 313  
     pulsus paradoxus in, 320  
     rheumatoid arthritis, 478  
 Pericardium  
     anatomy, 292  
 Pericytes, 511  
 Perinephric abscesses, 624  
 Periodic acid-Schiff stain, 125  
 Periorbital edema  
     acute poststreptococcal  
         glomerulonephritis, 620  
*Trichinella spiralis*, 159  
 thyroid disease and, 348  
 Peripartum mood disturbances, **585**  
 Peripheral blood smear  
     basophilic stippling, 429  
     in multiple myeloma, 440  
     RBC inclusions, 426  
     Rouleaux formation, 440  
     schistocytes, 433  
     Schüffner stippling, 157  
     smudge cells, 442  
     spherocytes and agglutinated  
         RBCs, 433  
 Peripheral edema  
     calcium channel blockers, 326  
     heart failure, 319  
         right heart failure, 319  
 Peripheral facial palsy, 550  
 Peripheral nerves, **510**  
 Peripheral nervous system (PNS)  
     origins of, 504  
 Peripheral neuropathy  
     alcoholism, 595  
     drug reactions and, 254  
     eosinophilic granulomatosis, 485  
     Fabry disease, 88  
     Krabbe disease, 88  
     lead poisoning, 434  
     NRTIs, 203  
     oxazolidinones, 193  
     sorbitol, 81  
         vitamin B<sub>6</sub> deficiency, 67  
 Peripheral precocious puberty, 660  
 Peripheral resistance, 295  
 Peripheral vascular disease, 310  
 Peripheral vertigo, 552  
 Periplasm  
     in bacteria, 124  
 Peristalsis  
     motilin receptor agonists and, 381  
     visible, 369  
 Peritoneum, 368  
     hernias and, 380  
 Peritonitis  
     appendicitis, 393  
     diverticulitis, 393  
     spontaneous bacterial, 400  
 Periventricular plaques multiple  
     sclerosis, 541  
 Permethrin  
     for scabies, 161  
 Pernicious anemia, 382  
     autoantibody, 115  
         vitamin B<sub>12</sub> deficiency, 69  
 Peroneus brevis, 462  
 Peroneus longus, 462  
 Peroxisome  
     metabolic processes, **48**  
 Persistent depressive disorder  
     (dysthymia), 584  
 Persistent thyroglossal duct, 334  
 Persistent truncus arteriosus, 289, 306  
 Personality, **588**  
     disorder, 588  
     personality trait, 588  
 Personality disorders, 588  
     Cluster A, 588  
     Cluster B, 588  
     Cluster C, 589  
 Pes cavus  
     Friedreich ataxia, 549  
 Petechiae  
     aplastic anemia, 431  
 Peutz-Jeghers syndrome, 221, 397  
 PEX genes, 48  
 Peyer patches, **384**  
     histology, 372  
     IgA antibody production, 105, 384  
     immune system organ, 96  
     intussusception and, 395  
 Peyronie disease, 675  
 PCI<sub>2</sub>, 499  
 P-glycoprotein  
     chemotherapy and, 228  
 Phagocyte dysfunction  
     exotoxin inhibition in, 132  
     immunodeficiencies, 117  
 Phagocytosis  
     group A streptococcal inhibition, 136  
 Phalen maneuver, 470  
 Pharmaceutical company  
     sponsorship, 277  
 Pharmacokinetics, 233  
     age-related changes in, **250**  
 Pharmacology  
     autonomic drugs, **239**, 242  
     cardiovascular, 324  
     endocrine, 362  
     gastrointestinal, 408  
     hematologic/oncologic, 445  
     musculoskeletal/skin/connective  
         tissue, **499**  
     neurology, 564  
     pharmacodynamics, 261  
     pharmacokinetics/  
         pharmacodynamics, 232  
     renal, 630  
     respiratory, 710  
     toxicities and side effects, 250  
 Pharyngeal apparatus, 643  
 Pharyngeal arch derivatives, **644**  
     1st pharyngeal arch, 644  
     2nd pharyngeal arch, 644  
     4th and 6th pharyngeal arches, 644  
     3rd pharyngeal arch, 644  
 Pharyngeal (branchial) cleft cyst, 643  
 Pharyngeal cleft derivatives, **643**  
 Pharyngeal pouch derivatives, 644  
     1st pharyngeal pouch, 644  
     2nd pharyngeal pouch, 644  
     4th pharyngeal pouch, 644  
 Pharyngitis  
     adenovirus, 164  
*Streptococcus pyogenes*, 136  
 mononucleosis, 165  
 prophylaxis (rheumatic fever), 198  
 unvaccinated children, 186  
 Pharyngoesophageal false  
     diverticulum, 394  
 Pharynx, 686  
 Phenelzine, 599  
 Phenobarbital, 566  
     epilepsy therapy, 564  
 Phenotypic mixing, 162  
 Phenoxylbenzamine, 247  
     for pheochromocytomas, 359  
 Phentolamine, 247  
 Phenylalanine  
     classification of, 81  
     tyrosine catabolism, 84  
 Phenylephrine, 711  
 Phenyl ketones  
     in urine, 84  
 Phenylketonuria  
     tyrosine in, 84  
 Phenytoin  
     epilepsy therapy, 564  
     gingival hyperplasia, 253  
     megaloblastic anemia, 253  
     peripheral neuropathy, 254  
     vitamin B<sub>6</sub> deficiency, 68  
 Pheochromocytomas  
     etiology and findings with, **359**  
     MEN 2A/MEN 2B and, 358  
     phenoxybenzamine for, 247  
 Philadelphia chromosome  
     in myeloproliferative disorders,  
         442, 443  
     translocations of, 444  
 Phlebitis  
     IV amphotericin B, 199  
 Phlebotomy  
     for hemochromatosis, 405  
 Phobias, 586  
     agoraphobia, 586  
     social anxiety disorder, 586  
 Phocomelia, 638  
 Phonophobia, migraine headache,  
     536  
 Phosphatases, 73  
 Phosphodiesterase (PDE) inhibitors  
     PDE-5, 711  
     type of inhibition, clinical use and  
         adverse effects, **249**  
 Phosphoenolpyruvate carboxykinase,  
     78  
 Phosphofructokinase-1 (PFK-1)  
     glycolysis and, 73  
     metabolic pathways, 73  
 Phospholipid bilayer sac  
     in bacteria, 124  
 Phospholipids, 212  
 Phosphorus  
     values in bone disorders, 476  
 Phosphorylases, 73  
 Phosphorylation, 45  
 Photophobia  
     migraine headache, 536  
     rabies, 171  
 Photosensitivity  
     drugs causing, 192, 194, 253  
 Phototherapy for jaundice, 404  
 Phrenic nerve, 687, 710  
 Phthirus pubis  
     disease and treatment, 161  
 Phyllodes tumor, 673  
 Physical abuse (child), 579  
 Physician-assisted suicide, 270  
 Physiologic dead space  
     determination, **688**  
 Physiologic neonatal jaundice, **403**  
 Physiology  
     cardiovascular, 293  
     endocrine, 336  
     gastrointestinal, 381  
 hematology/oncology, 420  
 musculoskeletal, skin, and  
     connective tissue, 456  
 renal, **605**  
 reproductive, 653  
 respiratory, 688  
 Physostigmine, 573  
     anticholinergic toxicity treatment,  
         251  
     anticholinesterase, 243  
 Pia mater, 511  
 Pica, 428, 590  
 Pick disease, 538  
     bodies, 538  
 Picornaviruses, 163  
     characteristics, 167, 168  
     genomes, 163  
 Pierre Robin sequence, 644  
 Pigmented skin disorders, **490**  
 Pigment stones, 406  
 "Pill-rolling tremor", 537  
 Pilocarpine, 573  
 Pilocytic astrocytoma, 546  
 Pimozide, 597  
 Pindolol, 248  
     antianginal therapy, 327  
 Pineal gland, 520  
 Pinealoma, 546  
 Pinworms, 159  
 Pioglitazone, 363  
 Piroxicam, 500  
 Pisiform bone, 459  
 Pitting edema, 319  
 Pituitary adenoma, 347  
 Pituitary apoplexy, 347  
 Pituitary drugs, 364  
 Pituitary gland, **335**, 505  
 Pituitary tumors  
     MEN 1 and, 360  
 Pityriasis rosea, 496  
*Pityrosporum* spp  
     cutaneous mycoses, 152  
 pKa, 235  
 PKD genes  
     renal cyst disorders and, 627  
 Placebo, 261  
 Placenta  
     estrogen production, 654  
     fetal component, **640**  
     hCG secretion by, 657  
     hormone secretion by, 657  
     parental component, 640  
     progesterone production, 654  
 Placenta accreta/increta/percreta, 664  
 Placental aromatase deficiency, 663  
 Placental insufficiency  
     preeclampsia, 667  
 Placenta previa, 664  
 Plague, 149  
 Plantar aponeurosis, 472  
 Plantar fasciitis, 472  
 Plantar flexion, 463  
 Plantaris, 463  
 Plantar reflex, 527  
 Plaque (skin)  
     squamous cell carcinoma, 498  
 Plaques (skin)  
     actinic keratosis, 496  
     characteristics, 489  
     hairy leukoplakia, 493  
     lichen planus, 496  
      pityriasis rosea, 496  
     psoriasis, 489  
     seborrheic dermatitis, 490  
     squamous cell carcinoma, 498

- Plasma acute-phase reactants (inflammation), 214
- Plasma cells, **419**
- Plasmalogens, 48
- Plasma membrane structure of, 49
- Plasmapheresis, 620
- Plasmids in drug resistance, 131
- Plasminogen, 447
- Plasmodium falciparum*, 200
- Plasmodium* spp hematologic infections, **157** stains for, 125
- Plasmodium malariae*, 157
- Plasmodium ovale*, 157
- Plasmodium vivax*, 157
- Platelet-activating factor, 416
- Platelet-derived growth factor (PDGF) in wound healing, 216, 217 signaling pathways for, 345
- Platelet disorders, 436 transfusion for, 436
- “Platelet inhibitors”, 249
- Platelet plug formation, **421**
- Platelets essential thrombocythemia, 443 functional liver markers, 400 transfusion of, 438
- Platinum compounds mechanism, use and adverse effects, 451
- Pleiotropy, 56
- Pleomorphic adenomas, 386
- Pleural effusion lymphatic/chylothorax, 705
- Pleural effusions asbestos, 701 mesothelioma, 702 physical findings, 704 types and characteristics of, **705**
- Pleuritis rheumatoid arthritis, 478
- Pleuroperitoneal membrane, 380
- Plicae circulares, 372
- Plummer-Vinson syndrome, 387, 428
- Pneumatosis intestinalis, 396
- Pneumococcal vaccine, 127
- Pneumoconioses, **701** asbestos-related disease, 701 berylliosis, 701 coal workers' pneumoconiosis, 701 silicosis, 701
- Pneumocystis jirovecii* asymptomatic infections, 154 HIV-positive adults, 177 opportunistic fungal infections, 154 prophylaxis, 194 stain for, 125 stains for, 125 TMP-SMX, 194
- Pneumocytes Types I and II, 685
- Pneumomediastinum, 696
- Pneumonia ARDS, 702 bronchopneumonia, 707 common causes by age, **179** cryptogenic organizing pneumonia, 707 *Haemophilus influenzae*, 142 interstitial (atypical) pneumonia, 707 *Pneumocystis jirovecii*, 154 *Streptococcus agalactiae*, 137 lobar, 707
- measles-associated death, 169 PPI adverse effects, 409 Q fever, 149 type, organisms and characteristics of, **707** VZV, 165
- Pneumoperitoneum, 390
- Pneumothorax physical findings, 704 presentation and types of, **706** secondary spontaneous pneumothorax, 706 tension pneumothorax, 706 traumatic pneumothorax, 706
- Podocyte damage, 619, 621
- Poikilocytosis, 417
- Point of service plan, 278
- pol* gene, 175
- Poliomyelitis, 549
- Poliovirus, 549 immunodeficient patients, 118 picornavirus, 168 unvaccinated children, 186
- Polyadenylation signal, 41
- Polyangiitis microscopic autoantibody, 115
- Polyarteritis nodosa, 174 Type III hypersensitivity, 113
- Polyarthralgias gonococcal arthritis, 480 rubella, 182
- Polyclastic ovarian syndrome (PCOS), **669** anovulation, 669 antiandrogens, 682 clomiphene, 680
- Polycythemia blood oxygen in, 690 Eisenmenger syndrome, 307 lab values and associations, 444 paraneoplastic syndromes, 229
- Polycythemia vera, 443 Budd-Chiari syndrome and, 402
- Polydactyly, 63
- Polydipsia, 354
- Polyhydramnios, 640 esophageal atresia and, 369
- Polymerase chain reaction (PCR), **52**
- Polymorphic ventricular tachycardia, 315
- Polymyalgia rheumatica ESR in, 215 giant cell arteritis and, 484 symptoms, findings and treatment, **483**
- Polymyositis autoantibody, 115 mixed connective tissue disease, 482
- Polymyositis/dermatomyositis, **483**
- Polymyxin B, 193
- Polymyxins mechanism and clinical use, **193**
- Polyneuropathies familial amyloid, 213
- Polyneuropathy, 434
- Polyomaviruses DNA viruses, 163 envelope and medical importance, 164 genome, 163
- Polyostotic fibrous dysplasia, 57
- Polyposis syndromes, 397
- Polyps adenomatous, 397 colonic, 397
- hyperplastic, 397 APC gene, 397 KRAS gene, 397 inflammatory pseudopolyps, 397 mucosal, 397 neoplastic transformation of, 397 serrated, 397 submucosal, 397 uterine, 657
- Polyuria diabetes mellitus, 354 hyperparathyroidism, 353 lithium, 598
- Pompe disease, 87
- Pontiac fever, 143
- Pontine syndrome, 532 “Pope's blessing”, 460
- Popliteal artery, 465 atherosclerosis in, 310
- Popliteal fossa, 465
- Popliteus, 463
- Porcelain gallbladder, 407
- Porphobilinogen deaminase, 434
- Porphyria, 434, 566
- Porphyria cutanea tarda, 434
- Portal hypertension ARPDK, 627 cirrhosis and, **399** *Schistosoma* spp, 160 pulmonary arterial hypertension, 703 serum markers for, 400 varices and, 375
- Portal triad, 371, 377
- Portal vein, 371, 377
- Portosystemic anastomoses, **375**
- Positive predictive value (PPV), 264
- Positive reinforcement, 576
- Positive skew distribution, 267
- Postauricular lymphadenopathy, 169
- Posterior cerebral artery, 532
- Posterior circulation strokes, 532
- Posterior circumflex artery, 465
- Posterior cruciate ligament (PCL) injury, 464
- Posterior drawer sign, 464
- Posterior fossa malformations, **506**
- Posterior inferior cerebellar artery stroke effects, 533
- Posterior nucleus (hypothalamus), 513
- Posterior pituitary (neurohypophysis), 335
- Posterior urethral valves, 602, **603**
- Postherpetic neuralgia, 165
- Postinfarction fibrinous pericarditis, 317
- Postinfectious encephalomyelitis, 542
- Postoperative ileus, 243
- Postpartum blues, 585
- Postpartum hemorrhage, 665 coagulopathy, 665
- Postpartum mood disturbances, 584
- Postpartum psychosis, 585
- Postpartum thyroiditis, 349
- Postrenal azotemia, 625
- Poststreptococcal glomerulonephritis Type III hypersensitivity, 113
- Poststreptococcal glomerulonephritis (acute), 620
- Post-traumatic stress disorder (PTSD) acute stress disorder, 587 diagnostic criteria/treatment, 587 drug therapy for, 596 prazosin for, 247 SSRIs for, 587
- Posttussive emesis, 132
- Postural hypotension midodrine for, 245 trazodone, 600
- Postviral infections pneumonias, 179
- Potassium amphotericin B, 199
- Potassium channels myocardial action potential, 301 opioid effect, 572
- Potassium chloride, 252
- Potassium iodide for thyroid storm, 350 *Sporothrix schenckii*, 154
- Potassium shifts hypokalemia/hyperkalemia, 614
- Potassium-sparing diuretics mechanism, use and adverse effects, **632**
- Pott disease, 180
- Potter sequence oligohydramnios and, **602**
- Potter sequence (syndrome) ARPKD, 627 pulmonary hypoplasia, 684
- Poxvirus envelope and medical importance, 164
- molluscum contagiosum, 493
- PR3-ANCA/c-ANCA autoantibody, 115
- Practice tests, 21
- Prader-Willi syndrome chromosome association, 64 ghrelin in, 381 imprinting disorder in, 58
- Pramipexole, 568
- Pramlintide, 252, 363
- Prasugrel, 421, 447
- Praziquantel antihelminthic therapy, 200 tapeworms, 160 trematodes, 160
- Prazosin, 247
- Precision (reliability), 265
- Precision vs accuracy, **265**, 268
- Precocious puberty adrenal steroids and, 343 leuprolide, 680 McCune-Albright syndrome, 57 pinealoma, 546 types, 660
- Predictive value, 264
- Prednisolone for thyroid storm, 350
- Preeclampsia, 667
- hydatidiform moles, 666
- Pregnancy complications placenta previa, 664
- Pregnancy, **657** aliskiren contraindication, 633 anemia caused by, 428 antimicrobial prophylaxis in, 195 carpal tunnel syndrome in, 470 complications, 279 contraindicated antimicrobials, 204 diabetes in, 638 estrogen in, 654 folate deficiency caused by, 430 folic acid supplementation, 68 heparin in, 445 hypertension and treatment in, 246, 324, 667
- Listeria monocytogenes* in, 139 lithium in, 308

Pregnancy (*continued*)  
 complications in, 279  
 phenylketonuria in, 84  
 physiologic changes in, **657**  
 neural tube defects, 505  
 pituitary infarcts with, 347  
 progesterone in, 654  
 pyelonephritis, 624  
 pyogenic granulomas and, 492  
 risks with SLE, 482  
 sex hormone-binding globulin, 345  
 Sjögren syndrome and, 480  
 stillbirth, 182  
*Streptococcus agalactiae* in, 137  
 syphilis in, 147  
 termination of, 681  
 Turner syndrome and, 661  
 urinary tract infections, 181  
 vitamin B<sub>9</sub> deficiency, 68

Pregnancy complications  
 abruptio placentae, **664**  
 choriocarcinomas and, 666  
 ectopic pregnancy, 665  
 hypertension, 667  
 placenta accreta spectrum, 664  
 postpartum hemorrhage, 665  
 vasa previa, 665

Prehn sign, 675, 678

Preload, 293

Premature ejaculation, 599

Premature ovarian failure, 659, 669

Preoptic nucleus, 513

Prepatellar bursitis, 471

Procollagen, 50

Preproinsulin, 342

Prerenal azotemia, 625

Presbycusis, 551

Presbyopia, 554

Preschool age development, 578

Presenilin, 538

Pressure-volume loops, 296

Presynaptic 2-autoreceptor, 245

Pretectal nuclei, 558

Preterm birth, death with, 279

Pretest probability, 263

Prevalence  
 incidence vs, 265  
 vs incidence, 265

*Prevotella* spp, 179

Priapism, 675  
 sickle cell anemia, 432  
 trazodone and, 600

Primaquine, 157  
 hemolysis in G6PD deficiency, 253

Primary adrenal insufficiency, 357

Primary amyloidosis, 213

Primary bacterial peritonitis, 400

Primary biliary cholangitis, 403, 405

Primary central nervous system  
 lymphoma  
 occurrence and associations, 439

Primary disease prevention, 278

Primary dysmenorrhea, **670**

Primary (essential) hypertension, 324

Primary glomerular disease, 618

Primary hemostasis, 417, 421

Primary hyperaldosteronism, 358  
 hypertension with, 308  
 renal disorder features, 615

Primary hyperparathyroidism, 353  
 lab values in, 476

Primary ovarian insufficiency, **669**

Primary polydipsia, 346

Primary sclerosing cholangitis, 403, 405  
 autoantibody, 115

Primary spontaneous pneumothorax, 706

Primary testicular lymphoma, 677

Primase  
 replication initiation by, 38

Primidone, 537

Primitive atrium, 290

Primitive reflexes, **527**  
 frontal lobe lesions, 528

Pringle maneuver, 371

PR interval, 315, 316  
 antiarrhythmic effects, 331  
 prolonged, 316  
 shortened, 315

Prinzmetal angina  
 calcium channel blockers for, 312  
 ischemic manifestations, 312

Prions, 178

Probencid, 255  
 cidofovir with, 202  
 gout, 501

Procainamide, 330

Procalcitonin, 214

Procarbazine, 254  
 mechanism, use and adverse  
 effects, 451

Procedure bias, 266

Process improvement model, 280  
 quality measurement, 280

Process quality measurement, 280

Processus vaginalis, 648

Procoagulation, 423

Progesterone  
 lactation and, 659  
 ovulation, 655  
 signaling pathways for, 345  
 source and function of, **654**

Progesterins, 681

Progressive multifocal  
 leukoencephalopathy  
 (PML), 508, 542  
 HIV-positive adults, 177  
 polyomaviruses, 164

Proguanil, 200

Projection, 577

Prokaryotes  
 RNA polymerases in, 42

Prolactin  
 function of, 336  
 lactation and, 659  
 signaling pathways for, 345  
 source, function, and regulation,  
**338**  
 tuberoinfundibular pathway, 514

Prolactin-inhibiting factor, 336

Proliferative glomerular disorders, 618

Prometaphase, 46

Promoters (gene expression), 41

Pronephros, 602

Proopiomelanocortin, 335

Proper hepatic artery, 371

Prophase, 46

Prophylaxis  
 antimicrobial, 198  
 antimycobacterial, 197  
 for RSV, 200  
 HIV/AIDS patients, 198  
*Trichomonas vaginalis*, 158  
 rabies postexposure, 171

Propionic acidemia, 85

Propionyl-CoA carboxylase  
 vitamin B<sub>7</sub> and, 68

Propofol, 570

Propranolol, 248, 331, 350  
 essential tremor, 537

Proprioception  
 Friedreich ataxia, 549  
 muscle receptors for, 468

Propylthiouracil  
 agranulocytosis, 253  
 aplastic anemia, 253  
 for thyroid storm, 350  
 thionamides, 364

Prostacyclin analogues, 711

Prostaglandin analogs, 257

Prostaglandins  
 aspirin effects, 500  
 cortisol effect on, 344  
 glaucoma therapy, 573

Prostate, 648

Prostate cancer  
 adenocarcinomas, 678  
 incidence/mortality of, 223  
 leuprolide for, 680  
 metastases of, 224

Prostatic acid phosphatase (PAP), 678

Prostatic adenocarcinoma, **678**

Prostatitis, 678  
 gonorrhea, 184  
*Escherichia coli*, 678

Prosthetic devices  
*Staphylococcus epidermidis*, 128

Prosthetic heart valves, 433

Protamine sulfate, 251

Protease inhibitors  
 fat redistribution, 253  
 HIV therapy, 203  
 naming convention for, 256

Proteases  
 pancreatic secretion, 383

Proteasome, **48**

Protein A  
 bacterial virulence, 129

Proteinases, 416

Protein C/S deficiency, 435  
 hereditary thrombophilias, 437

Protein-energy malnutrition, **71**

Protein kinase A  
 fructose bisphosphatase-2 and, 76

Protein metabolism  
 amino acids, 81

Proteins  
 free radical effect on, 210

Protein synthesis, **45**  
 elongation, 45  
 exotoxin inhibition of, 132  
 initiation of, 42, 45  
 metabolic site, 74  
 posttranslational modification, **45**  
 sequence of, 45  
 termination, 45  
 trimming, 45

Protein synthesis inhibitors  
 antimicrobial therapy, 191

Proteinuria  
 ACE inhibitors for, 633  
 diabetes mellitus, 354  
 glomerular disease and, 619  
 nephritic-nephrotic syndrome,  
 619  
 nephrotic syndrome, 619, 621  
 preeclampsia, 667  
 serum sickness, 113

Proteolysis  
 cortisol and, 344

Proteolytic processing in collagen  
 synthesis, 50

*Proteus* spp  
 xanthogramulomatous  
 pylonephritis, 624

*Proteus mirabilis*  
 cephalosporins, 189  
 penicillins for, 188  
 urinary tract infections, 181, 624

Prothrombin  
 complex concentrate transfusion,  
 438  
 warfarin effect on, 437

Prothrombin time  
 functional liver markers, 400

Proton pump inhibitors  
 Beers criteria, 250  
 for *Helicobacter pylori*, 191  
 mechanism, use and adverse  
 effects, **409**

Protozoa  
 CNS infections, **156**  
 GI infections, **155**  
 hematologic infections, 157  
 visceral infections, **158**  
 watery diarrhea, 179

Proximal convoluted tubules (PCT)  
 glucose clearance, 608  
 relative concentrations in, **611**

Proximal renal tubular acidosis (RTA)  
 type 2, 617

PRPP (glutamine-phosphoribosyl  
 pyrophosphate)  
 amidotransferase, 73

Pruritis  
 pseudofolliculitis barbae, 491

Pruritus  
 anal, 159  
 atopic dermatitis, 491  
 biliary tract disease, 405  
 chloroquine, 200  
 cutaneous mycoses, 152  
 ectoparasites, 161

Prussian blue stain, 701

PSA  
 serum tumor marker, 227  
 stains for, 228

Psammoma bodies  
 calcification, 212  
 mesotheliomas, 702  
 tumor identification, 228

Pseudoappendicitis  
*Yersinia enterocolitica*, 144

Pseudodivericulum, 393

Pseudoephedrine, **711**

Pseudofolliculitis barbae, 491

Pseudofractures, 475

Pseudohypoparathyroidism  
 type 1A, 352

Pseudomembranous colitis  
 clindamycin, 192  
 drug reaction and, 252  
*Clostridium difficile*, 138  
 penicillins, 188  
 watery diarrhea, 179

*Pseudomonas aeruginosa*  
 bronchiectasis, 699

*Pseudomonas* spp  
 ceftazidime, 188  
 cystic fibrosis, 60  
 epididymitis and orchitis, 678  
 fluoroquinolones, 195  
 immunodeficient patients, 118  
 multidrug-resistant, 198  
 nosocomial infection, 185  
 osteomyelitis, 180  
 penicillins for, 188  
 pyocyanin of, 109  
 tricuspid valve endocarditis, 321  
 UTIs, 181

- Pseudomonas aeruginosa*, **143**  
 biofilm production, 128  
 exotoxin in, 132
- Pseudo-Pelger-Huet anomaly, **441**
- Pseudotumor cerebri, **540**
- Pseudovirion, **162**
- Psittacosis, **149**
- Psoas sign, **393**
- Psoriasis, **489, 491**  
 cyclosporine, 120  
 etanercept for, 502  
 hyperkeratosis/parakeratosis, 489  
*infliximab/adalimumab* for, 502  
 methotrexate for, 450  
 skin lesions, 489  
 therapeutic antibodies, 122  
 therapeutic antibodies for, 122
- Psoriatic arthritis, **481**  
 HLA subtype, 100  
*leflunomide* for, 500  
 psoriasis and, 491  
 therapeutic antibodies for, 122
- PSV23 (pneumococcal polysaccharide) vaccine, **127**
- Psychiatric emergencies, **593**  
 acute dystonia, 593  
 delirium tremens, 593  
 hypertensive crisis, 593  
 lithium toxicity, 593  
 neuroleptic malignant syndrome, 593  
 serotonin syndrome, 593  
 transtheoretical model of change, **592**  
 tricyclic antidepressant overdose, 593
- Psychiatry, **575**  
 conditions and preferred medications, 596  
 pharmacology, 596  
 psychology, 575
- Psychoactive drug intoxication/  
 withdrawal, 594  
 depressants, 594  
 hallucinogens, 595  
 stimulants, 594
- Psychosis, **582**  
 corticosteroids, 120  
 LSD and, 595
- Psychotherapy techniques  
 behavioural therapy, 596  
 cognitive behavioral therapy, 596  
 dialectical behavioral therapy, 596  
 interpersonal therapy, 596  
 motivational interviewing, 596  
 supportive therapy, 596
- PTEN gene, **225**
- Pterygoid muscles, **524**
- PTH, **475**
- PTHrP (parathyroid hormone-related protein), **229**
- Ptosis  
 CN III damage, 561  
 Horner syndrome, 559  
 myasthenia gravis, 486  
 saccular aneurysm, 534
- Puberty  
 Kallmann syndrome and, 663  
 precocious, 57  
 Tanner stages, 660
- Pubic tubercle, **380**
- Public health sciences, **260**  
 communication skills, 273  
 ethics, 270  
 quality and safety, 280
- Pudendal nerve, **376, 463**
- Pulmonary anthrax, **137**
- Pulmonary arterial hypertension (PAH), **703**
- Pulmonary artery, **289, 687**
- Pulmonary capillary wedge pressure (PCWP), **304**
- Pulmonary circulation, **692**
- Pulmonary edema  
 left heart failure, 319  
 LV failure, 317  
 nitrates for, 326  
 opioids for, 572  
 physical findings, 704
- Pulmonary emboli  
 direct factor Xa inhibitors for, 445  
 presentation and treatment, **696**
- Pulmonary fibrosis  
 amiodarone and, 254  
 diffusion limited gas exchange, 692  
 drug reaction and, 254  
 restrictive lung disease, 700
- Pulmonary hypertension, **703**  
 acute respiratory distress syndrome, 702  
 chronic thromboembolic, 703  
 drug therapy, 711  
 etiologies of, 703  
 left heart disease, 703  
 lung diseases or hypoxia, 703  
 multifactorial, 703  
 sildenafil, 711
- Pulmonary hypoplasia, **684**
- Pulmonary Langerhans cell histiocytosis, **699**
- Pulmonary surfactant  
 club cells, 685
- Pulmonary vascular resistance (PVR), **692**
- Pulmonic stenosis  
 wide splitting in, 298
- Pulmonic valves  
 physiologic splitting, 298  
 "Pulseless disease", 484
- Pulse pressure  
 equation for, 294
- Pulse-temperature dissociation, **144**
- Pulsus paradoxus  
 asthma attack, 698  
 cardiac tamponade, 320
- "Punched out" bone lesions (X-ray), **440**
- Punched-out ulcers, **387**
- Punishment (conditioning), **576**
- Pupil  
 CN III palsy, 561  
 control, **558**  
 light reflex, 558  
 pupillary light reflex, 558  
 syphilis, 184
- Pupillary reflex, **523**
- Pupil size, drugs affecting, **255**
- Pure motor stroke, **532**
- Pure red cell aplasia, **229, 430**  
 thymoma and, 98
- Purines, **479**  
 de novo synthesis, 36, 73  
 Lesch-Nyhan syndrome, 37  
 salvage deficiencies, **37**  
 structure, 35  
 structure of, 34
- Purkinje cells  
 in paraneoplastic cerebellar degeneration, 229  
 of cerebellum, 210
- Purkinje fibers, **302**
- Purpura  
 aplastic anemia, 431
- Pustular psoriasis, **489**
- Pustules  
 acne, 491  
 characteristics, 489  
*pseudofolliculitis barbae*, 491  
*rosacea*, 491
- Putamen  
 neurodegenerative disorders, 538
- Pyelonephritis, **181**  
 acute and chronic, **624**  
 kidney stones, 622  
 WBC casts in, 618
- Pygmalian effect, **266**
- Pyloromyotomy, **369**
- Pyoderma gangrenosum  
 inflammatory bowel disease, 392
- Pyogenic granulomas, **492**
- Pyramidal cells, **210**
- Pyramidal tract demyelination  
 multiple sclerosis, 541
- Pyrantel pamoate, **200**
- Pyrazinamide  
 gout, 253  
 mechanism and clinical use, **197**
- Pyridostigmine, **243**  
 myasthenia gravis treatment, 486
- Pyridoxal phosphate, **67**
- Pyridoxine, **67**
- Pyrimethamine, **200**  
 effect on purine synthesis, 36
- Pyrimidines  
 de novo synthesis, 36  
 structure, 35
- Pyrimidine synthesis, **500**
- Pyruvate carboxylase, **78**  
 vitamin B<sub>7</sub> and, 68
- Pyruvate dehydrogenase complex  
 deficiency, **76**  
 deficiency, 77  
 vitamin B<sub>1</sub> and, 66
- Pyruvate dehydrogenase complex deficiency, **77**
- Pyruvate kinase  
 deficiency, 432
- Pyruvate kinase deficiency  
 causes and findings, 432
- Pyruvate metabolism, **77**
- Pyuria  
 sterile, 624  
 urinary tract infections and, 181
- Q**
- Q fever  
 rickettsial disease, 149  
 transmission, 150
- QRS complex, **302**
- QT interval  
 ondansetron effect on, 410
- Quadrantanopia, **562**
- Quantifying risk  
 terminology and examples of, **262**
- Quaternary amines, **204**
- Quaternary disease prevention, **278**
- Quetiapine, **256, 597**
- Quiescent (stable) cells, **46**
- Quinidine, **200**  
 cinchonism, 254
- Quinine, **200**
- Quinupristin, **198**
- R**
- Rabies, **166**  
 active and passive immunity, 110  
*rhabdovirus*, 167
- Rabies virus  
 characteristics, **171**
- Rachitic rosary, **475**
- Radial head subluxation, **473**
- Radial nerve  
 injury and presentation, 456  
 neurovascular pairing, 465
- Radiation exposure  
 acute myelogenous leukemia and, 442  
 aplastic anemia, 431  
 apoptosis caused by, 208  
 hypopituitarism, 347  
 malignancies related to, **211**  
 toxicity levels and tissues affected, **211**  
 X-ray teratogenic effects, 638
- Radiation-induced fibrosis, **211**
- Radiation therapy  
 acute pericarditis and, 323  
 angiosarcomas, 492  
 lymphopenia, 433  
 neutropenia, 433  
 papillary thyroid carcinoma risk, 351
- Radiculopathy  
 lumbosacral, 465
- Radon carcinogenicity, **226**
- RAG mutation  
 immunodeficiency, 117
- Ragged red muscle fibers, **59**
- Rales  
 in heart failure, 319
- Raloxifene  
 estrogen receptor modulator (selective), 680
- Raltegravir, **203**
- Ramelteon, **567**
- Ramipril, **633**
- Random plasma glucose  
 diabetes mellitus diagnosis, 354
- RANKL  
 immunotherapy, 122
- RANK-L (RANK ligand), **340**
- Ranolazine  
 mechanism and clinical use, 327
- Raphe nucleus, **510**
- Rapid acting insulins, **362**
- Rapid automated broth cultures, **126**
- Rapid-eye movement (REM) sleep, **512**
- Rapidly progressive (crescentic) glomerulonephritis, **620**
- RAS gene, **351**
- Rasagiline, **568, 569**
- Rasburicase, **453**
- rash, **169**
- Rashes  
 "blueberry muffin", 169  
 carbapenems, 190  
 childhood, 183  
 desquematting, 484  
 fluoroquinolones, 195  
 heliotrope, 229  
 macrolides, 193  
 malar, 482  
 palms and soles, 150  
 penicillinase-sensitive penicillins, 188  
 petechial, 182  
 rickettsial infections, 150  
 rubella, 182  
 syphilis, 184  
 unvaccinated children, 186

Rashes of childhood  
associated disease and presentation, **183**  
Rathke pouch, 335, 546  
tumor, 637  
Rationalization, 577  
Raynaud disease, 486  
Raynaud phenomenon, **486**  
Buerger disease, 484  
calcium channel blockers for, 326  
scleroderma and, 487  
Raynaud syndrome, 486  
“Razor bumps”, 491  
*RBL* gene, 225  
RBC inclusions  
associated pathology, **426**  
RBC morphology (pathologic), **424–425**  
Reabsorption and secretion rate, **608**  
calculation of, 606  
Reaction formation, 577  
Reactive arthritis, **481**  
chlamydia, 184  
HLA subtype, 100  
Type III hypersensitivity, 113  
Reassortment  
influenza viruses, 169  
viral, 162  
Recall bias in studies, 266  
Receiver operating characteristic curve, **264**  
Receptor binding  
potency and efficacy with antagonists, **237**  
Receptor fusion proteins  
naming conventions for, 258  
Receptor-mediated endocytosis, 47  
Receptor tyrosine kinase  
endocrine hormone signaling pathways, 345  
recessive, 117  
Recklinghausen disease, 543  
Recombinant cytokines, **121**  
Recombination  
bacterial genetics, 130  
viral, 162  
Rectal sparing, 392  
Rectum  
blood supply and innervation, 376  
familial adenomatous polyposis, 397  
portosystemic anastomosis, 375  
Rectus abdominis muscle, 380  
Recurrent branch of median nerve injury and presentation, 457  
Recurrent laryngeal nerve compression of, 709  
Pancoast tumor, 710  
Red cell casts  
Granulomatosis with polyangiitis, 485  
Red hepatization, 707  
Red infarct, 210  
Red nucleus (midbrain) lesion effects, 528  
Redox reactions  
vitamin B<sub>2</sub> and, 67  
Redundant/degenerate genetic code, 37  
Reed-Sternberg cells, 438  
Refeeding syndrome (anorexia nervosa), 590  
Referred pain  
cholecystitis, 406  
diaphragm irritation, 687  
Reflex bradycardia, 612

Reflexes  
clinical, 527  
cranial nerves, 523  
motor neuron signs, 547  
primitive, 527  
Reflex tachycardia, 247  
Refractive errors (vision), **553**  
Refractory angina, 327  
Refsum disease, 48  
Refusing care  
minors, 272  
Regadenoson, 312  
Regan-Lowe medium, 126  
Registering for exam, 5–6  
Regression, 577  
Regulation of cell cycle  
Cyclin-dependent kinases (CDKs), 46  
p53, 46  
tumor suppressors, 46  
Regulation of gene expression, **41**  
regulator, 102  
Regulatory T cells, **102**  
cell surface proteins, 110  
Regurgitation  
in GERD, 387  
Reichert cartilage, 644  
Reid index, 698  
Reinforcement, 576  
Relapsing fever  
animal transmission, 149  
lice, 161  
Relationship with patients, 276  
Relative afferent pupillary defect (RAPD), 559  
Relative risk reduction (RRR), 262  
Relative risk (RR), 260, 262  
Reliability (precision), 265  
Remodeling (tissue), 217  
Renal agenesis, 602, 603  
pulmonary hypoplasia association, 684  
Renal artery  
stenosis, 628, 633  
Renal blood flow (RBF)  
renal plasma flow and, 606  
Renal cell carcinoma  
chromosome association, 64  
hypercalcemia and, 229  
metastases of, 224  
presentation and treatment, **628**  
recombinant cytokines, 121  
risk with complex cysts, 627  
Renal clearance  
calculation of, **606**  
Renal disease  
drug dosages in, 233  
genitourinary trauma, 651  
Renal disorders/failure  
conditions and features of, **615**  
consequences of, 626  
diffuse cortical necrosis, 626  
ESR in, 215  
Fabry disease, 88  
gout and, 479  
myoclonus in, 537  
renal cyst disorders, 627  
tetracycline use in, 192  
waxy casts in, 618  
Wilson disease, 405  
Renal/genitourinary drug reactions, **254**  
Renal hypoxia, 690  
Renal insufficiency  
staphylococcal scalded skin syndrome, 493  
Renal ischemia, 500  
NSAIDs, 500  
Renal oncocytoma, **629**  
Renal osteodystrophy, 353, 626, 627  
Renal papillary necrosis, **626**  
pyelonephritis and, 624  
sickle cell anemia, 432  
Renal plasma flow, 606  
Renal sympathetic discharge, 612  
Renal toxicity  
ganciclovir, 202  
Renal tubular acidosis  
types and parameters of, **617**  
Renal tubular defects  
effects and causes, **610**  
Renal vascular smooth muscle, 241  
Renin  
aliskiren effect on, 633  
primary hyperaldosteronism, 358  
renal disorders and, 615  
renin-angiotensin-aldosterone system, 612  
Renin-angiotensin-aldosterone system, **612**  
Renin-secreting tumor  
renal disorder features, 615  
Renomegaly  
Von Gierke disease, 87  
Renovascular disease, **628**  
Renovascular hypertension, 358  
Reoviruses  
characteristics, 167  
genome, 163  
segmented, 168  
Repaglinide, 363  
Reperfusion injury, 210  
Reperfusion therapy, 317  
Replication fork, 38  
Reportable diseases  
confidentiality exceptions, 273  
Repression, 577  
Repressor proteins  
lactose effects on, 40  
Reproductive/endocrine drug reactions, **252**  
Reproductive hormones, control of, **679**  
Reproductive system  
anatomy, 648  
pathology, 661  
pharmacology, 679  
physiology, 653  
Rescheduling exam, 6  
Reserpine  
Parkinson-like syndrome, 254  
Residual volume, 688  
Resistance in vessels, 295  
Respiration  
exercise response, **694**  
high altitude response, **694**  
Respiratory acidosis  
laboratory findings with, 616  
Respiratory alkalosis  
high altitude, 694  
laboratory finding with, 616  
Respiratory burst  
actions of, **109**  
in chronic granulomatous disease, 117  
Respiratory depression  
anesthetics, 570  
barbiturates, 564, 594  
benzodiazepines, 564, 594  
epilepsy drugs, 564  
inhaled anesthetics, 570  
opioids, 570, 594  
psychoactive drug intoxication, 594  
tricyclic antidepressants, 593, 599  
Respiratory syncytial virus (RSV)  
paramyxovirus, 167, 168  
pneumonia, 707  
prophylaxis, 122  
Respiratory system  
pharmacology, 710  
Respiratory tract infections  
C3 deficiency, 107  
Respiratory tree  
conducting zone, **686**  
respiratory zone, 686  
Respiratory zone, 686  
Resting tremor, 537  
Restless legs syndrome, 536  
Restricting type (anorexia nervosa), 590  
Restrictive cardiomyopathy, 318  
hemochromatosis, 405  
Restrictive/infiltrative cardiomyopathy, **318**  
Restrictive lung diseases, **699**  
ankylosing spondylitis, 481  
flow volume loops, 697  
RET gene  
Hirschsprung disease, 394  
Reteplase (rPA), 447  
Rete testis, 676  
Reticular activating system (midbrain)  
lesion effects, 528  
Reticulin, 50  
Reticulocyte production index, 427  
Reticulocytes  
in aplastic anemia, 431  
intravascular hemolysis, 431  
Retina  
chronic hyperglycemia, 556  
Retinal hemorrhage  
hypertensive emergency, 308  
Retinal pathology  
degeneration, 556  
detachment, **557**  
hemorrhage, 555  
retinitis, 555  
vein occlusion, 555  
Retinal vein occlusion, 555, **556**  
Retinitis  
cidofovir, 202  
Retinitis pigmentosa, **557**  
abetalipoproteinemia, 94  
Retinoblastoma  
chromosome association, 64  
heterozygosity loss, 56  
Retinoblastomas  
osteosarcomas, 477  
Retinoids, 491  
Retinol, 66  
Retinopathy  
chloroquine, 200  
of prematurity, 685  
sorbitol, 81  
RET/PTC rearrangements, 351  
Retrograde amnesia, 581  
Retroperitoneal fibrosis, 623  
Retroperitoneal structures, **370**  
Retrospective studies, 266  
Rett syndrome, **62**  
Reverse transcriptase, 175  
telomerase, 38  
Reye syndrome, **400**  
Reynolds pentad, 407  
Rhabdomyolysis  
daptomycin, 195  
potassium shifts and, 614

- refeeding syndrome and, 590  
with heat stroke, 534
- Rhabdomyomas, 324**  
nomenclature for, 221
- Rhabdomyosarcomas**  
dactinomycin for, 449  
variant, 668
- Rhabdoviruses**  
characteristics and medical importance, 167  
negative-stranded, 168
- Rhagades, 147**
- Rheumatic fever, 322**  
chorea with, 537  
heart murmur with, 300  
*Streptococcus pyogenes*, 136  
myocarditis with, 323  
streptolysin O, 133  
type II hypersensitivity, 112
- Rheumatoid arthritis**  
autoantibody, 115  
azathioprine for, 450  
carpal tunnel syndrome and, 470  
celecoxib for, 500  
etanercept for, 502  
extraarticular manifestations, 478  
HLA subtype, 100  
immunosuppressants, 120  
infliximab/adalimumab for, 502  
leflunomide for, 500  
methotrexate for, 450  
pathogenesis, findings and treatment, 478  
therapeutic antibodies for, 122  
Type III hypersensitivity, 113
- Rheumatoid factor, 115**
- Rh hemolytic disease of newborn, 415**
- Rhinitis**  
phenylephrine for, 245
- Rhinophyma, 491**
- Rhinosinusitis, 695**
- Rhinovirus**  
characteristics of, 168  
picornavirus, 167, 168  
receptors for, 163
- Rhizopus spp**  
opportunistic infections, 153
- Ribavirin, 204**  
contraindicated in pregnancy, 204  
purine synthesis, 36
- Riboflavin, 67**
- Ribose, 79**
- Ribosomes, 45**
- Rice-water diarrhea**  
*Vibrio cholerae*, 146  
organisms causing, 179
- Richter transformation, 442**
- Rickets**  
hypophosphatemic, 615  
lab values in, 476  
metaphyseal cupping/fraying, 475  
vitamin D and, 70
- Rickettsia spp**  
stains for, 125  
tetracyclines, 192
- Rickettsia prowazekii, 149**  
transmission of, 149, 161
- Rickettsia rickettsii, 149**  
animal transmission, 149  
chloramphenicol, 192  
Rocky Mountain spotted fever, 150
- Rickettsia typhi, 149**  
transmission, 149
- Rickettsial diseases**  
rash common, 150  
rash rare, 150
- Riedel thyroiditis, 349**
- Rifabutin, 196**
- Rifampin**  
as prophylaxis, 198  
hepatitis, 252  
*Mycobacterium leprae*, 141  
*Mycobacterium tuberculosis*, 196
- Rifamycins**  
mechanism and clinical use, 196
- Rifaximin**  
hepatic encephalopathy treatment, 401
- Rift Valley fever, 167**
- Right bundle branch, 302**
- Right bundle branch block, 298**
- Right coronary artery (RCA)**  
occlusions of, 313
- Right heart failure, 319**
- Right lower quadrant (RLQ) pain, 394**
- Right-to-left shunts, 288, 306**
- Right upper quadrant (RUQ) pain, 406**
- Right ventricular hypertrophy (RVH)**  
high altitude, 694
- Riluzole, 569**
- ring-enhancing lesions (MRI)**  
*Toxoplasma gondii*, 156
- Ringworm**  
griseofulvin, 200  
tinea corporis, 152
- rinuclear ANCA (p-ANCA)**  
autoantibody, 115
- Risedronate, 500**
- Risk quantification, 262**
- Risperidone, 597**
- Ristocetin, 421**
- Ritonavir**  
HIV therapy, 203
- Rituximab, 452**
- Rivaroxaban, 446**
- Rivastigmine, 243, 569**
- River blindness, 159**
- RNA**  
capping, 41  
interference, 56
- RNA polymerases, 42**  
types and functions of, 42
- RNA processing (eukaryotes), 41**
- RNA viral genomes, 163**
- RNA viruses**  
characteristics and medical importance, 167
- RNA genome, 163**
- Robertsonian translocation, 64**
- Rocker-bottom feet, 63**
- "Rocket tails", 139**
- Rocky Mountain spotted fever, 149, 150**
- animal transmission, 149  
chloramphenicol, 192
- Roflumilast, 249**
- Romaña sign, 158**
- Romano-Ward syndrome, 315**
- Romberg sign, 548**
- Romiplostim (TPO analog), 121**
- Root cause analysis, 281**
- Rooting reflex, 527**
- Ropinirole, 568**
- Ropivacaine, 571**
- Rosacea, 491**
- Rose gardener's disease, 154**
- Rosenthal fibers, 546**
- Roseola**  
rash, 183
- Roseola infantum**  
HHV-6/HHV-7, 165
- Rose spots, 144**
- Rosiglitazone, 363**
- Rotator cuff muscles, 456**
- Rotavirus**  
characteristics, 168
- Rotenone, 78**
- Roth spots, 321**
- Rotor syndrome, 404**  
hyperbilirubinemia in, 403
- Rough endoplasmic reticulum, 47**
- Rouleaux formation, 440**
- Round ligament of uterus**  
male/female homologs, 648  
structures in, 649
- Rovsing sign, 393**
- RSV F protein**  
immunotherapy, 122
- Rubella, 169**  
cardiac defect association, 308  
heart murmur with, 300  
rash, 182  
TORCH infection, 183  
unvaccinated children, 186
- Rubeola (measles) virus, 170**
- Ruffini corpuscles, 509**
- Rule of 9's, 497**
- Ruxolitinib, 443, 453**
- Ryanodine receptor, 466**
- S**
- S-100**  
Langerhans cell histiocytosis, 444
- S-100 immunohistochemical stain, 228**
- S-100 tumor marker**  
keratoacanthoma, 498
- Saber shins, 147**  
congenital syphilis, 147  
syphilis, 182
- Sabin poliovirus vaccine, 167**
- Sabouraud agar, 126**
- Saccular aneurysms, 534**  
Ehlers-Danlos syndrome, 51  
renal cyst disorders and, 627
- Sacrococcygeal teratomas, 676**
- Sacubitril**  
mechanism and clinical use, 327
- Saddle embolus, 696**
- Saddle nose**  
syphilis, 182
- Safety culture, 280**
- Salicylates**  
toxicity treatment for, 251
- Salivary gland tumors, 386**
- Salmeterol, 245**
- Salmonella spp, 118**  
animal transmission, 149  
bloody diarrhea, 179  
encapsulated bacteria, 127  
food poisoning, 178  
intracellular organism, 127  
*Shigella* spp vs, 144
- Salmonella vs Shigella, 144**
- Salmonella typhi, 144**
- Sampling bias, 266**
- Sandfly fever, 167**
- SA node, 301**
- Saponification, 209**
- Saprophyticus**  
urease-positive, 127
- Sarcoidosis, 700**  
characteristics and associations, 700
- erythema nodosum, 496
- Sarcoma botryoides, 668**
- Sarcomas**  
metastasis of, 224  
nomenclature of, 221
- Sarcoplasmic reticulum, 466**
- Sarcopetes scabiei**  
disease and treatment, 161
- Sargamostim, 453**
- Sargamostim (GM-CSF), 121**
- SARS (sudden acute respiratory syndrome), 167**
- Satiety/hunger regulation, 513**
- Saturday night palsy, 456**
- "Sausage fingers", 481
- "Saw-tooth" crypt pattern, 397
- Saxagliptin, 363**
- Scabies, 200**
- Scalded skin syndrome**  
*Staphylococcus aureus*, 133  
toxic shock syndrome toxin, 133
- Scales (skin)**  
characteristics, 489  
seborrheic dermatitis, 490
- Scar formation, 219**
- Scarlet fever**  
*Streptococcus pyogenes*, 136  
rash with, 183
- S cells**  
secretin production, 381
- Schaumann bodies, 700**
- Schilling test, 430**
- Schistocytes, 433**  
associated pathology, 424  
disseminated intravascular coagulation, 437  
in intravascular hemolysis, 431
- Schistosoma haematobium**  
bladder cancer, 227  
disease association, 161  
squamous cell carcinoma of bladder, 627
- Schistosoma spp**  
disease and treatment, 160
- Schistosomiasis**  
portal hypertension, 399  
pulmonary arterial hypertension, 703
- Schizoaffection disorder, 583**
- Schizophrenia**  
atypical antipsychotics for treatment, 583  
diagnostic criteria, 583  
hallucinations with, 582  
neurotransmitter changes with, 510
- Schizophrenia spectrum disorders, 583**
- delusional disorder, 583  
schizoaffection disorder, 583  
schizophrenia, 583  
schizotypal personality disorder, 583
- Schizopreniform disorder, 583**
- Schizotypal personality, 588**
- Schizotypal personality disorder, 583**
- Schüffner stippling**  
in blood smear, 157
- Schwann cells**  
functions of, 508  
Guillain-Barré syndrome, 542
- Schwannomas, 543, 545**
- Sciatic nerve, 462**
- SCID (severe combined immunodeficiency)**  
causes of, 37  
lymphopenia caused by, 433
- Sclerae**  
alkaptonuria, 84  
osteogenesis imperfecta, 50, 51

- Scleritis with rheumatoid arthritis, 478  
 Sclerodactyly, 487  
**Scleroderma, 487**  
 Scleroderma (diffuse)  
     autoantibody, 115, 487  
 Sclerodermal esophageal involvement, 387  
 Scleroderma (limited), 487  
 Sclerosing adenosis, 673  
 Sclerosing cholangitis, 403  
     ulcerative colitis association, 392  
 Scombrid poisoning, 250  
 Scopolamine, 244  
 Scoring of USMLE Step 1 exam, 7, 8–9  
 Scorpion sting, 407  
 Scotoma, 562  
 Scrotal lesions, benign, 676  
 Scrotum  
     lymphatic drainage, 648  
 Scurvy  
     collagen synthesis and, 50  
     vitamin C deficiency, 69  
 Seafood toxins (ingested), **250**  
 Seal-like barking cough, 170  
 Seasonal affective disorder, 584  
 Seborrheic dermatitis, 490  
 Seborrheic keratosis, 491  
 Sebum, 491  
 Secobarbital, 566  
 Secondary amyloidosis, 213  
 Secondary and tertiary adrenal insufficiency, 357  
 Secondary biliary cholangitis, 405  
 Secondary disease prevention, 278  
 Secondary glomerular disease, 618  
 Secondary hyperaldosteronism, 358  
 Secondary hyperparathyroidism, 353  
     lab values in, 476  
 Secondary spontaneous pneumothorax, 706  
 Second-degree AV block, 316  
 Second messengers  
     G-protein linked, 241  
 Second-wind phenomenon, 87  
 Secretin  
     secretory cell location, 382  
     somatostatinomas and, 361  
     source and action of, 381  
 Secretory (exported) protein synthesis, 47  
 Secukinumab  
     target and clinical use, 122  
 Segmented viruses, 167  
 Seizures  
     anti-NMDA receptor encephalitis, 229  
     benzodiazepine withdrawal, 566  
     characteristics and forms of, **535**  
     febrile, 534  
 Selection bias, 266  
 Selective estrogen receptor modulators (SERMs), 452, **680**  
 Selective media, 126  
 Selective mutism, 580  
 Selegiline, 568, 569, 599  
 Selenium sulfide  
     tinea versicolor, 152  
 Self-mutilation  
     Lesch-Nyhan syndrome, 37  
 Semimembranosus, 461  
 Seminal vesicles, 645  
 Seminiferous tubules  
     cells and functions of, **652**  
     seminoma, 677  
     Sertoli cells  
         secretions of, 652  
         sexual differentiation, 646  
         tumors of, 677  
     Sertoli-Leydig cell tumor, 671  
     Sertraline, 599  
     Serum amyloid A  
         acute phase reactants, 214  
     Serum iron  
         iron study interpretation, 429  
     Serum markers (liver pathology), 400  
     Semen, 677  
     Sensitivity (diagnostic tests), 263  
     Sensorineural hearing loss, 551  
     Sensory cortex, 532  
         topographic representation, 518  
     Sensory innervation  
         derivation of, 644  
         lower extremity, 463  
         tongue, 507  
     Sensory loss  
         conversion disorder and, 589  
         stroke effects, 532  
     Sensory modalities/pathways  
         thalamus in, 513  
     Sensory receptors  
         fiber type, location and modality, **509**  
     Separation anxiety disorder, 580  
     Sepsis, 320  
         ARDS, 702  
         immunodeficient patients, 118  
         *Streptococcus agalactiae*, 137  
         lymphopenia with, 433  
         neutropenia with, 433  
     Septate uterus, 646  
     Septic arthritis, 480  
     Septicemia  
         *Listeria monocytogenes*, 139  
     Septic shock  
         diffuse cortical necrosis (renal), 626  
         norepinephrine for, 245  
     Septum primum, 288  
     Septum secundum, 288  
     Sequence (morphogenesis), 637  
     Serine, 225  
     Serine/threonine kinase receptor endocrine hormone signaling pathways, 345  
     Serologic markers  
         hepatitis, 174  
     Seronegative spondyloarthritis, **481**  
     Serotonergic drugs, 599  
     Serotonin  
         changes with disease, 510  
     Serotonin syndrome, 410  
         atypical antidepressants, 599  
         cause, manifestation and treatment, 593  
         dextromethorphan, 711  
         MAOIs, 599  
         MDMA, 595  
         oxazolidinones, 193  
     Serous cystadenoma, 670  
     Serpentine cord, 140  
     Serrated polyps, 397  
     *Serratia* spp  
         immunodeficient patients, 118  
     *Serratia marcescens*, 128  
         in immunodeficiency, 128  
         treatment of, 189  
     UTIs, 181  
     Sertoli cells  
         secretions of, 652  
         sexual differentiation, 646  
         tumors of, 677  
     Sertoli-Leydig cell tumor, 671  
     Sertraline, 599  
     Serum amyloid A  
         acute phase reactants, 214  
     Serum iron  
         iron study interpretation, 429  
     Serum markers (liver pathology), 400  
     Sigmoid colon, 393  
     Sigmoid volvulus, 396  
     Signaling pathways  
         steriod hormones, 345  
     Signaling pathways of endocrine hormones, **345**  
     Signal recognition particle (SRP), 47  
     Signet ring cells, 389  
     Sign of Leser-Trélat, 229  
     Sildenafil, 249, 675  
     Silencer (gene expression), 41  
     Silica  
         carcinogenicity, 226  
         inflammation stimulus, 217  
     Silicosis, 701  
     Silver stain, 125  
     Simeprevir, 204  
     Simple partial (focal) seizures, 535  
     Simple pneumothorax physical findings, 704  
     Simple vs complex renal cysts, 627  
     Single nucleotide (point) mutation, 40  
     Single nucleotide polymorphisms (SNPs), 54  
     Single nucleotide substitutions, 40  
     Single-stranded binding proteins, 38  
     Sinusitis  
         brain abscesses, 180  
         granulomatosis with polyangiitis, 485  
         *Streptococcus pneumoniae*, 136  
         Kartagener syndrome, 49  
     Sirolimus (Rapamycin)  
         immunosuppression, 120  
     Sister Mary Joseph nodules, 389  
     Sitagliptin, 363  
     6-mercaptopurine  
         for ulcerative colitis, 392  
         purine synthesis, 36  
     Sjögren syndrome  
         autoantibody, 115  
         characteristics, **480**  
         pilocarpine for, 243  
         rheumatoid arthritis, 478  
     Skeletal muscle  
         ACh receptors in, 239  
         atrophy and hypertrophy in, 467  
         blood flow regulation to, 304  
         fiber types and metabolism, 467  
         glycogen in, 86  
         glycogen metabolism in, 86  
         ossification in, 483  
     Skewed distributions, 267  
     Skin, 253  
         blood flow regulation to, 304  
         collagen in, 50  
         common disorders, **491**  
         drug reactions, **253**  
         inflammatory diseases, 135  
         normal flora, 178  
         normal flora of, 135  
         pigmentation, 56  
         wrinkles of aging, 52  
     Skin anatomy  
         layers of, 487  
         morphology, 487  
     Skin cancer, **498**  
         albinism and, 490  
         Lynch syndrome and, 398  
     Skin infections, **493**  
         bacterial infections, 493  
         HSV1 and HSV2, 493  
         viral, 493  
     Skin lesions  
         autoimmune disorders, 494  
         black nodules, 159

- café-au-lait spots, 57  
crust, 489  
erythema multiforme, 151  
Gottron papules, 229  
hyperlipidemia signs, 309  
hyperpigmentation, 364  
inflammatory bowel disease, 392  
Kaposi sarcoma, 165  
kwashiorkor, 71  
macroscopic terms, **489**  
macule, 489  
microscopic terms, 489  
nodules, 498  
papule, 489  
patch, 489  
petechiae, 417  
pigmentation disorders, 490  
plaque, 489  
pustule, 489  
scale, 489  
scaling, 152  
scaly, 66  
seborrheic keratoses, 229  
splinter hemorrhages, 321  
striae, 356  
target lesions, 495  
T-cell lymphoma, 439  
telangiectasia, 324, 487  
ulcers, 158  
vascular tumors, 492  
vasculitides, 485  
wheal, 489  
Skip lesions, 392  
Skull thickening, 475  
Slapped cheek rash, 183  
Sleep apnea, **703**  
  central, 703  
  obesity hypoventilation syndrome, 703  
  obstructive, 703  
Sleep disturbance  
  sleep terror disorder, 591  
Sleep disturbance  
  benzodiazepines and, 594  
Sleep physiology  
  stages and EEG, **512**  
Sleep terror disorder, **591**  
SLE (systemic lupus erythematosus), **482**  
  antiphospholipid syndrome and, 482  
  autoantibody, 115  
  glomerulonephritis with, 620  
  HLA subtypes, 100  
  mixed connective tissue disease, 482  
  Raynaud phenomenon, 486  
  Type III hypersensitivity, 113  
Sliding hiatal hernia, 380  
Slime (S) layer (bacteria), 124  
Slipped capital femoral epiphysis  
  osteonecrosis, 473  
Slow acetylators, 234  
SMAD4 (DPC4) gene, 225  
Small cell carcinoma of lung  
  carcinogens for, 204  
  Lambert-Eaton myasthenic  
    syndrome, 486  
  location and characteristics, 709  
  oat cell carcinoma, 709  
  paraneoplastic syndromes, 229  
Small interfering RNA (siRNA), 56  
Small intestine  
  migrating motor complexes  
    production, 381  
Small lymphocytic lymphoma (SLL), **442**  
Small molecule inhibitors  
  naming conventions for, 258  
Smallpox, 164  
Small vessel disease  
  diabetes mellitus, 354  
Small-vessel vasculitis  
  presentation and pathology, 484  
Smoking, tobacco  
  abdominal aortic aneurysms and, 310  
  aneurism risks, 534  
  atherosclerosis and, 310  
  Buerger disease and, 484  
  bupropion for cessation, 600  
  carcinogenicity, 226  
  carcinogenicity of, 709  
  emphysema, 698  
  esophageal cancer risk, 388  
  lung cancer, 709  
  mesothelioma, 702  
  renal cell carcinoma, 628  
  stomach cancer and, 389  
  teratogenic effects of, 638  
  transitional cell carcinoma, 629  
  varenicline for cessation, 600  
"Smooth brain", 505  
Smooth endoplasmic reticulum, **47**  
Smooth muscle  
  contraction of, 467  
  glomus tumors, 492  
  tumor nomenclature, 221  
Smooth muscle (vascular)  
  arteriosclerosis, 309  
  contraction and relaxation, 467  
Smudge cells, 442  
SNARE proteins  
  in neurotransmission, 132  
SNc (substantia nigra pars compacta), 510  
SNRIs (serotonin-norepinephrine  
  reuptake inhibitors)  
  clinical use, 596  
  major depressive disorder, 584  
  mechanism and clinical use, 599  
Snuffles, 147  
"Soap bubble" appearance/lesions  
  giant cell tumor, 476  
Social anxiety disorder, 586  
  drug therapy for, 596  
  SSRIs for, 599  
Sodium channel blockers (class I), 330  
  antiarrhythmics, 330  
Sodium channels  
  cystic fibrosis, 60  
  epilepsy drug effects, 564  
  local anesthetic effects, 570  
  pacemaker action potential and, 301  
  permethrin, 200  
Sodium-glucose co-transporter 2  
  (SGLT2) inhibitors, 363  
Sodium oxybate (GHB)  
  narcolepsy treatment, 591  
Sodium-potassium pump, **49**  
Sodium stibogluconate, 200  
Sofosbuvir, 204  
Solifenacin, 244  
Solitary functioning kidney, 603  
Solitary nucleus of medulla, 303  
Somatic hypermutation, 101  
Somatic mosaicism, 57  
Sturge-Weber syndrome, 543  
Somatic nerves  
  male sexual response, 651  
Somatic symptom and related  
  disorders  
    characteristics of, **589**  
    conversion, 589  
    somatic symptom disorder, 589  
    vs malingering and factitious  
      disorders, 589  
Somatic symptom disorder, 589  
Somatic symptoms  
  illness anxiety disorder, 589  
Somatomedin, 337  
Somatostatin  
  function of, 336  
  secretory cell locations, 382  
  source, action, and regulation of, 381  
Somatostatin (octreotide)  
  hypothalamic/pituitary drugs, 364  
Somatostatinoma, 361  
Somatotropin, 337  
Sonic hedgehog (*SHH*) gene, 636  
Sorbitol metabolism, 81  
Sotalol, 331  
Southern blot, 53  
Southwestern blot, 53  
Space of Disse, 377  
Spaghetti and meatballs appearance,  
  152  
Spasmolytics, 572  
Spastic paralysis  
  tetanospasmin, 132  
Spastic paresis, 547  
Specialized transduction, 130  
Special senses  
  ophthalmology, 553  
  otology, 551  
Specificity equation, 263  
Specific learning disorder, 580  
Speckled ANA, **482**  
Spermatocole, 676  
Spermatocytes, 652  
Spermatogenesis, 652  
  cryptorchidism and, 675  
  process of, 652  
Spermatogonia, 652  
Spermiogenesis  
  process of, **653**  
Spherocytes  
  associated pathology, 425  
Spherocytosis  
  extrinsic hemolytic anemia, 431  
  hereditary, 432  
Spherule, 151  
Sphincter of Oddi, 381  
Sphingolipidoses, 88  
Sphingomyelin, 88  
Sphingomyelinase, 88  
Spina bifida occulta, 505  
Spinal cord  
  associated tracts, **525**  
  lesions of, 548  
  lower extent of, **524**  
Spinal cord syndromes  
  multiple sclerosis, 541  
Spinal lesions  
  disease and area affected, **548**  
Spinal muscular atrophy, 548  
  splicing of pre-mRNA in, 42  
Spinal nerves, **524**  
Spinal tract anatomy/function  
  ascending tracts, **526**  
  descending tract, 526  
Spinocerebellar degeneration  
  abetoliproteinemia, 94  
Spinothalamic tract, 526  
Spirochetes, **146**  
Spironolactone, 632, 682  
  for heart failure, 319  
Spleen  
  anatomy, **98**  
  embryology, 370  
  platelet destruction in, 436  
Splenectomy, 432  
  peripheral blood smear after, 432  
Splenic artery, 371  
splenomegaly, 442  
Splenomegaly  
  anemia, 157  
  cirrhosis, 399  
  hereditary spherocytosis, 432  
  malaria, 157  
  myelofibrosis, 442, 443  
  visceral leishmaniasis, 158  
  with rheumatoid arthritis, 478  
Splenoorenal ligament, 371  
Splice site mutation, 40  
Splicing of pre-mRNA, 41, **42**  
  alternative splicing, 43  
Splinter hemorrhages, 321  
Splinter hemorrhages (nails), 321  
Splitting, 577  
Splitting of heart sounds, 298  
Splitting (twinning), 641  
Spondyloarthritis (seronegative), 481  
Spongiosis  
  characteristics, 489  
Spontaneous abortion  
  *Listeria monocytogenes*, 139  
  *Listeria monocytogenes*, 184  
Spontaneous bacterial peritonitis, **400**  
Spontaneous pneumothorax, 706  
Sporadic porphyria cutanea tarda, 174  
Spore (bacteria), 124  
Spores (bacteria), 129  
*Sporothrix schenckii*, 154  
Sporotrichosis, 154  
Sprain (ankle), **465**  
Sprue  
  vitamin B<sub>12</sub> deficiency, 69  
"Spur cells", 424  
Sputum  
  rusty, 136  
Squalene epoxidase, 199  
Squamous cell carcinoma, 498  
  anus and cervix, 177  
  bladder, 160, 629  
  carcinogens in, 226  
  cervix, 669  
  esophagus, 388  
  head and neck, 695  
  hypercalcemia and, 228  
  lungs, 709  
  of skin, 496  
  pectinate line and, 376  
  penis, 675  
  vaginal, 668  
Squamous epithelium, 650  
  vulvar pathology, 668  
SRY gene, 645  
SSRIs (selective serotonin reuptake  
  inhibitors)  
  anxiety disorders, 586  
  atypical depression, 584  
  clinical use, 596  
  major depressive disorder, 584  
  mechanism and clinical use, 599  
  obsessive-compulsive disorder, 586  
  panic disorder, 586  
  phobias, 586  
  postpartum depression, 584  
  SIADH caused by, 252  
Stable angina, 312

- Stable (quiescent) cells, 46  
 Stab wounds and winged scapula, 458  
 Staghorn calculi, 622  
**Stains, 125**  
 Standard deviation  
     dispersion, 267  
     variability, 267  
 Standard error of the mean, 267  
 Stanford type A aortic dissection, 311  
 Stanford type B aortic dissection, 311  
 Stapedial artery, 289  
 Stapedius muscle, 644  
 Stapes (ossicles), 551  
 Staphylococcal scalded skin syndrome, 493  
 Staphylococcal toxic shock syndrome (TSS), 135  
**Staphylococci**  
     antibiotic tests, 134  
***Staphylococcus aureus*, 135**  
     bacterial endocarditis, 321  
     bullous impetigo, 493  
     food poisoning, 178  
     toxin production, 133  
***Staphylococcus epidermidis*, 135**  
     antibiotic tests, 134  
     biofilm production, 128  
     normal flora, 180  
     nosocomial infection, 182  
     osteomyelitis, 180  
     urease-positive, 127  
     vancomycin for, 190  
***Staphylococcus pyogenes***  
     necrotizing fasciitis, 493  
***Staphylococcus pyogenes***  
     skin infections, 493  
***Staphylococcus saprophyticus*, 136**  
     antibiotic tests, 134  
     gram-positive testing, 135  
     kidney tones and, 622  
     UTIs, 181  
 Starling curves, 294  
 "Starry sky" appearance of B cells, 439  
 Start and stop codons, 44  
 Startle myoclonus, 539  
 Starvation phases, 91  
 Statins  
     hepatitis, 252  
     myopathy, 253  
**Statistical distribution, 267**  
**Statistical hypothesis testing, 268**  
     common tests, 269  
     confidence interval, 269  
     correct result, 268  
     outcomes, 268  
     testing, 268  
 Statistical tests, common, 269  
 Status epilepticus, 535  
     treatment, 566  
 Steady state, 233  
 Steatorrhea  
     abetalipoproteinemia, 94  
     chronic pancreatitis, 407  
     malabsorption syndromes and, 391  
     octreotide effect, 410  
     with orlistat, 411  
 Steatosis (hepatic), 401  
 Stellate cells, 399  
 Stellate ganglion, 710  
 Stem cells  
     aplastic anemia, 431  
     myelodysplastic syndromes and, 440  
     paroxysmal nocturnal hemoglobinuria, 432  
 Steppage gait, 462  
 Sterile pyuria, 624  
 Sterilization/disinfection methods, 204  
 Steroids  
     acute pancreatitis, 407  
     berylliosis, 701  
     multiple sclerosis, 541  
     synthesis of, 47  
 Stevens-Johnson syndrome, 194  
     atypical variant of, 150  
     drug reaction and, 253, 495  
     sulfa drug allergies, 253  
 Stimulants  
     intoxication and withdrawal, 594  
     laxative, 411  
 St. John's wort, 255  
 St. Louis encephalitis, 167  
 Stomach  
     histology, 372  
     secretin effect on, 382  
 Stone bone, 475  
 Strategies  
     clinical vignette, 23  
     test-taking, 22–23  
 "Strawberry cervix"  
     *Trichomonas vaginalis*, 158  
 Strawberry cervix, 181, 184  
 Strawberry hemangiomas, 492  
 Strawberry tongue, 136  
     Kawasaki, 484  
     scarlet fever, 136  
 Streak gonads, 646  
**Streptococci**  
     antibiotic tests, 134  
***Streptococcus agalactiae* (group B strep), 137**  
     hippurate test for, 137  
     β-hemolytic nature of, 137  
***Streptococcus aureus***  
     septic arthritis, 480  
***Streptococcus bovis*, 137**  
***Streptococcus spp***  
     septic arthritis, 480  
***Streptococcus mutans***  
     normal flora, 178  
***Streptococcus pneumoniae*, 136**  
     antibiotic testing, 135  
     chloramphenicol, 192  
     encapsulated bacteria, 127  
     IgA protease and, 127  
     IV drug use and, 178  
     meningitis, 178  
     pneumonia, 178, 707  
     postviral infection, 178  
     rusty sputum, 136  
***Streptococcus pyogenes***  
     toxin production, 133  
***Streptococcus pyogenes* (group A strep), 136**  
***Streptococcus pyogenes***  
     signs and symptoms, 183  
 Streptogramins, 198  
 Streptokinase, 447  
 Streptolysin O, 133  
 Streptomycin, 191  
     mechanism and clinical use, 197  
 Stress incontinence, 623  
 Stress-related disorders, 587  
 Striated muscle  
     tumor nomenclature, 221  
 Striatum, 516  
 stroke, 446  
 Stroke  
     central post-stroke pain syndrome, 533  
     eclampsia, 667  
     homocystinuria, 85  
     hypertension, 308  
     ischemic, types of, 529  
     lesion area and symptoms, 532  
     sickle cell anemia, 432  
     syphilis, 147  
     thrombolytic drugs with, 447  
 Stroke volume  
     equation for, 293, 294  
***Strongyloides* spp, 158**  
***Strongyloides stercoralis***  
     intestinal infections, 159  
 Structural quality measurement, 280  
 ST segment, 302  
 ST-segment elevation MI (STEMI)  
     acute coronary syndrome, 317  
     diagnosis of, 312  
     ECG localization of, 314  
     NSTEMI comparison, 312  
 Studying for USMLE Step 1 exam timeline for, 16–19  
 Study materials, 20–21  
 Study schedule, 16–20  
 Sturge-Weber syndrome, 543  
     presentation, 543  
 Stylohyoid ligament, 644  
 Stylohyoid muscle, 644  
 Styloid process, 644  
 Stylopharyngeus, 644  
 Subacute bacterial endocarditis, 321  
 Subacute combined degeneration (SCD), 69, 548  
 Subacute endocarditis  
     enterococci, 137  
     *Staphylococcus gallolyticus*, 137  
 Subacute granulomatous thyroiditis, 349  
 Subacute sclerosing panencephalitis (SSPE), 170  
 Subarachnoid hemorrhage, 530  
     aneurysms, 534  
     nimodipine for, 326  
 Subarachnoid space, 511  
 Subclavian arteries, 289  
 Subcutaneous emphysema  
     esophageal perforation, 387  
 Subcutaneous fat  
     erythema nodosum in, 496  
     skin layers, 487  
 Subcutis, 487  
 Subdural hematomas, 531  
 Subendocardium, 210  
 Sublimation, 577  
 Sublingual gland  
     stones in, 386  
 Submandibular gland  
     stones in, 386  
 Submucosa, 372  
 Submucosal polyps, 397  
 Substance abuse  
     parental consent, 270  
     tricuspid valve endocarditis and, 321  
 Substance P, 536, 572  
 Substance use disorder, 591  
 Subthalamic nucleus  
     lesion effects, 528  
 Subunit vaccines, 111  
 Succimer  
     heavy metal toxicity, 251  
     lead poisoning, 429  
 Succinate dehydrogenase, 67  
 Succinylcholine, 570, 614  
 Succinyl-CoA  
     gluconeogenesis, 78  
     TCA cycle, 76  
 Sucking reflex, 527  
 Sucralfate, 409  
     mechanism and clinical use, 409  
 Sudden cardiac death, 312  
 Sudden death  
     cardiac death, 312, 323  
     cocaine use, 595  
     sleep apnea, 703  
     with myocarditis, 323  
 Sudden infant death syndrome (SIDS), 658  
 Suicidal patients, 273  
     elderly, 273  
 Suicide  
     deaths from, 279  
     physician-assisted, 276  
     risk factors for completion, 585  
 Sulbactam, 189  
 Sulfadiazine, 194  
     *Toxoplasma gondii*, 156  
 Sulfa drugs, 253  
     adverse effects, 255  
     megaloblastic, 253  
 Sulfamethoxazole (SMX), 194  
 Sulfapyridine, 410  
 Sulfasalazine  
     mechanism and clinical use, 410  
 Sulfatides, 140  
 Sulfisoxazole, 194  
 Sulfonamides, 204  
     hemolysis in G6PD deficiency, 253  
     hypothyroidism, 252  
     mechanism and clinical use, 194  
     photosensitivity, 253  
     trimethoprim, 194  
     vitamin B<sub>9</sub> deficiency, 68  
 Sulfonamides (TMP-SMX)  
     Bordetella pertussis, 143  
     Nocardia treatment, 139  
 Sulfonylureas  
     disulfiram-like reaction, 254  
 Sulfonylureas (1st gen), 363  
 Sulfonylureas (2nd gen), 363  
 Sulfur granules, 128  
 Sumatriptan, 567  
     cluster headaches, 536  
     coronary vasospasm with, 251  
 Sunburn, 496  
 Sunburst pattern (X-ray), 477  
 Superficial burn, 497  
 Superficial inguinal nodes, 648  
 Superficial partial-thickness bur, 497  
 Superior gluteal nerve, 463  
 Superior mesenteric artery  
     embryology, 368  
 Superior mesenteric artery (SMA), 368  
 Superior mesenteric artery (SMA) syndrome, 373  
 Superior oblique muscle, 560  
 Superior rectus muscle, 560  
 Superior sulcus tumor, 710  
 Superior vena cava syndrome, 98, 710  
     lung cancer, 710  
     Pancoast tumor, 710  
 Superoxide dismutase, 127  
 Supination  
     deficit in Erb palsy, 458  
     forearm, 456  
 Supine hypotensive syndrome, 667  
 Supportive therapy, 596  
 Suppression (defense mechanism), 577  
 Suprachiasmatic nucleus (SCN)  
     circadian rhythm, 513  
     sleep physiology and, 512  
 Supracondylar fracture, 457

- Supraoptic and paraventricular nuclei, 513
- Suprascapular nerve, 456
- Supraspinatus
- Erb palsies, 458
  - Supraspinatus muscle, 456
  - Supraventricular tachycardia
    - adenosine for diagnosing, 332
    - etiology and treatment, 315
- Suramin, 200
- Surface F protein, 169
- Surgical neck of humerus, 465
- Surrogate decision-maker, 271, **272**
- Sustained angiogenesis, 222
- Suvorexant, 567
- Swallowing
- tongue movement in, 523
- Swan-Ganz catheter, 304
- Swarming, 181
- Sweat glands, 239
- pilocarpine effects, 243
- Swiss cheese model, **280**
- Sydenham chorea, 322, 537
- Sympathetic nervous system
- derevation of face, 559
  - male sexual response, 651
  - receptor targets, 239
  - venous return and, 295
- Sympatholytics ( $\alpha$ -agonists)
- applications and adverse effects, **246**
- Sympathomimetics, **245**
- direct, 245
  - indirect, 245
- Sympathomimetics, physiologic effects of, **246**
- Synaptophysin
- tumor identification, 228
- Syncope
- atrial tumors, 324
  - during exercise, 318
  - pulsus parvus et tardus, 300
- Syndrome of apparent mineralocorticoid excess
- markers in, 615
  - renal tubular defects, 610
- Syndrome of inappropriate antidiuretic hormone secretion, **346**
- drug reaction and, 252
  - renal disorders features, 615
- Synthase, 73
- Syntrophoblast, 640
- Syphilis, 125
- diagnosis, **148**
  - heart disease with, 322
  - STI, 184
  - testing for, 125
  - TORCH infection, 182
- Syphilitic heart disease, **322**
- Syringomyelia, 506, 548
- Syrinx, 506
- Systemic amyloidosis, 213
- Systemic mycoses, 151
- Systemic primary carnitine deficiency, 89
- Systemic sclerosis
- mixed connective tissue disease, 482
- Systemic senile (age-related) amyloidosis, 213
- Systolic ejection, 296
- Systolic heart murmurs, 300
- T**
- Tabes dorsalis, 147, 184
- spinal cord lesions, 548
- Tachyarrhythmia
- isoproterenol for evaluating, 245
  - thyroid storm, 350
- Tachycardia
- phenylcyclidine, 595
  - phenoxybenzamine, 247
  - reflex, 247
  - stimulants and, 594
  - supraventricular, 248
  - thyroid hormones, 364
  - Wolff-Parkinson-White syndrome, 315
  - PCP, 595
- Tacrolimus
- hyperglycemia, 252
- Tactile hallucinations
- cocaine, 595
- Tadalafil, 249, 678
- Taenia solium*
- intestinal infection, 160
  - Praziquantel, 160
- Takayasu arteritis, 484
- Takotsubo cardiomyopathy, 318
- Tamoxifen
- estrogen receptor modulator, 680
  - hot flashes with, 252
  - mechanism, use and adverse effects, 452
- Tamsulosin, 247, **682**
- T-and B-cell activation, 103
- Tanner stages (sexual development), **660**
- Tardive dyskinesia
- metoclopramide adverse effect, 410
  - nigrostriatal pathway, 514
- Target cells
- associated pathology, 425
- "Target sign" (ultrasound/CT), 395
- Tarsal tunnel syndrome, 463
- Taste
- cranial nerve lesions and, 550
- TATA box, 41
- Tay-Sachs disease
- lysosomal storage disease, 88
- Tazobactam, 189
- TCA cycle, **77**
- hyperammonemia, 78
  - metabolic site, 74
  - pyruvate metabolism, 77
  - rate-determining enzyme for, 73
- T cells, 120, **419**
- activation, 103
  - anergy, 110
  - cell surface proteins, 110
  - corticosteroid effects, 120
  - cytokines secreted by, 108
  - cytotoxic, 102
  - diabetes mellitus, 355
  - differentiation of, **102**
  - disorders of, 116, 117
  - exhaustion/dysfunction, 223
  - functions of, 101
  - neoplasms of, **439**
  - regulatory, 102
  - sirolimus effect, 120
  - thymus, 98
- Tea-colored urine, 434
- "Teardrop" RBCs, 424, 443
- Teeth
- congenital syphilis, 147
  - dentinogenesis imperfecta, 51
  - discoloration, 192
  - osteogenesis imperfecta, 51
- Telangiectasias
- basal cell carcinomas, 498
  - hereditary hemorrhagic, 324
- Telencephalon, 504
- Tellurite agar, 126
- Telomerase
- action of, **38**
- Telophase, 46
- Temazepam, 566
- Temperature receptors, 509
- Temperature sensation
- cape-like distribution loss, 506, 548
- Temporal arteritis, 484
- Temporalis muscle, 524
- Temporal lobe, 513
- Temporal lobe encephalitis, 118
- Temporomandibular disorders, 472
- Tendinopathy (rotator cuff), 456
- Tendinous xanthomas, 309
- familial hypercholesterolemia, 94
- Tendons
- collagen in, 50
- Tenecteplase (TNK-tPA), 447
- Teniposide, 452
- Tennis elbow, 469
- "Tennis rackets" (Birbeck granules), 444
- "Tennis rackets" (Birbeck) granules, 444
- Tenofovir, 203
- Tenosynovitis, 480
- Tension headaches, 536
- Tension pneumothorax
- physical findings, 704
  - presentation and treatment, 706
- Tensor fascia latae muscle, 461
- Tensor tympani muscle, 644
- Tensor veli palatini muscle, 644
- Teratogen
- medications, **638**
- Teratogens
- ACE inhibitors, 633
  - aminoglycosides, 191
  - angiotensin II receptor blockers, 633
  - griseofulvin, 200
  - in fetal development, 633
  - in organogenesis, **638**
  - leflunomide, 500
  - propylthiouracil in pregnancy, 364
  - ribavirin, 204
  - susceptibility to, 636
- Teratoma, 677
- immature, 670
  - testicular, 677
- Terazosin, 678
- Terbinafine
- mechanism and clinical use, **199**
- Teres minor, 456
- Teriparatide, **501**
- Tertiary disease prevention, 278
- Tertiary hyperparathyroidism, 353
- Tertiary syphilis
- presentation, 184
- Testes
- descent of, 648
  - progesterone production, 654
- Testicular atrophy
- alcoholism, 595
  - muscular dystrophy, 61
- Testicular cancer, 677
- Testicular torsion, **675**
- Testicular tumors
- germ cell, **676**
  - gynecomastia, 673
  - non-germ cell tumors, 677
- Testing agencies, 25
- Testis-determining factor, 645
- Testosterone, 659, **682**
- androgen insensitivity syndrome, 662
  - Leydig cell secretion, 652
  - Sertoli cells, 652
  - spermatogenesis, 652
- Testosterone-secreting tumors, 662
- Testosterone synthesis, 199
- Test-taking strategy, 22–23
- Tetanospasmina
- effects of, 132
- Tetanus, 131
- unvaccinated children, 186
- Tetanus toxin
- passive vs active immunity, 110
- Tetany
- hypocalcemia, 615
  - hypoparathyroidism, 352
- Tetrabenazine, 569
- Tourette syndrome, 596
- Tetracaine, 571
- Tetracyclines
- esophagitis, 252
  - Fanconi syndrome, 254
  - mechanism and clinical use, **192**
  - pseudotumor cerebri and, 540
  - teratogenicity of, 191, 638
- Tetrahydrobiopterin ( $BH_4$ )
- in phenylketonuria, 84
- Tetrahydrofolic acid (THF), 68
- Tetralogy of Fallot, 306
- 22q11 syndromes, 308
- Tetrodotoxin, 250
- TGF- $\beta$
- in wound healing, 217
- Th1 cells
- cytokines secreted by, 108
- Th2 cells
- cytokines secreted by, 108
- Thalamus
- limbic system and, 514
  - neuropathic pain, 533
  - nuclei and sensory relay, **513**
- Thayer-Martin agar, 126
- Theca lutein cysts, 670
- Theca-lutein cysts, 666
- Thecoma, 671
- Thenar muscles, 457
- Theophylline, 249, 712
- Therapeutic antibodies, **122**
- Therapeutic index, **237**
- Therapeutic window
- lithium, 593
  - safety and, 237
- Thermogenin, 78
- Thiamine, 66, 76
- Thiazide diuretics
- in gout, 253
  - in heart failure, 319
  - in hypertension, 324
  - mechanism, use and adverse effects, **632**
- Thiazolidinediones, 363
- Thionamides
- mechanism and clinical use, 364
- Thiopental, 566, 570
- Thiopurines
- mechanism and clinical use, **450**
- Thioridazine, 597
- Third-degree (complete) AV block, 316
- 3rd pharyngeal pouch, 644
- Thoracic aortic aneurysm, 308, 310
- Thoracic outlet syndrome
- injury and deficits, 458
- Threadworms, 159

- Threonine, 81  
 Threonine kinase, 225  
 Thrombi  
 mural, 317  
 post-MI, 317  
 Thrombin, 447  
 Thromboangiitis obliterans, 484  
 Thrombocytes (platelets), **417**  
 disorders, 436  
 liver markers, 362  
 Thrombocytopenia  
 Class IA antiarrhythmics, 330  
 drug reaction and, 253  
*ganciclovir*, 202  
 recombinant cytokines, 121  
 sulfa drug allergies, 253  
*Wiskott-Aldrich syndrome*, 117  
 Thrombogenesis, **421**  
 Thrombolytic drugs, 423, 447  
 Thrombopoietin  
 clinical use, 121  
 Thrombosis  
*celecoxib*, 500  
 contraceptive and hormone replacement, 253  
*homocystinuria*, 85  
 Thrombotic microangiopathies  
 diagnosis and presentation, 436  
 Thrombotic stroke, 529  
 Thrombotic thrombocytopenic purpura, 436  
 Thromboxane A<sub>2</sub> (TXA), 421  
 thrombogenesis, 421  
 Thrush, 117  
*hairy leukoplakia* vs, 493  
*Candida albicans*, 153  
*nystatin*, 199  
 "Thumbprint" sign (imaging) colonic ischemia, 396  
 "thumb sign" (x-ray), 142  
 "Thunderclap headache", 534  
 Thymic aplasia, 116  
 Thymic shadow, 117  
 Thymidine, 202  
 Thymidine kinase, 202  
 Thymidylate synthase, 36  
 Thymoma  
*myasthenia gravis* and, 229  
 paraneoplastic syndromes, 229  
 thymus  
*immune system organs*, 98  
 Thymus  
*benign neoplasm*, 98  
*T cell origination* in, 419  
 Thymus-dependent antigens, 105  
 Thymus-independent antigens, 105  
 Thyroid adenoma, **350**  
 Thyroid cancer  
*diagnosis and treatment*, **351**  
*metastasis* of, 224  
*undifferentiated/anaplastic carcinoma*, 351  
 Thyroid development, **334**  
 Thyroideectomy, 351  
 Thyroid hormones  
*in toxic multinodular goiter*, 350  
*source, function, and regulation*, **339**  
*synergism with GH*, 339  
 Thyroidization of kidney, 624  
 Thyroid-stimulating immunoglobulin (TSI), 339  
 Thyroid storm  
*causes and findings*, 350  
*corticosteroids for*, 350  
 Thyrotoxicosis, 339  
 Thyrotropin-releasing hormone (TRH)  
*function of*, 336  
 Thyroxine-binding globulin (TBG), 339  
 Thyroxine (T4), 339, 347  
 TIBC (total iron-binding capacity)  
*lab values in anemia*, 429  
*microcytic anemia*, 428  
 Tibial nerve, 463  
 Ticagrelor, 447  
 Ticlopidine, 421, 447  
 Tidal volume (TV), 688  
 Tigecycline  
*mechanism and clinical use*, **192**  
 Tight junctions, 488, 511  
 Timolol, 331, 573  
 Tinea, 152  
*Tinea capitis*, 152  
*Tinea corporis*, 152  
*Tinea cruris*, 152  
*Tinea pedis*, 152  
*Tinea unguium*, 152  
*Tinea versicolor*, 152  
 Tinel sign, 470  
 Tiotropium, 712  
 Tirofiban, 421, 447  
 Tissue factor activation, 133  
 Tizanidine, 572  
 TMP-SMX, 194  
*for *Pneumocystis jirovecii**, 154  
*prophylaxis*, 198  
 TNF (tumor necrosis factor), 214, 216, 218  
 TNF- $\alpha$   
*immunotherapy target*, 122  
 TNF- $\alpha$  inhibitors  
*mechanism, use and adverse effects*, 502  
 Tocolytics, **681**  
 Toddler development, 578  
 Togaviruses  
*rubella*, 167  
 Tolbutamide, 363  
 Tolcapone, 568  
 Toll-like receptors (TLRs), 99  
*clinical use*, 121  
 Tolterodine, 244  
 Tolvaptan, 364  
 Tongue  
*development and innervation*, **507**  
*ectopic thyroid tissue in*, 334  
*glossoptosis*, 644  
*pharyngeal arch derivation*, 644  
 Tonic-clonic (grand mal) seizure, 535  
 Tonic-clonic seizures, 535  
 Tonic seizures, 535  
 Tonsils  
*immune system organ*, 96  
*pharyngeal pouch derivation*, 644  
 Tooth abnormalities  
*opalescent teeth*, 51  
 Tophus formation, 479  
 Topiramate  
*epilepsy therapy*, 564  
*pseudotumor cerebri*, 540  
 Topoisomerase inhibitors  
*mechanism, use and adverse effects*, **452**  
 Topotecan, 452  
 TORCH infections, 182  
*cataracts*, 554  
 Torsades de pointes, 315  
*Class IA antiarrhythmics*, 330  
*drug reaction and*, 251  
 magnesium for, 332  
*sotalol*, 331  
 Torsemide, 631  
 Torticollis, 537  
 Torus (buckle) fracture, 474  
 Total lung capacity (TLC), 688  
 Total parenteral nutrition (TPN), 406  
 Total peripheral resistance (TPR), 295  
 Tourette syndrome, 580  
*drug therapy for*, 596  
*obsessive-compulsive disorder and*, 586  
*sympatholytic drugs for*, 246  
 Toxic epidermal necrolysis (TEN), 495  
 Toxicities and side effects of drugs, 250  
*imunosuppressants*, 119  
 Toxicity treatments, specific, **251**  
 Toxic megacolon  
*Clostridium difficile*, 138  
 Toxic multinodular goiter  
*causes and findings*, 350  
 Toxic shock-like syndrome, 136  
 Toxic shock-like syndrome, 133  
 Toxic shock syndrome  
*presentation*, 135  
*toxin*, 133  
 Toxins  
*myocarditis with*, 323  
*seafood (ingested)*, 250  
 Toxins (bacterial)  
*exotoxins*, 130  
*lysogenic phage encoding*, 130  
*Toxocara canis*, 158  
*tissue infections*, 159  
*Toxocara* spp, 158  
 Toxoid, 110  
 Toxoid vaccines, 111  
*Toxoplasma gondii*  
*CNS infections*, 156  
*HIV-positive adults*, 177  
*in HIV positive adults*, 177  
*TORCH infection*, 182  
*Toxoplasma* spp, 180  
 Toxoplasmosis  
*prophylaxis*, 198  
*pyrimethamine*, 200  
 TP53 gene, 225  
 Tracheal deviation, 704  
 Tracheoesophageal anomalies, **369**  
 Tracheoesophageal fistula (TEF), 369  
 Traction apophysitis, 473  
 Tractus solitarius, 511  
 Tramadol  
*mechanism, use and adverse effects*, 573  
*seizures with*, 254  
 "tram-track" appearance, 620  
 "Tram-track" appearance, 620  
 Transcription factor, 225  
 Transduction bacterial genetics, 130  
 Transference, 576  
 Transferrin  
*acute phase reactants*, 214  
*free radical injury*, 210  
*indirect measure of*, 429  
*iron study interpretation*, 429  
*lab values in anemia*, 429  
 Transformation, bacterial genetics, 130  
 Transformation zone (cervix)  
*dysplasia*, 669  
*histology of*, 650  
 Transfusion-related acute lung injury, 114  
 Transgender, 590  
 Transient ischemic attack  
*effects and treatment of*, 529  
 Transitional cell carcinoma (bladder), 629  
 Transitional cell carcinomas, 226  
 Transjugular intrahepatic portosystemic shunt (TIPS), 375  
 Transketolase  
*vitamin B<sub>1</sub> and*, 66  
 Translocation  
*Down syndrome*, 63  
*fluorescence in situ hybridization*, 55  
*in protein synthesis*, 45  
*Mantle cell lymphoma*, 439  
*Robertsonian*, 63  
 Translocations  
*Burkitt lymphoma*, 439  
*follicular lymphoma*, 439  
 Transpeptidases, 124  
 Transplant rejection  
*pathogenesis and features*, **119**  
 Transplants  
*immunosuppressants in*, 120  
 Transposition of great vessels  
*diabetes during pregnancy and*, 308  
*embryologic development*, 289  
 Transtheoretical model of change, **592**  
 Transudate characteristics, 705  
 Transversalis fascia, 380  
 Transversion mutation, 40  
 Transversus abdominis, 462  
 Tranylcypromine, 599  
 Trapezium bone, 459  
 Trapezoid bone, 459  
 TRAP (tartrate-resistant acid phosphatase)  
*tumor identification*, 228  
 Trastuzumab, 452  
 Trauma and stress-related disorders, **587**  
*adjustment disorder*, 587  
 Trauma-informed communication, **274**  
 Traumatic aortic rupture, 311  
 Traumatic pneumothorax, 706  
 Travelers' diarrhea, 145  
 Trazodone, 600  
 Treacher Collins syndrome, 644  
 "Tree bark" appearance (aorta), 322  
 Trematodes  
*infections*, 160  
 Tremor  
*at rest*, 528  
*essential*, 537  
*immunosuppressants*, 120  
*intentional*, 537  
*resting*, 537  
 Trench fever, 161  
*Treponema* spp  
*dark-field microscopy*, 146  
*Gram stain for*, 125  
*Treponema pallidum*  
*penicillin G/V for*, 184  
*STI*, 184  
 Triamterene, 632  
 Triazolam, 566  
 Triceps reflex, 527  
 Triceps surae, 463  
*Trichinella spiralis*, 159  
 Trichinosis, 159

- Trichomonas* spp  
metronidazole, 195  
vaginitis, 181
- Trichomonas vaginalis*, 181, 184  
sexually transmitted infections, 158
- Trichomoniasis, 184
- Trichophyton* spp, 152
- Trichotillomania, 586
- Trichuris, 158
- Trichuris trichiura  
intestinal infections, 159
- Tricuspid atresia, 289, 306
- Tricuspid regurgitation, 296
- Tricuspid valve endocarditis, 321
- Tricyclic antidepressants (TCAs)  
mechanism and clinical use, 599  
naming convention for, 256  
overdose and treatment, 593  
torsades de pointes, 251  
toxicity treatment, 251
- Trentine  
Wilson disease, 405
- Trifluoperazine, 597
- Trigeminal nerve (CN V), 523  
lesion of, 550  
neuralgia, 536  
pharyngeal arch derivation, 644
- Triglycerides  
Von Gierke disease, 87
- Trihexyphenidyl, 568
- Triiodothyronine (T3), 339
- Trimethoprim  
mechanism and use, 194  
pyrimidine synthesis and, 36
- Trimming (protein synthesis), 45
- Trinucleotide repeat expansion  
diseases, 61  
myotonic dystrophy, 61
- Triple-blinded studies, 261
- Triptans  
angina triggers, 312  
for migraine headaches, 536  
mechanism, use and adverse effects, 567
- Triquetrum bone, 459
- Trismus (lockjaw)  
tetanospasmin, 132
- Trisomies (autosomal), 61  
ventral wall defect association, 368
- Trisomy 13 (Patau syndrome), 63  
hCG in, 658
- Trisomy 18 (Edwards syndrome), 63  
hCG in, 658
- Trisomy 21 (Down syndrome), 63
- tRNA, 44  
structure, 44
- Trochlear nerve (CN IV), 523  
damage to, 561  
ocular motility, 560  
palsy of, 563
- Tropheryma whipplei*, 391  
stain for, 125
- Tropheryma whipplei  
GI disease with, 391
- Tropical sprue, 391
- Tropicamide, 244
- Tropomodins, 314, 466
- Trousseau sign, 352, 615
- Trousseau syndrome  
pancreatic cancer, 408
- True<sup>”</sup> diverticulum, 393
- True-negative rate, 263
- True-positive rate, 263
- Truncal ataxia, 515
- Trypanosoma brucei*, 200  
CNS infections, 156
- Trypanosoma cruzi*  
nifurtimox for, 200  
visceral infections, 158
- Trypanosomes  
stains for, 125
- Trypsin, 383
- Trypsinogen  
pancreatic secretion, 383
- Tryptase, 418
- Tryptophan, 81
- TSC1/TSC2 genes  
oncogenicity of, 225
- t-test, 269
- T-tubule membrane, 466
- Tyrosine catabolism/catecholamine synthesis, 83
- Tubercloid leprosy, 141
- Tuberculosis, 140  
erythema nodosum, 496
- Tuberin protein, 225
- Tuberoinfundibular pathway, 514
- Tuberous sclerosis, 543
- Tubulointerstitial inflammation  
WBC casts in, 618
- Tubulointerstitial nephritis, 625
- Tularemia, 149
- Tumor lysis syndrome, 445
- Tumor markers (serum)  
pancreatic adenocarcinomas, 408
- Tumor nomenclature  
benign vs malignant, 221
- “Tumor plop” sound, 324
- Tumors, grade vs stage, 221
- Tumor suppressor genes, 46, 225
- Tunica albuginea, 675
- Tunica vaginalis, 648
- Turcot syndrome, 397
- Turner syndrome  
cardiac defect association, 308  
characteristics of, 661  
coarctation of aorta and, 307
- T wave (ECG), 302
- 21-hydroxylase, 343
- 22q11 deletion syndromes, 116
- 22q11 deletion syndromes, 308
- Twin concordance study, 260
- Twinning  
dizygotic, 641  
monozygotic, 641
- Twin-twin transfusion syndrome, 641
- 2-naphthylamine, 226
- Type 1 vs type 2 diabetes mellitus, 355
- Type I collagen, 50
- Type I error ( $\alpha$ ) (statistical testing), 268
- Type I hypersensitivity reaction  
antibody-mediated, 112  
atopic dermatitis, 491
- Type II collagen, 50
- Type II error ( $\beta$ ) (statistical testing), 268
- Type II hypersensitivity reaction  
antibody-mediated, 112  
organ transplants, 119  
*pemphigus vulgaris/bullous pemphigoid*, 494  
rheumatic fever, 322
- Type III collagen, 50
- Type III hypersensitivity reaction, 112  
immune complex, 113  
SLE, 482
- Type II skeletal muscle fibers, 467
- Type I skeletal muscle fibers, 467
- Type IV hypersensitivity reaction  
cell-mediated, 113  
contact dermatitis, 491
- DRESS syndrome, 253
- graft-versus-host disease, 119
- Typhoid fever, 144
- Typhus, 149  
transmission of, 149, 150
- Typical (1st-generation) antipsychotic, 597
- Tyrosinase, 490
- Tyrosine  
in phenylketonuria, 84
- U**
- Ubiquitination, 45
- Ubiquitin-proteasome system, 48
- UDP-glucuronosyltransferase  
physiologic neonatal jaundice, 404
- Ulcerative colitis  
autoantibody, 115  
spondyloarthritis, 481  
sulfasalazine for, 410
- Ulcers (gastrointestinal)  
bismuth/sucralfate for, 409  
complications, 390  
Curling, 389  
Cushing, 389  
esophageal, 387  
obstruction of GI tract, 390  
palatal/tongue, 151  
Zollinger-Ellison syndrome, 361
- Ulcers (skin)  
Raynaud syndrome, 486
- Ulipristal, 681
- “Ulnar claw”, 460
- Ulnar claw, 457
- Ulnar nerve  
injury, 460  
injury and presentation, 457
- Umbilical cord  
blood flow in, 642  
late separation of, 117
- Umbilical hernia  
congenital, 368
- Umbilicus  
portosystemic anastomosis, 375
- UMP synthase, 430
- Unambiguous genetic code, 37
- Uncal herniation, 547
- Uncinate process, 370
- Unconjugated bilirubin, 385
- Unconjugated (indirect)  
hyperbilirubinemia, 403
- Uncoupling agents, 78
- Undifferentiated thyroid carcinomas, 351
- Undulant fever, 143
- “Unhappy triad” (knee injuries), 471
- Unilateral renal agenesis, 603
- Uniparental disomy, 57
- Universal electron acceptors, 75
- Universal genetic code, 37
- Unnecessary procedure requests, 276
- Unstable angina  
acute coronary syndrome, 317
- Upper extremity  
innervation of, 456
- Upper extremity nerves  
injury and presentation, 456–502
- Upper GI bleeding, 390
- Upper motor neuron (UMN), 526  
Brown-Séquard syndrome, 549  
facial nerve lesion, 550  
facial paralysis, 532  
in amyotrophic lateral sclerosis, 548  
lesion signs, 547
- Urachal cysts, 642
- Urachus, 291, 642
- Urea cycle, 82  
metabolic site, 72  
ornithine transcarbamylase deficiency and, 83  
rate-determining enzyme for, 73
- Ureaplasma* spp, 127  
Gram stain for, 125
- Uremia  
acute pericarditis, 323
- Ureter, 649  
course of, 605  
damage in gynecologic procedures, 605
- Ureteric bud, 602
- Ureteropelvic junction  
development of, 603  
embryology, 602
- Urethra  
BPH, 678  
genitourinary trauma, 651
- Urethritis  
chlamydia, 148  
*Chlamydia trachomatis*, 148  
reactive arthritis, 481
- Urge incontinence  
drug therapy for, 244
- Urgency incontinence, 623
- Uric acid  
kidney stones, 622  
Lesch-Nyhan syndrome, 37  
Von Gierke disease, 87
- Urinalysis  
reducing sugar, 80
- Urinary incontinence  
drug therapy for, 244  
enuresis, 591  
ephedrine for, 245  
hydrocephalus, 540  
mechanisms and associations of, 623
- Urinary retention, 240  
atropine, 244  
bethanechol for, 240  
delirium, 581  
neostigmine for, 243  
treatment of, 240
- Urinary tract infections (UTIs)  
antimicrobial prophylaxis for, 198  
BPH, 678  
interstitial nephritis, 254  
presentation and causes of, 181
- Urinary tract obstruction  
hydronephrosis, 623  
pyelonephritis, 624
- Urine  
Bence Jones proteinuria, 440  
diuretic effects on, 632  
drug elimination in, 235  
electrolyte changes with diuretics, 632  
in acute kidney injury, 625  
pregnancy test, 658  
type and significance of casts in, 618
- Urine protein electrophoresis (UPEP)  
plasma cell dyscrasias, 440
- Urobilinogen  
extravascular hemolysis, 431  
intravascular hemolysis, 432
- Urogenital sinus, 645
- Urosepsis, 624
- Urothelial carcinoma (bladder), 629
- Urticaria, 489  
mast cell degranulation, 491  
scombroid poisoning, 250  
sulfa drug allergies, 255

Use of interpreters, **275**  
 USMLE Step 1 exam  
 check-in process, **7**  
 clinical vignette strategies, **23**  
 content areas covered in, **2**  
 goal-setting for, **12**  
 leaving exam early, **8**  
 overview of, **2**  
 passing rates for, **10**  
 practice exams for, **11, 21–22**  
 registering for, **5–6**  
 rescheduling, **6**  
 score notifications for, **7**  
 scoring of, **8–9**  
 testing agencies, **25**  
 testing locations, **6**  
 test-taking strategies, **22–23**  
 time budgeting during, **7–8**  
 types of questions on, **8**

Ustekinumab  
 target and clinical use, **122**

Uterine conditions  
 neoplasms, **672**  
 non-neoplastic, **672**

Uterine (Müllerian duct) anomalies, **646**

Uterine neoplasms, **672**

Uterine procidentia, **649**

Uterovaginal agenesis, **662**

Uterus  
 anomalies of, **646**  
 collagen in, **50**  
 didelphys, **646**  
 epithelial histology, **650**  
 zygote implantation, **657**

Uterus didelphys, **646**

Uveitis, **555**  
 inflammatory bowel disease, **392**  
 in sarcoidosis, **700**  
 seronegative spondyloarthritis, **481**

U wave in ECG, **302**

**V**

Vaccination  
 vaccine types, **111**

Vaccine, **105, 127**  
 B-cell disorders, **116**  
*Haemophilus influenzae*, **142**  
*meningococci*, **142**  
 PPSV23, **105**  
*Salmonella typhi*, **144**  
 toxoids as, **139**  
 types of, **111**

Vagal nuclei  
 nucleus and function, **521**

Vagina  
 drainage of, **648**  
 epithelial histology, **650**

Vaginal bleeding  
 cervical cancer, **669**

Vaginal candidiasis  
*nystatin*, **199**

Vaginal infections  
 common, **181**

Vaginal squamous cell carcinoma, **668**

Vaginal tumors, **668**

Vaginismus, **590**

Vaginitis  
*Trichomonas spp.*, **181**  
*Trichomonas vaginalis*, **158**  
*trichomoniasis*, **184**

Vagus nerve (CN X), **523**  
 baroreceptors/chemoreceptors and, **303**  
 cardiac glycoside effects, **329**

diaphragm innervation, **687**  
 lesions of, **550**  
 pharyngeal arch derivation, **644**

Valacyclovir, **202**

Validity (accuracy), **269**

Valine  
 classification of, **81**  
 maple syrup urine disease, **81**

Valproic acid  
 epilepsy therapy, **564**  
 hepatic necrosis, **252**

Valsartan, **633**

Valvular disease  
 pressure-volume loops, **297**

Valvular dysfunction, **320**

Vancomycin  
 cutaneous flushing, **251**  
 mechanism and clinical use, **190**  
*MRSA*, **198**  
 toxicity of, **251**

Vanishing bile duct syndrome, **119**

Vardenafil, **249**

Varenicline, **600**

Variable expressivity, **56**

Variance, **267**

Variant angina, **312**

Variceal bleeding, **248**

Varicella zoster virus  
 guanosine analogs, **202**  
 HHV-3 transmission and clinical significance, **165**  
 immunity, **110**  
 immunodeficient patients, **118**  
 rash and clinical presentation, **183**  
 skin infection, **493**  
 vesicles with, **489**

Varicocele, **675**

Vasa previa, **665**

Vasa vasorum  
 syphilis, **147**

Vascular dementia  
 symptoms and histologic findings, **539**

Vascular tumors of skin, **492**

Vasculitides, **484**

Vasculitis  
 focal necrotizing, **485**  
*immunoglobulin A*, **485**  
 intraparenchymal hemorrhage, **531**  
 large-vessel, **484**  
 medium-vessel, **484**  
 small-vessel, **484**

Vasculopathy  
 noninflammatory, **487**

Vasoactive intestinal polypeptide (VIP)  
 source and action of, **381**

Vasoconstrictors, **571**

Vasodilation  
 sympathetic receptors, **241**

Vasodilators  
 aortic dissection, **311**  
 coronary steal syndrome, **312**  
 nitrates as, **326**

Vasopressin, **335**

Vasopressors, **295**

Vasospastic angina, **312**

V(D)J recombination, **99**

VDJ recombination defect  
 immunodeficiency, **117**

Vector-borne illnesses, **150**

Vedolizumab  
 target and clinical use, **122**

Vegetative state  
 axonal injury and, **533**

Velocardiofacial syndrome, **116**

Vemurafenib, **453**

Venlafaxine, **599**  
 phobias, **586**

Venous gonadal drainage, **648**

Venous return, **295**

Venous sinus thrombosis (dural), **519**

Venous thrombosis  
 paroxysmal nocturnal hemoglobinuria, **432**

Venous ulcer, **495**

Ventilation, **688**  
 alveolar ventilation, **688**  
 high altitude, **694**  
 minute ventilation, **688**

Ventilation/perfusion (V/Q) mismatch, **693**

Ventilation/perfusion (V/Q) ratio  
 exercise response, **694**

Ventral lateral (VL) nucleus, **513**

Ventral pancreatic bud, **370**

Ventral posterolateral (VPL) nucleus, **513**

Ventral posteromedial (VPM) nucleus, **513**

Ventral tegmentum, **510**

Ventricles  
 contractility of, **292**

Ventricular action potential, **301**

Ventricular aneurysm  
 pseudoaneurysm, **317**  
 true, **313, 317**

Ventricular fibrillation (VF)  
 ECG tracing, **316**

Ventricular filling  
 early diastole, **296**  
 ECG and, **302**

Ventricular free wall rupture, **317**

Ventricular myocytes, **303**

Ventricular noncompliance, **296**

Ventricular septal defect, **300**

Ventricular septal defect (VSD), **307**  
 congenital rubella, **308**  
*cri-du-chat* syndrome, **64**  
 Down syndrome, **308**  
 heart murmurs, **300**

Ventricular system (CNS), **520**

Ventricular tachycardia  
 Torsades de pointes, **315**

Ventriculomegaly, **505, 540**

Ventromedial nucleus (hypothalamus), **513**

Verapamil, **318, 326, 536**  
 antianginal therapy, **327**

Verrucae, **491**

Verrucous thrombi, **482**

Vertebral compression fractures, **474**

Vertebral landmarks  
 gastrointestinal structure innervation, **374**

Vertical gaze palsy, **546**

Vertigo, types of, **552**

Vesicle  
 characteristics, **489**

Vesicles  
 dermatitis herpetiformis, **495**  
*varicella zoster virus*, **493**

Vesicourachal diverticulum, **642**

Vesicoureteral reflux, **603**  
 hydronephrosis, **623**

Vesicular monoamine transporter (VMAT), **569**

Vesicular tinea pedis, **152**

Vesicular trafficking proteins, **47**

Vestibular schwannomas, **543**

Vestibulocochlear nerve (CN VIII), **523**

VHL gene, **225**  
 oncogenicity, **225**

*Vibrio cholerae*, **146**  
 exotoxin production, **132**  
 toxin in, **132**  
 watery diarrhea, **179**

*Vibrio parahaemolyticus*, **178**  
 food poisoning, **178**

*Vibrio vulnificus*  
 food poisoning, **178**

*Vibrio vulnificus*, **178**

Vilazodone, **600**

Vimentin  
 cytoskeletal element, **48**  
 tumor identification, **228**

Vinca alkaloids, **451**

Vincristine, **451**  
 microtubules and, **33**  
 toxicities of, **451**

Vinyl chloride carcinogenicity, **226**  
 angiosarcomas, **492**

VIPomas  
 MEN 1 syndrome, **360**  
 octreotide for, **410**  
 regulatory substances, **381**

Viral envelopes, **163**

Viral infections  
 skin, **493**

Viral structure  
 general features, **162**

Virchow node, **389**

Viridans group streptococci, **136**

Viridans streptococci  
 antibiotic testing, **135**  
 biofilm production, **128**

Virilization, **343**

Virulence factors  
 bacterial, **135**  
*Bordetella pertussis*, **143**

Virulence factors, bacterial, **129**

Viruses  
 as cause of myocarditis, **323**  
 causing diarrhea, **179**  
 causing meningitis, **180**  
 genetic/antigenic drift, **169**  
 immunocompromised patients, **178**  
 in immunodeficiency, **118**  
 naked (nonenveloped), **163**  
 naked viral genome infectivity, **163**  
 negative-stranded, **168**  
 receptors for, **166**  
 segmented, **167**  
 structure of, **162**

Visceral leishmaniasis, **158**

Viscosity (blood), **295**

Visual cortex, **513**

Visual field defects, **562**  
 craniopharyngiomas, **546**  
 idiopathic intracranial hypertension, **540**  
 saccular aneurysms and, **532**  
 with stroke, **532**

Visual hallucinations, **582**

Visual impairment  
 cataract, **554**  
 drug-related, **254**  
 glaucoma, **555**  
*Toxocara canis*, **159**  
 pituitary apoplexy, **347**  
 refractive errors, **553**  
 Takayasu arteritis, **484**

Vital capacity, **688**

Vitamin and mineral absorption, **384**

- Vitamin A (retinol)  
function, deficiency and excess, **66**  
idiopathic intracranial  
hypertension, 254, 540  
measles morbidity and mortality,  
170  
storage of, 377
- Vitamin B<sub>1</sub> (thiamine), **66**  
function and deficiency, 66  
functions of, 73  
solubility of, 65  
Wernicke-Korsakoff syndrome  
treatment, 595
- Vitamin B<sub>2</sub> (riboflavin)  
function and deficiency, **67**  
pyruvate dehydrogenase complex,  
76  
solubility, 65
- Vitamin B<sub>3</sub> (niacin)  
function, deficiency and excess,  
**67**  
pyruvate dehydrogenase complex,  
76  
solubility, 65
- Vitamin B<sub>5</sub> (pantothenic acid)  
function and deficiency, **67**  
pyruvate dehydrogenase complex  
and, 77
- Vitamin B<sub>6</sub> (pyridoxine), **67**  
deficiency, 67  
functions and deficiency, **67**  
solubility of, 65
- Vitamin B<sub>7</sub>, 68
- Vitamin B<sub>7</sub> (biotin)  
activated carriers, 75  
function and deficiency, **68**  
pyruvate metabolism, 68  
solubility of, **65**
- Vitamin B<sub>9</sub> (folate)  
function and deficiency, **68**  
solubility, 65
- Vitamin B<sub>12</sub> (cobalamin), **69**  
causes and effects of deficiency,  
430  
deficiency, 160  
function and deficiency, **69**  
malabsorption, 409  
solubility, 65  
spinal cord lesions, 548
- Vitamin C (ascorbic acid)  
free radical elimination by, 204  
functions, **69**  
methemoglobin treatment, 251,  
690
- Vitamin D (calciferol)  
calcitriol production, 613  
excess, 70  
functions, 70  
hyperparathyroidism, 476  
hypocalcemia with, 352  
osteomalacia/rickets, 475  
osteoporosis and, 474  
production, 613  
solubility of, **70**
- Vitamin E, **70**  
deficiency in abetalipoproteinemia,  
94  
function, 69  
solubility of, 65
- Vitamin K, **71**  
coagulation disorder, 435  
in coagulation, 421  
vitamin E interaction, 70
- Vitamin K-dependent coagulation,  
**423**
- Vitelline duct, **642**
- Vitelline duct cyst, 642
- Vitiligo, 490
- Vitreous body  
collagen in, 50
- VLDL (very low-density lipoprotein),  
94
- Volume, 303
- Volume contraction  
alkalemia from diuretics, 632
- Volume of distribution (Vd), 233
- Volvulus, 394  
midgut, **396**  
Onchocerca, 158  
sigmoid, 396
- Vomiting, 370  
area postrema and, 511  
biliary colic, 406  
bilious, 394  
fructose intolerance, 80  
*Histoplasma capsulatum*, 177  
in stroke, 532  
maple syrup urine disease, 84  
MI and, 313  
posttussive, 132, 143, 186  
toxic shock syndrome, 135  
trichinosis, 159  
vitamin C toxicity, 69
- Vomiting center, **511**
- Von Gierke disease, 87
- von Hippel-Lindau disease  
chromosome association, 64  
tumor suppressor genes and, 225
- Von Hippel-Lindau disease, 543
- von Willebrand disease, 421
- Von Willebrand disease, 437
- Voriconazole, 199
- Vortioxetine, 600
- VRE (vancomycin-resistant  
enterococci)  
treatment of highly resistant, 198
- V<sub>max</sub>, 232
- Vulnerable child syndrome, 579
- Vulva  
epithelial histology, 650  
lymphatic drainage of, 648
- Vulvar carcinoma, 668
- Vulvar pathology  
neoplastic, 668  
non-neoplastic, 668
- Vulvovaginitis, 153, 181  
*Candida* spp, 181
- W**
- WAGR complex/syndrome, 629
- “Waiter’s tip”, 458
- Waldenstrom macroglobulinemia,  
440
- Walking milestone, 578
- Wallenberg syndrome, 533
- Wallerian degeneration, 510
- Wall tension, 293
- Warburg effect, 222
- Warfarin  
adverse effects of, 445  
griseofulvin and, 200  
heparin vs, 446  
mechanism and clinical use, 446
- PT measurement, 435  
refers of, 447
- teratogenicity of, 638  
toxicity treatment, 251, 423  
vitamin K antagonist, 71
- Warthin tumor, 386
- Waterhouse-Friderichsen syndrome,  
357
- meningococci, 142
- Watershed areas  
hypoxic stroke in, 529
- Watershed zones, **518**
- Water-soluble vitamins, **65**
- Waxy casts in urine, 618
- WBC casts in urine, 618
- Weakness  
amyotrophic lateral sclerosis, 548  
motor neuron signs, 547  
poliomyelitis, 549  
spinal muscular atrophy, 548
- “Wear and tear” pigment, 212
- Weight gain  
danazol, 682  
mirtazapine, 600
- Weight loss  
chronic mesenteric ischemia, 396  
diabetes mellitus, 354  
glucagonoma, 361  
*Histoplasma capsulatum*, 177  
orlistat for, 411  
pancreatic cancer, 407  
polyarteritis nodosa, 484  
polymyalgia rheumatica, 177  
renal cell carcinoma, 628  
sleep apnea treatment, 703
- Well-patient care, 277
- Werdnig-Hoffmann disease, 548
- Wernicke aphasia, 532, 534
- Wernicke area, 534
- Wernicke encephalopathy, **66**, 595
- Wernicke-Korsakoff syndrome, 66,  
528, 595
- Wernicke (receptive) aphasia, 534
- Western blot, 53
- Wet beriberi, 66
- Wharton duct, 386
- Wharton jelly, 665
- Wheals  
characteristics, 489  
urticaria, 489
- Whipple disease, 361, **391**
- Whispered pectoriloquy, 704
- White blood cells (WBCs)  
in leukemias, 442
- White matter  
demyelinating disorders, 542  
multiple sclerosis, 541
- Whooping cough  
*Bordetella pertussis*, 143  
pertussis toxin, 132
- Wickham striae, 496
- Wide splitting, 298
- Williams syndrome  
cardiac defect association, 308
- Wilms tumor  
neuroblastomas vs, 358  
tumor suppressor genes and, 225
- Wilson disease  
chromosome association, 64
- Winged scapula  
injury and deficits, 458
- Winters formula, 616
- “Wire looping” of capillaries, 620
- Wiskott-Aldrich syndrome, 117  
X-linked recessive disorder, 61
- “Soap bubble” appearance/lesions  
*Cryptococcus neoformans*, 153
- Wnt-7 gene, 636
- Wobble, 37
- Wolff-Chaikoff effect, 349, 350
- Wolfian duct, 645
- Wolff-Parkinson-White syndrome,  
**315**
- “Word salad”, 582
- “Worst headache of my life”, 534
- Wound healing  
keratinocytes, 217  
phases of, 217  
scar/keloid formation, 219  
tissue mediators, **217**
- Woven bone, 468
- Wright-Giemsa stain, 417
- Wright stain  
Borrelia spp, 146
- Wrist  
bones, **459**  
overuse injuries of, 469
- Wrist drop  
lead poisoning, 429
- Written advance directives, 272
- WT1 gene  
oncogenicity, 225
- WT1/WT2 mutations  
nephroblastoma, 629
- Wuchereria bancrofti  
tissue infections, 159
- Wuchereria bancrofti, 158
- X**
- Xanthelasma, 309
- Xanthogranulomatous pyelonephritis,  
624
- Xanthomas, 309  
familial dyslipidemias, 94  
palmar, 94
- Xerophthalmia, 66
- Xerosis cutis, 66
- Xerostomia, 243, 246, 480
- X-inactivation (lyonization)  
Barr body formation, 61
- X-linked (Bruton)  
agammaglobulinemia, 116
- X-linked dominant inheritance, 59
- X-linked recessive disease  
adenosine deaminase deficiency,  
37
- G6PD deficiency, 432  
hyper-IgM syndrome, 117
- X-linked recessive diseases, **61**  
adrenoleukodystrophy, 48  
agammaglobulinemia, 116  
Menkes disease, 51  
Wiskott-Aldrich syndrome, 117
- X-linked recessive inheritance, 59
- X-ray/imaging findings  
bamboo spine, 481  
Bird’s beak sign, 386  
Bone-in-bone, 475  
Codman triangle, 477  
Coffee bean sign, 396  
Coin lesion, 709  
pencil-in-cup, 481  
punched out bone lesions, 440  
Steeple sign (x-ray), 170  
String sign, 392  
Sunburst pattern, 477
- X-rays (teratogenicity), 638
- Y**
- Yellow fever virus  
characteristics, **171**
- Yersinia enterocolitica*, 179  
transmission and treatment, **144**
- Yersinia pestis*  
animal transmission, 149  
facultative intracellular organisms,  
127
- Yolk sac tumor, 671, 677  
ovarian, 670  
testicular, 677

**Z**

Zafirlukast, 712  
Zanamivir, 201  
Zellweger syndrome, 48  
Zenker diverticulum, **394**  
Zero-order elimination, 234  
Zidovudine, 203

Ziehl-Neelsen stain, 125  
Zika virus  
    characteristics, **172**  
Zileuton, 712  
Zinc  
    function and deficiency effects, **71**  
    Wilson disease treatment, 405

Ziprasidone  
    long QT, 315  
    mechanism, 597  
Zoledronate, 500  
Zollinger-Ellison syndrome  
    duodenal ulcer, 390  
    effects and diagnosis, **361**

gastrin in, 381  
MEN 1 syndrome, 360  
    proton pump inhibitors for, 409  
Zona fasciculata, 344  
Zoonotic bacteria, **149**

▶ NOTES

► NOTES

▶ NOTES

► NOTES

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# About the Editors



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Tao developed a passion for medical education as a medical student. He currently edits more than 15 titles in the *First Aid* series. In addition, he is Founder and Chief Education Officer of USMLE-Rx for exam preparation and ScholarRx for undergraduate medical education. As a medical student, he was editor-in-chief of the University of California, San Francisco (UCSF) *Synapse*, a university newspaper with a weekly circulation of 9000. Tao earned his medical degree from UCSF in 1996 and completed his residency training in internal medicine at Yale University and fellowship training at Johns Hopkins University. Tao subsequently went on to cofound Medsn, a medical education technology venture, and served as its chief medical officer. He is currently chief of adult allergy and immunology at the University of Louisville.



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Kristina earned a degree in mathematics from Lake Forest College in 2011 and had a brief career as a software development consultant in Chicago. She graduated from the University of Iowa Carver College of Medicine in 2020 and is applying to the 2021 Match for residency. She has a lifelong passion for emergency medicine with other strong interests including medical education and mental health. Outside of medicine, Kristina's family includes husband Kevin and cats Lemma and Kylo. She enjoys a wide variety of games, trivia, puzzles, escape rooms, trying new recipes, stargazing, and percussion.



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